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PRACTICE OF MEDICINE

VOLUME IV

PRACTICE OF MEDICINE

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SECTION II: INFECTIOUS DISEASES (CONTINUED)

CHAPTER XX

YELLOW FEVER

BY ARISTIDES AGRAMONTE, M.D., SC.D.

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Etiology.—The *germ* or *causative agent* of yellow fever has not been as yet demonstrated. Early investigators (Freire, Carmona, Finlay, Sanarelli, etc.), at one time or another thought they had discovered it in the form of some bacterial organism. Of all claimants in this direction, perhaps the one who had the most semblance of truth was Sanarelli, with his *Bacillus icteroides*, while the organism most exploited, commercially, was the so-called *Cryptococcus xanthogenicus* of Freire, in Brazil. The latter had no scientific basis for his claims and, in fact, several organisms obtained by him were called by the same name and utilized for the supposedly immunizing vaccinations, bringing a fortune to the schemer and his followers. Sanarelli's bacillus was shown, after painstaking and prolonged investigations by American bacteriologists, to be an organism belonging to the hog-cholera group of bacteria,[5] and to have no connection with yellow fever; further, when it was found

by the writer in autopsies of cases, the causes of their death had been foreign to yellow fever infection (dysentery, accidental drowning, etc.).[6] More recently, the experiments hereinafter outlined have shown that the parasite of yellow fever cannot be a bacterium, but is more likely a protozoön. Dr. Harold Seidelin, who worked in Yucatan, Mexico, and afterwards became attached to the Liverpool School of Tropical Medicine, thought that he had discovered an organism present in the blood of all cases of yellow fever, the exact morphology of which could not be established, since the description of the various stages of the supposed parasite was so indefinite. His investigations are given in the different articles devoted to fix the guilt of yellow fever germ upon it.[7] The fact that Dr. Seidelin found it in his own blood on three different occasions at varying intervals, presuming that he had suffered three attacks of yellow fever, without the symptoms of the disease, served more than anything else to cast serious doubt upon the identity of the so-called parasite. Besides this, the writer has shown the same bodies in impoverished blood from any other pathological conditions,[8] which are certainly nothing but nuclear fragments, chromatoid residue, etc., which, taking the Giemsa stain, particularly, have the appearance of blood parasites or protozoa when examined with the microscope and often are seemingly inside the red cell, but really only resting upon it, or under it. Finally, it has been shown that bodies identical with Seidelin's parasite are to be found in the blood of newborn guinea pigs[9] in England, where no yellow fever exists, and also in most laboratory animals after an injection of blood from the same or other species.[10] The recent investigations, tending to establish the endemic presence of yellow fever on the West coast of Africa, has definitely settled the question against the claims put forth by Dr. Seidelin, who curiously enough had a share in the English Yellow Fever Commission (West Africa).

The Rockefeller Foundation, which has done so much for the promotion of the medical sciences, took a hand in the proper direction towards eradicating yellow fever from the port of Guayaquil, in Ecuador, where the disease had acquired its strongest hold for more than a century. Coincident with the work undertaken by the Commission appointed to devise such means, applicable to the peculiar conditions of that city, that would finally stamp out the infection, much attention was paid to the question of the parasite or germ of the disease. In this connection, the research carried out by Dr. Hideyo Noguchi deserves the greatest consideration, inasmuch as he claims, with no little reason as will be seen later, to have found the real causative agent of yellow fever, which he has called **Leptospira icteroides.**

These pages are intended mainly to record the latest advances in the investigations undertaken and therefore it would be out of place here to initiate what might be considered as an attempt at controversy by going very deeply into a discussion of the *pros* and *cons* in Noguchi's claims. As it is, there are many broken strands in the web so exquisitely woven by this wonderful investigator, which must be replaced or rearranged before we can definitely accept his views as conclusive.

As a result of the inoculation of blood taken from yellow fever cases Noguchi obtained the development of a spirochaete in the blood and tissues of guinea pigs in a relatively small number of experiments so made. This organism, the **Leptospira icteroides,** has subsequently, although rarely, with great difficulty and in very limited quantity, been seen in the blood of yellow fever patients by means of reflected light or dark-field examination. The organism is quite virulent for guinea pigs although it seems that a fairly large quantity of the culture is necessary to produce marked or fatal infection. Young dogs have been artificially infected and also marmoset monkeys. Noguchi succeeded in obtaining an infection of a guinea pig by the bites of mosquitoes that had taken blood from a case of yellow fever, but failed several other times as well as in his attempts to transmit the infection from one guinea pig to another. These animals seem to become protected against the **Leptospira** by the injection of sérum from yellow fever convalescents. Guinea pigs that survive the inoculation with this organism, regularly remain immune to subsequent inoculations with the same.

The relations between **Leptospira icteroides** and the Leptospira icterohemorrhagicae, the causative agent in infectious icterus (Weil's disease), was studied by Noguchi, carrying out protective and Pfeiffer tests, the results of which convinced him that they are entirely different organisms: according to him, although some similarity does exist, it is not sufficiently remarkable to warrant their being considered as belonging to the same species and he compares this similarity to that existing clinically between the two diseases in which, he says, they differ only in the predominance of some of the symptoms.

The **Leptospira icteroides** has been profusely cultivated and strains have been obtained from Ecuador, Yucatan and Peru. Experimental inoculations produce an infection characterized by icterus and hemorrhagic tendencies, the organism often multiplying in great numbers in the blood, liver, spleen, etc. of the animals treated. The pathologic lesions, in Noguchi's opinion, are the same as those of yellow fever in man.

A protective vaccine or serum has been prepared with the purpose of protecting non-immune individuals in such districts as may be invaded

by yellow fever or that may be considered endemic foci of the disease; unfortunately, the protective inoculations have been tried so far, in places where other prophylactic measures had also been implanted so that their real benefit can only be conjectured.

From all the data presented by Noguchi, it is evident that the **Leptospira icteroides** is a facultative saprophite: this has been lately corroborated by spontaneous infections that have taken place in animals and by experimental oral infection brought about by Lebredo in dogs, with a strain of the **Leptospira** which was obtained by him from Noguchi. If such is the case with the germ of yellow fever, we will have to go back to the days of the dreaded "fomites." a factor in the transmission of the disease that was definitely eliminated by the experiments of the U. S. Army Board and those of Ross in Havana.

The facts appearing in the numerous contributions made by Noguchi, which serve as a basis for his claim that the **Leptospira icteroides** is the etiologic agent in yellow fever may be summed up as follows:

(1) The organism has been seen in the blood of a few cases of yellow fever, though in small quantity and with some difficulty: only by dark-field illumination.

(2) It has been obtained from the blood and tissues of guinea pigs that had been injected with yellow fever blood, in a limited number of experiments.

(3) It has been obtained from cases of yellow fever in Ecuador, Yucatan and Peru by the means above stated.

(4) Inoculations with cultures of **Leptospira** produce, according to Noguchi, all the symptoms and lesions of yellow fever in guinea pigs.

(5) A successful experiment with mosquitoes has shown that it can be transmitted by this insect.

(6) It is agglutinated by the serum of convalescents from yellow fever and a positive Pfeiffer reaction is obtained with the same.

(7) The serum of yellow fever convalescents has marked protective action against the **Leptospira icteroides.**

Subsequent to Noguchi's discovery, there has been little opportunity for other investigators to work upon the same lines, nevertheless, whatever has been evolved certainly does not corroborate his findings in all respects; some of this may be set here for further elucidation.

The organism isolated by him has been observed only in a very small proportion of the cases by Noguchi; it could not be seen or isolated by Noguchi's methods in five cases of yellow fever which were studied in Havana, imported from Vera Cruz. Guinea pigs injected with the blood from these cases, within the first three days of the disease, gave uniform negative results.

During the worst epidemics of yellow fever no unusual diseases or deaths occurred among domestic animals, notwithstanding the fact that the **Leptospira** is very infectious for dogs, both young and adult, as well as for guinea pigs.

Contact infection with **Leptospira** is very easy to produce, while in yellow fever, the blood, excreta and tissues of cases are absolutely innocuous as demonstrated by autopsies being performed by non-immunes with absolute safety and by the experiments with soiled linen and bedding which produced no infection.

Blood taken by Noguchi after the third day of the disease seemed to contain the **Leptospira icteroides,** while experiments had demonstrated that the parasite of yellow fever was not in the circulating blood beyond that date. In the experimental inoculations this organism is found in the blood of the animals up to the moment of their death and in increasing quantities, according to Lebredo.

The only successful experiment with mosquitoes made by Noguchi is not very convincing: the date of the disease at the time that the mosquitoes were contaminated is not very definite. Mosquito experiments made by the Rockefeller Commission to Africa (reported by Guiteras), were uniformly negative. Accidental inoculation by other means than the mosquito with **Leptospira icteroides** is quite possible and even probable when dealing with this organism. Lebredo has reported the spontaneous (natural) infection of a bitch from her own pups, two of which had been experimentally inoculated with Noguchi's **Leptospira.**

The pathologic lesions obtained with **Leptospira icteroides** in animals is very much unlike those we see in cases of yellow fever, Noguchi's assertion to the contrary notwithstanding; on the other hand, they are identical with those we find in cases of Weil's disease, produced by L. icterol hemorrhagicae, and in animals inoculated with this organism: this is particularly so, regarding the pulmonary lesions present in Weil's disease and the absence of any fatty degeneration of the tissues so prominent in yellow fever.

Leptospira icteroides and L. icterohemorrhagicae are species extremely closely allied (one is tempted to consider them varieties of the same species), and yet, except for the icterus and the hemorrhagic tendency,

no two diseases could be more unlike in their clinical and epidemiologic aspects than yellow fever and Weil's disease, although Noguchi believes them to be very similar. The greatest divergence might be seen in the proportional blood count: while in yellow fever there is a marked leucopenia with high hemoglobin per cent., in Weil's disease as well as in the infections produced in animals by **both leptospirae**, above cited, there is a gradual and progressive diminution in the number of red blood cells as well as in the hemoglobin, accompanied by a hyperleucocytosis such as we see in the undulating fevers.

Personally, I am inclined to believe that Noguchi's **Leptospira icteroides** when found in cases of yellow fever is there in the capacity of a secondary infection and that the real parasite of this disease must be another less saprophitic in its mode of life. As other workers take hold of this interesting subject, light will be made that will no doubt result in the greatest benefit to the cause of public hygiene.

But if the parasite of yellow fever has not been demonstrated, its *method of propagating the infection* has been thoroughly elucidated by the experiments which showed its transmission through the bites of infected mosquitoes.

As early as 1853, Dr. Louis Daniel Beauperthuy, a French West Indian physician and naturalist, pointed to the relation of mosquitoes and yellow fever,[11] the absence of infection where mosquitoes did not abound and how, by destroying the mosquitoes or protecting against their stings, yellow fever could be eliminated, believing that the insects obtained their contamination from the swamps and stagnant waters where they are known to breed. Other physicians, in a manner more or less vague, seemed to see some connection between insects, mosquitoes and the spread of yellow-fever infection, when it came into a favorable locality (Nott, King, Dowell), but nothing very definite can be found in the literature until 1881, when Dr. Carlos Finlay, of Havana, hypothetically considered the mosquito as the transmitter of yellow fever, from man to man, from the sick to the non-immune, thus serving to spread the infection.[12] This theory, so happily conceived in the very midst of one of the most dreaded epidemic foci, was doomed to remain uncorroborated for a period of twenty years. The errors natural to every newly formed idea clung to it and kept the genial originator from making it evident to the scientific world. Dr. Finlay made attempts to inoculate individuals with mosquitoes which, we now know, were not infective, as he applied the insects to the sick at too late a period for them to derive contamination. He was not sure of the harmlessness of the excreta of yellow fever patients, even as late as 1899. At one time

he thought he had discovered the germ, a tetracoccus, which the mosquito presumably injected after sucking the infected blood, etc. And so all these wrong premises, leading to his repeated failures and to general disbelief, only tended to discredit his theory, though, as we shall see, it was fundamentally correct. (Dr. Finlay's writings are collected in a volume, "Trabajos Selectos, etc.," published by the Cuban Government. It may be obtained free, on request.)

In 1900, Surgeon-General Geo. M. Sternberg, U. S. Army, appointed a board of medical officers to investigate the infectious diseases in the Island of Cuba, and incidentally yellow fever, which had not abated in spite of the thorough sanitary work accomplished in Havana and larger cities. The report of the work performed and the results obtained by the Board were published in 1901,[2] and the history of the labor which culminated in the epoch-making demonstration was prepared by the writer, who is to-day the only survivor of that Board, and was published in *Scientific Monthly,* December, 1915 (q. v.).

The experiments undertaken, subjected to the strict observance of the most exacting scientific rules, performed upon men who volunteered, some for love of humanity, others for a monetary consideration, were surrounded by all the safeguards imaginable that would make them, as they turned out to be, absolutely reliable. The findings were as follows:

(1) It was determined that the guilty mosquito, as indicated by Finlay, belonged to a peculiar species, now known as *Aëdes calopus,* then classified as *Stegomyia faciata.* (To be described presently.)

(2) The period during which the blood of a yellow fever case can contaminate the insect is during the first three days of the disease; it probably does not extend to the fourth day.

(3) The mosquito, once contaminated, cannot transmit the disease even though he may sting during this interval, until after the twelfth day subsequent to its contamination.

(4) The period of incubation in man does not extend beyond the sixth day after being stung by an infected mosquito.

(5) The disease is strictly a blood disease and may be produced by subcutaneous injection of yellow fever blood (taken during the first three days of the disease), when administered to a non-immune individual.

(6) The germ, whatever it may be, is filterable, that is, it passes through a porcelain filter that holds back bacteria.

(7) The excreta (feces, vomit, urine, etc.) are incapable of transmitting the disease, either by contact or when taken into the body.

These findings of the U. S. Army Board have been corroborated by various commissions appointed, which repeated the experiments in Cuba, Mexico and Brazil; unfortunately, nothing new has been added to the etiology of this disease since the publication of their results in 1901.

The writer has shown that the parasite is present in the blood serum allowed to separate naturally from the coagulum, and that it is not affected by an altitude of 7,800 feet.[28]

THE YELLOW FEVER MOSQUITO.—The separation of this genus from the great *Culex* family, into a group by itself, we owe to the eminent

English entomologist F. V. Theobald, who, while studying the insect *Culex faciatus,* or *Culex teniatus,* found that it differed in many particulars from the type of the genus in which it was then classified. More than twenty species of this genus, first known as *Stegomyia* and now under the name of *Aëdes,* have been described by Theobald.[18]

The yellow fever transmitter, under the name of *Aëdes calopus,* has general characteristics as follows:

The palpi are short in the female and long in the male, having four joints in the former and five in the latter. The head is completely cov-

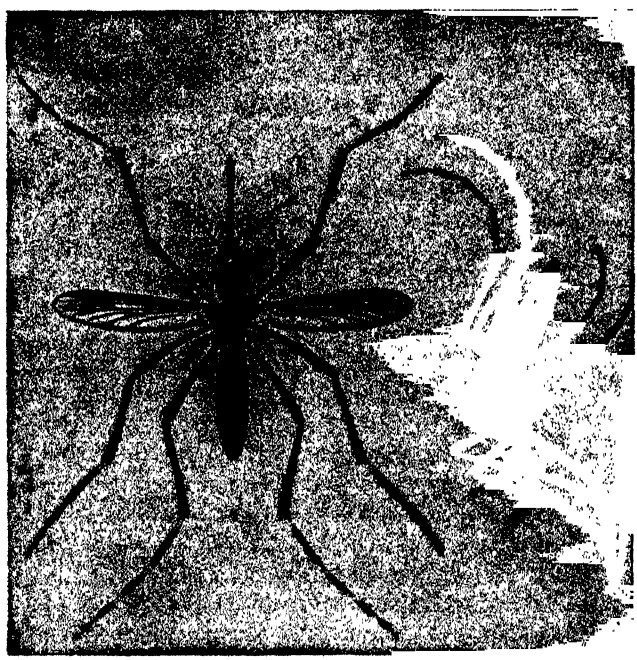


FIG. 1.—AËDES CALOPUS (FEMALE) (Meigen, 1827), THE TRANSMITTER OF YELLOW FEVER, AND ITS USUAL POSE WHILE STINGING. (After Goeldi.)

ered by an armor of broad and flat scales; the mesothorax is covered by thin, curved or fusiformed scales; the scutellum (the trilobular plate between the mesothorax and the front of the metathorax) is covered always by broad flat scales over the central lobe, and often over the lateral lobes as well; the ventrum is entirely covered by flat scales, with rings or without them, and with lateral white spots. The palpi in the female are small, never more than one-third the length of the proboscis, and usually smooth. The wings have venation similar to that of the typical *Culex,* but the forked cells are short.

Aëdes calopus can be readily recognized with the naked eye. Upon the thorax, directly in front of the wing, may be seen lines, composed of white silvery scales, which in their distribution or arrangement assume the outlines of a lyre (the external line is thicker), with the foot

of the instrument towards the head of the insect; four distinct white lines appear upon the metanotum. The palpi in the male are even longer than the proboscis. The short palpi of the female have white ends. When the palpi are held together, their white tops give the impression of a ring around the base of the proboscis; but this contains no ring whatever, being entirely black its whole length. The sides of the insect are dark brown with white spots. The abdominal segments have a white band about their bases, more evident upon the front or ventral aspect. The bases of the tarsi are white. The front claws in

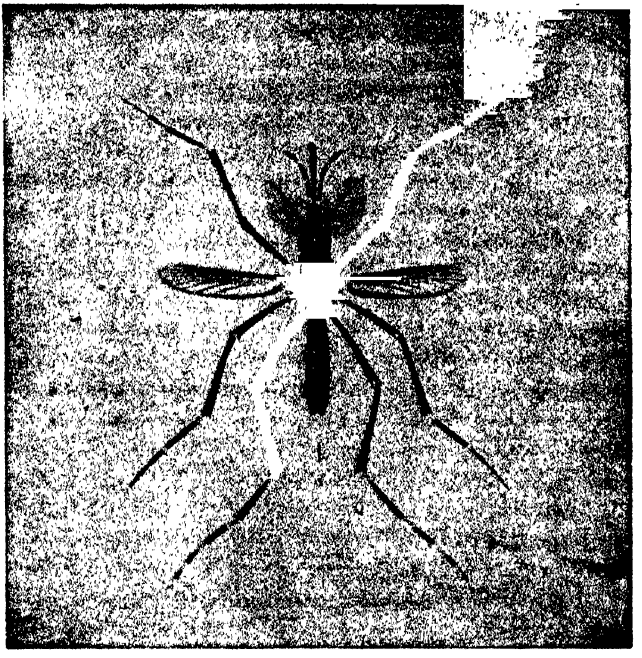


FIG. 2.—AËDES CALOPUS (Meigen 1827). (After Goeldi.)

the female have each a tooth upon the lower side; in the male, only one of the claws has a tooth.

Geographical Distribution.—Aëdes calopus is found extensively disseminated over all the cities of South America, as far as the Rio de la Plata, and in all those of Central America. Its presence has been demonstrated as far north as the 33° parallel of latitude on the Atlantic coast (Charleston). It is quite prevalent in the West India Islands, although in Cuba it was formerly met with only in the large cities of the coast. The facilities of communication throughout the interior of this island, the promotion of commercial enterprise and the great development obtained by the sugar industry, have all contributed in widely spreading the habitat of this mosquito.

In Europe, specimens may be gathered from Portugal, Spain, South-

ern Italy and Greece. In Africa, this mosquito is spread through Morocco, Egypt, Algiers, along the Western coast and in some of the Eastern states. In Asia, it is found in Palestine, India, Indo-China, Siam and Japan. It is also found in many of the South Sea Islands and in Australia.

Evolution and Life Habits of the Mosquito.—The first insects that leave the water in their aërial stage are generally males; as soon as they emerge from the pupa skin, their tissues acquire rigidity, their wings dry and they begin to fly about. Immediately after, the males and females join each other, copulation taking place face to face, while flying, and lasting a period of time that may be fixed at 30 seconds, on the average. The male may be seen to repeat the act four or five times each with a different female, in as many minutes. The females may thus be said to become fecundated as soon as they begin aërial life.

Three or four days after fecundation, seldom before that, the females of *Aëdes calopus* lay their eggs, after having sucked blood. Most observers state that the ingestion of blood is necessary for *ovulation.* There is reason, however, to believe that in certain places mosquitoes lay their eggs without having had opportunity to bite any animal. The author finds among his notes records of two occasions on which eggs were obtained from cages where the mosquitoes had not been able to suck blood; these eggs, however, had little vitality and hatched in less proportion than those of mosquitoes nourished with blood. At all events, it is a fact that, as soon as the females are fecundated, they are in a condition to bite and are anxious to do so.

These mosquitoes *deposit their eggs* on the water, or so near to it that the slightest increase in the volume of the liquid will cause them to be wet and thus enable them to hatch out. I have seen a mosquito of this species lay its eggs in the following manner:

After standing on the water with its legs well spread out and its abdomen curved downwards, it inclines (or dips) its entire body until it touches the surface of the water with its last abdominal segment. Then it straightens out its body, walks a few paces and stoops once more, touching the water with its ovipositor. This movement is repeated numerous times (from twelve to twenty-two), and it seems to represent efforts which the insect makes at expelling the egg, because, after various attempts, it remains for a slightly longer period with its last abdominal segment in contact with the water, while a small white egg makes its appearance. In this way the mosquito lays on the average three eggs per minute, resting some thirty seconds after having deposited six or eight eggs. The writer believes this manner of oviposition has not been described in any of the species which are connected with the infectious diseases. The eggs do not tend to crowd together, but remain separated and if they are heaped, as in a test tube, for instance, they remain on the surface of the water with their long axes parallel.

Brackish water is unfit for the development of the larvæ and, besides, the mosquito prefers water that may be relatively clean. Like other *Culicidæ,* this mosquito lays its eggs generally during the night, re-

maining persistently in the neighborhood of houses. It is never found hiding among shrubs, in the plains or in woods, and this fact explains why yellow fever has been held to be a domiciliary or house infection by the majority of observers.

The eggs of *Aëdes calopus*, after being deposited in the water, turn to a uniform black color; they have an elongated cone-shaped form, rather flat on one side and are about one-half millimeter long. Their surface is checkered, as though the egg were surrounded by a fine reticulated membrane; this rugosity of the surface makes it retain minute bubbles of air which contribute in a very direct manner to keep it afloat. Any movement which shakes off these bubbles causes the egg to sink to the bottom; this notwithstanding, the egg does not lose the power of hatching and even does so after becoming dry for two or three days in the receptacle where it may be cultivated. Some eggs have hatched thirty days after they were laid and subjected to various desiccations. The average number of eggs laid each time is from 50 to 60, though one mosquito has laid as many as 144 eggs at one sitting.

The time required for the complete *evolution of the egg* depends upon various factors, the most important of which evidently are the season, the temperature of the air and the chemical composition of the water.

Other conditions being equal, the season of the year no doubt exerts the most direct influence upon the rapidity with which the egg of this variety of mosquito will hatch; the larvæ certainly appear much sooner in summer than in the winter months. This may be due also to peculiar conditions of the parent insect at the time of the year.

The *process of hatching* is retarded when the water is cooled to 13° C. (55° F.), which also happens with the egg of other varieties of mosquitoes. Certain inherent conditions of the medium appear to accelerate or retard its evolution; for instance, the lye made by boiling ashes, prepared by washerwomen in the tropics to bleach linen, seems to be a favorite breeding material, the eggs developing there into larvæ sooner than when laid on dirty, stagnant, surface water, though the latter contain a richer store of organic matter for their nourishment. The shortest period observed by us in the evolution of the egg, until the production of larvæ, has been 15 hours, but this process generally lasts more than 36 hours, even taking three days, according to the environment. When the hatching is interrupted by desiccation or any other circumstance, this period is considerably prolonged.

The young *larvæ* escape from the eggs by an opening which takes place at their broader extremity. The differences between the larvæ of *Aëdes* and those of other *Culicidæ* are not many; however, we have the buccal brush-like organs which are slightly more developed in *Aëdes* and the respiratory syphon is a bit shorter, thicker and of a darker, almost black color, in the larvæ of this genus.

The larvæ of *Aëdes* molt three or four times before attaining their fullest development, when they are converted into the pupa or nymph; this change takes place, in summer, 8 days after hatching, and in winter

it takes from 12 to 14 days. A larval period of 20 days, though it has been observed, is exceptionally prolonged.

The larvæ of this genus seem to be more vigorous than those of other *Culicidæ;* they swim by means of undulatory movements of their entire body, aided by the hair-like bunches at each segment, remaining head downwards only a few minutes upon the surface of the water. They eat voraciously, darting from time to time to the bottom of the container, where they find the microscopic animals and plants and the organic matter upon which they feed. The most developed larvæ remain at the bottom for even four minutes; the younger ones must ascend to the surface with greater frequency in quest of air, remaining there for a longer period.

The larvæ of this species will not stand complete freezing, though not particularly affected by a temperature of 6° to 8° C. (43° to 46° F.) during four days. From an epidemiologic standpoint it is important to consider the possibility of the larvæ being enabled to live outside of their natural element. The dry season in the countries of its habitat is never so extensive as to desiccate completely its breeding places, and, besides, some water containers can be found in the neighborhood of houses, in the backyards or gardens, such as flower-pots, empty cans, broken bottles, etc., constituting ideal breeding places.

The *pupa* or *nymph* of *Aëdes* is but little different from that of other *Culicidæ:* there is a slight elongation of the thoracic portion and greater thickness of the abdominal segment. This stage in the evolution lasts for two or three days, during which time the insect does not feed, living a merely passive existence. At the end of this period, the covering breaks upon the dorsal side and allows the *imago* or *perfect insect* to emerge. We thus have a minimum period of evolution lasting 10 days from the laying of the egg to the birth of the mosquito.

The usual proportion of males to females born each time is 1 to 6, though sometimes even more in favor of the females. Rarely, the opposite takes place.

The newly-born fecundated females remain quiet during three or four days. It is seldom that this mosquito can be urged to bite before the third day; after that, it generally lays its eggs. The mosquito will then suck blood at intervals of few days, as long as it lives.

The *longevity of the mosquito* is an important question, since it bears very directly upon the prophylactic measures against yellow fever, particularly when new epidemic outbreaks occur after a long interval, without the possibility of new infectant cases having been introduced. *Aëdes calopus* is a long-lived insect; one of our specimens, born in the laboratory, lived from March to May, a period of 76 days, producing a case of experimental yellow fever 56 days after its having been infected. Another insect lived at "Las Animas" Hospital for 154 days.

Very likely they do not attain to such an age while free in nature; they have their natural enemies among the animals and insects, besides being exposed to many accidents from which they are protected in our laboratories. Ants have wrought serious damage among our breeds and

ruined our experiments more than once. The voracity with which dragon-flies devour mosquitoes is well known and some bats and night-birds destroy them in large quantity. Any injury causes their death and they never survive the loss of a leg, antenna or palpus.

The nourishment of the male mosquitoes consists essentially of the juice of plants, the honey of flowers and water, it being materially impossible for them to penetrate the tissues of animals on account of the anatomical configuration of their proboscides. The caged females also may be fed upon fruit juices for a time, but they cannot live very long without extracting blood from some animal. They sting at any hour of the day or night, but preferably at twilight.

The author considers this mosquito incapable of undertaking long flights, but, aided by the wind, it may wander as much as 500 meters from its birthplace. Other more probable means of *transportation* are the railroad cars (not the sleeping cars, but the closed freight and passenger cars), and the staterooms of vessels (both steamer and sailing craft). It is less likely for a mosquito to be carried alive from one point to another in the baggage of passengers, unless it remains shut up in a box that will have enough space inside to permit the insect freedom from contact with the other contents, since the delicate structure of the mosquitoes renders them liable to be killed by any blow or pressure they may receive inside of baggage of any kind.

Acclimatization Fever.—There really is no fever that may be rightly assumed to protect against this disease, except yellow fever itself. Early writers evidently mistook the mild attacks suffered by newcomers in an infected locality as representing another form of protective pyrexia. The name of "inflammatory fever" was also given to such conditions probably on account of the sudden onset, with general congestion, which marks the early symptoms of the disease. These terms are little used now by modern observers and the sooner they are dropped from the nomenclature the better.

Race Incidence.—It cannot be positively asserted that any one race or people is immune to yellow fever, but the most experienced students of this disease are of the opinion that the Chinese seem to present some remarkable resistance to the germ. During the later days of slavery, thousands of Chinese laborers were introduced in the Spanish colonies to supplant the negro labor in the plantations, as well as in the cities of Cuba, yet during extensive epidemics of yellow fever no cases were observed among the Chinese. It is likely that some may have escaped observation, but if that is the case, the proportion of cases must have been very low. Not having been transported to the Far East, the disease in this connection has not been subjected to a final test. During severe epidemics of yellow fever, the negro population has been severely attacked. Such was the case in the great epidemic of Philadelphia and has been in Barbados, but usually the blacks are attacked in less proportion than the whites, and in a general way, the disease seems to run a milder course, being less fatal.[14] The English Yellow Fever Commission found that in West Africa they could recognize two forms of the

disease, one more severe, often fatal, affecting the foreign white population and another milder, rarely causing death, attacking mainly the natives. This lesser susceptibility of the negro race has been observed in epidemics occurring in the United States and some West India islands; no case has been recorded in a Cuban negro.

It may be safely stated that every white man coming for the first time within the area of a yellow fever focus is liable to become infected at any moment and the susceptibility is not greater among the northern races than among the more tropical ones. Scandinavians and Syrians, Russians and Italians are as easily and gravely infected when exposed.

AGE INCIDENCE.—The old and the young suffer from yellow fever, though probably not in the same relative proportion. It is a fact that during epidemics the greater number of cases range in age from the fifteenth to the forty-fifth year, but this may be due in a measure to the low population ratio before and after those ages and also because the older inhabitants of a given locality may have obtained their immunity during a previous epidemic.

In children the disease usually runs a milder or an atypical course; such has been the experience of investigators in America and the late reports of the endemic West Africa foci seem to bear this out. In Cuba the disease was rather frequently seen in native children, from two to ten years of age, under the name of "fiebre de borras," proving fatal in many instances; with the disappearance of yellow fever from the island, this other has not been seen again. It is very likely, if, as surmised, the disease often assumes a mild character in children, they suffer their attack unrecognized or mistaken for some gastro-intestinal trouble, thus obtaining immunity and explaining this condition so characteristic in the native-born, be he white or black, in communities where the disease has been endemic.

ENDEMICITY.—The prevalence of yellow fever in a country or community has been due undoubtedly to the coexistence of the transmitting mosquito and cases of the disease, recognized as such or unrecognized, in greater or lesser number. It is often seen that epidemics apparently end at a certain period of the year; then weeks or even months may elapse, when another epidemic is started seemingly without the introduction of new infection. This has led some observers to believe that another host than the mosquito and man may be responsible for maintaining the infection in a latent state. We are convinced, however, that no other explanation can be as satisfactory and none certainly more logical than the one given in numerous writings upon the matter, which is, that the infection is kept up in a community, when not in epidemic form, by so-called sporadic or isolated cases, occurring during the intervals between epidemics and principally by the disease preying upon young children, in whom it is not recognized as yellow fever, or is mistaken for some type of gastro-intestinal infection.

In Cuba, during the yellow fever years, we had numerous cases of fever, with more or less "black vomit," in children and native adult

Cubans, which were called "fiebre de borras"; since the stamping out of yellow fever, these cases have also disappeared.

The coexistence of yellow fever with an increase in the infant mortality from all causes, showing the relation of the disease with young children, has been ably presented by Dr. J. Guiteras,[15] not only in Cuba, but also in Venezuela and elsewhere. By keeping down the proportion of mosquitoes in any locality the endemicity of yellow fever has been repeatedly abolished.[16]

IMMUNITY.—As suggested above, only an acquired immunity can be accepted, since a racial immunity cannot be said to have been proven in any case. From the data at hand, a greater or lesser susceptibility may be appreciated, but no natural immunity has been observed. It is safe to believe in the probability of a previous unrecorded attack in cases where repeated exposures seem to point to a natural immunity. When the disease has disappeared from a locality during several years, its new advent has been accompanied by wide-spread dissemination among the natives as well as foreigners, regardless of race (Philadelphia, Barbados, Trinidad).

On the other hand, the immunity conferred by one attack is sufficiently lasting to carry through man's usual span of life. Like in other infectious diseases, known to protect very efficiently against subsequent attacks (scarlet fever, measles, whooping-cough, mumps, etc.), now and then we see a case in which the attack has been repeated. This is exceptional, and the possibility of an erroneous diagnosis of the first attack is always to be considered. Multiple repetitions of yellow fever attacks in the same individual can hardly be accepted. Those who oppose this theory (Marchoux, Simond, Seidelin) base their opinion upon the observance of cases of fever of short duration without explicable cause. Inasmuch as there is as yet no definite tangible means of making a positive diagnosis in any mild case of yellow fever, they may have been due to other less severe and more elusive infections.

Some observers believe that prolonged absence from a yellow fever focus will cause a gradual loss of the immunity previously acquired and although the limit of such a period has never been clearly determined, it is quite possible that a child removed for a decade from an endemic area may develop a second attack upon his return, since the antibodies formed at the time of the attack in childhood, through the natural evolution into manhood, may have been lost or destroyed, supposing that he had already suffered an attack when removed. Had this not occurred, the liability to infection would be quite natural and as great as in any foreigner non-immune.

Symptomatology.—GENERAL DESCRIPTION.—During the period of *incubation*, which may be from a few hours to six and a half days, it cannot be said that yellow fever manifests itself in any way; there seem to be no prodromes. This has been demonstrated in the experimental cases produced by the United States Army Board, by the various commissions that followed upon its footsteps and also by the observation of special cases in well-known and limited epidemics.[20]

The *onset* is rather sudden, the initial symptoms developing within very few hours. At first there is oppressive headache accompanied by a chill or "chilly sensations"; also undetermined muscular pains (myalgias), backache and fever, the patients being overcome during their ordinary work or awakened from a sleep that had been tranquil as ever. They will then continue for a few hours with the headache and lumbar pain, in a state of languor and great lassitude, when the fever, after rising to 39° or 40° C. (102.2° or 104° F.) generally during the night, will remit towards morning, to rise again and remain so until the end of the disease. At this period, the pulse will be found quick and tense; the face flushed, sometimes to a purplish hue, and exceptionally it is pale, with an anxious expression, the eyes bright, glary, the conjunctivæ injected; the skin, usually dry, may then be moist and hot, showing some capillary stasis upon pressure.

The very malignant cases, which die within forty-eight or seventy-two hours, do not show the same series of symptoms as outlined above; in them, the disease is ushered in by intense headache and chill, high fever, lumbar pains, quickly followed by gastric symptoms, marked albuminuria, the patient soon falling into a condition of deep depression, even into coma, or often dying in convulsions.

Ordinary cases, after the first remission of the fever, from the second to the third day, go on with a new rise of temperature; albuminuria is almost always present; the headache is more or less intense and gastric disturbance quickly makes its appearance in the shape of epigastric pain, tenderness on pressure, or slight nausea which may go on to actual vomiting of food. The pains in the loins and large joints may persist, accompanied by fever, seldom above 39° C. (102.2° F.), with a comparatively slow pulse (Faget's sign), 60 to 70 beats per minute. At this, which may be considered as the second stage of the disease and may last for several days (four to seven), the icterus becomes pronounced and the symptoms acquire varying degrees of severity until defervescence begins, or the third, more frequently fatal, stage of the disease becomes established. Then we have marked exacerbation of all symptoms, indicating extreme toxemia; the patients become delirious or fall in a semicomatous condition, the vomiting becomes frankly of the "black" variety, with "coffee-grounds" or fresh blood mixed with gastric contents. The high temperature with comparatively low pulse may persist. The urine will be scanty, highly colored, albuminous and may contain bile-pigmented casts. There will be constipation or, if purgatives have been used, the stools will be more or less soft and of normal color; sometimes they are streaked with blood or contain some of the "black vomit" found in the stomach. There is great thirst and death occurs as the result of cardiac esthesia.

The writer has endeavored in the above paragraphs to outline the regular course of typical cases of yellow fever. Each one of the principal and peculiar symptoms, however, requires further handling, and certain groups of symptoms, such as are also seen in other infec-

tions, appear during the course of this disease in a definite order, at a definite time, with a definite intensity that shall be later described.

THE FEVER.—This feature of the disease may be considered as peculiar in the manner of its appearance and subsequent development. Beginning in the majority of cases with a distinct chill, or less frequently with only sensations of cold or heat, the temperature has a tendency to rise gradually during the first twenty-four hours, reaching the maximum from the twelfth to the twenty-fourth hour after the onset, less rapidly than is generally described by writers; the highest temperature may be even 41° C. (105.8° F.), though rarely more than 39.5° C. (103.1° F.). This temperature with very slight alterations is kept up for less than forty-eight hours, when a distinct remission may be observed in all cases, very rarely reaching normal temperature, accompanied by an abatement of all subjective symptoms. The duration of this first stage in ten experimental cases carefully tested every three hours, was as follows, the average duration being forty-three hours:

Number of cases	1	1	1	1	1	3	1	1
Duration of paroxysm, in hours	33	33½	36	39	41	45	52	60

In the very mild cases, so-called abortive cases, once the temperature starts to descend, it continues with slight oscillations and the patients go on to recovery with that one access of fever only.

In the ordinary cases, the secondary febrile paroxysm immediately follows the remission above described which lasts only a few hours (from three to twenty-seven hours in experimental cases), the temperature slowly rising again and reaching its maximum and remaining there from two to five days, with very slight fluctuations, these depending mainly upon subsequent events, such as hemorrhage, cardiac failure, etc., or as a result of antithermic treatment.

It is during this secondary paroxysm that the second and third stages in which the disease may be divided actually occur, since it is only exceptionally that an intermission between them can be demonstrated in the temperature charts.

In yellow fever, as in all acute infectious processes where marked lesions are developing in a relatively short space of time, it is not frequent to see marked oscillations in the temperature curve, so that when we are treating of a secondary paroxysm, it does not mean to imply that an equable persistent high temperature is maintained; a rise or drop of one-half to one degree may be observed, secondary infection, hemorrhage, etc., determining the extent of these fluctuations.

In curable cases, from the fifth to the eighth day, the fever begins rapidly to descend and in a few hours reaches even below normal, remaining generally so until complete recovery. In fatal cases the fever is present until the last, in some showing a tendency to drop, in others rising inordinately. When the temperature curve shows a tendency to remain high, at the same level for several days, such cases are likely to terminate fatally, usually in a condition of uremia.

Extremes of fever, or hyperpyrexia, are rare in yellow fever and can generally be attributed to complications. The author has seen this in cases of malaria coexisting with yellow fever, a symbiosis met with more frequently than it was acknowledged in the old yellow fever centers.

A very prolonged febrile condition is certainly not characteristic, and, when present, it will be found to be due to some other infective

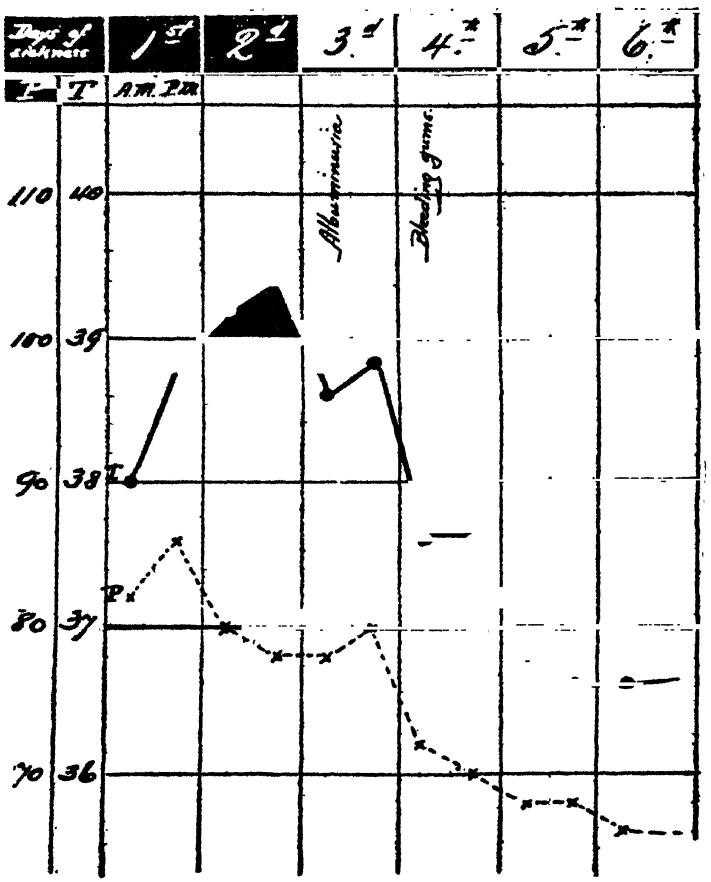


FIG. 3.—CHART IN CASE OF YELLOW FEVER OF MILD CHARACTER.
P, Pulse curve; T, Temperature curve.

process which has become engrafted, as it were, upon the yellow fever access.

A close study of the charts herein presented will show the peculiar characters above outlined.

CIRCULATORY SYSTEM.—The yellow fever toxin seems to exert its action more potently upon this than upon any other part of the human economy. The examination of a patient in the first or second day reveals a marked congestion of the skin of the face, the capillaries are injected in the conjunctivæ and the flushed condition gives him the look

of one under the influence of alcoholic intoxication. The congestion of the superficial vessels goes on even to the second febrile paroxysm, when the skin of the neck, chest and sometimes of the lower extremities will be found purplish, dry, pressure with the fingers leaving their impression for an appreciable length of time.

Bleeding from mucous membranes is usually present. At first there

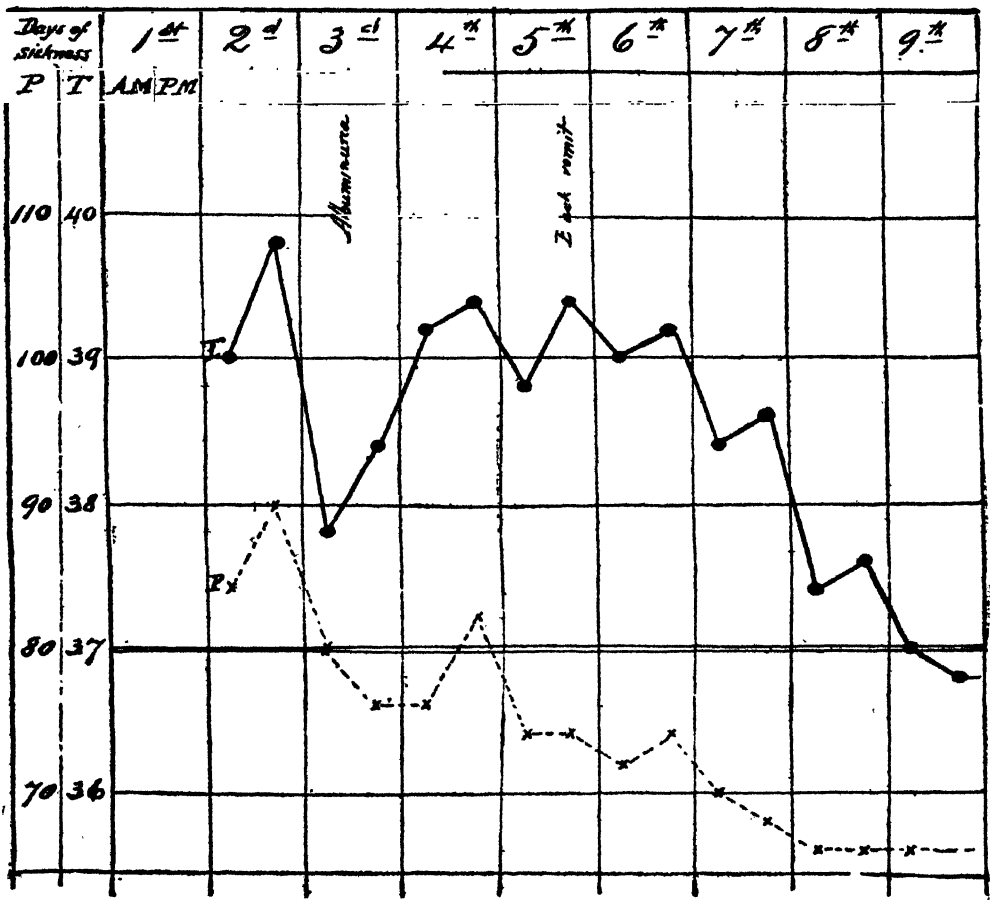


FIG. 4.—CHART IN CASE OF YELLOW FEVER OF MODERATE INTENSITY.

may be epistaxis, though this is not common; after two or three days, there is a peculiar spongy condition of the gums, they bleed easily on pressure, being swollen and congested without any other evidences of gingivitis. Later in the disease, we frequently see the border of the gums, the lips and surface of the tongue streaked with bloody mucus, staining the whole interior of the mouth and mixing with the saliva.

More active hemorrhage takes place from the stomach. It is of importance to remember that very profuse bleeding may appear to have taken place into this organ without particularly endangering the

patient's life; the blood, when vomited, has the characters described under symptoms in the digestive system.

It is very rarely that we see fresh blood in the vomitus; a coincident hemoptysis, bleeding from nose, throat, etc., may be suspected when this occurs.

Intestinal hemorrhage is not frequent, yet it has been reported by

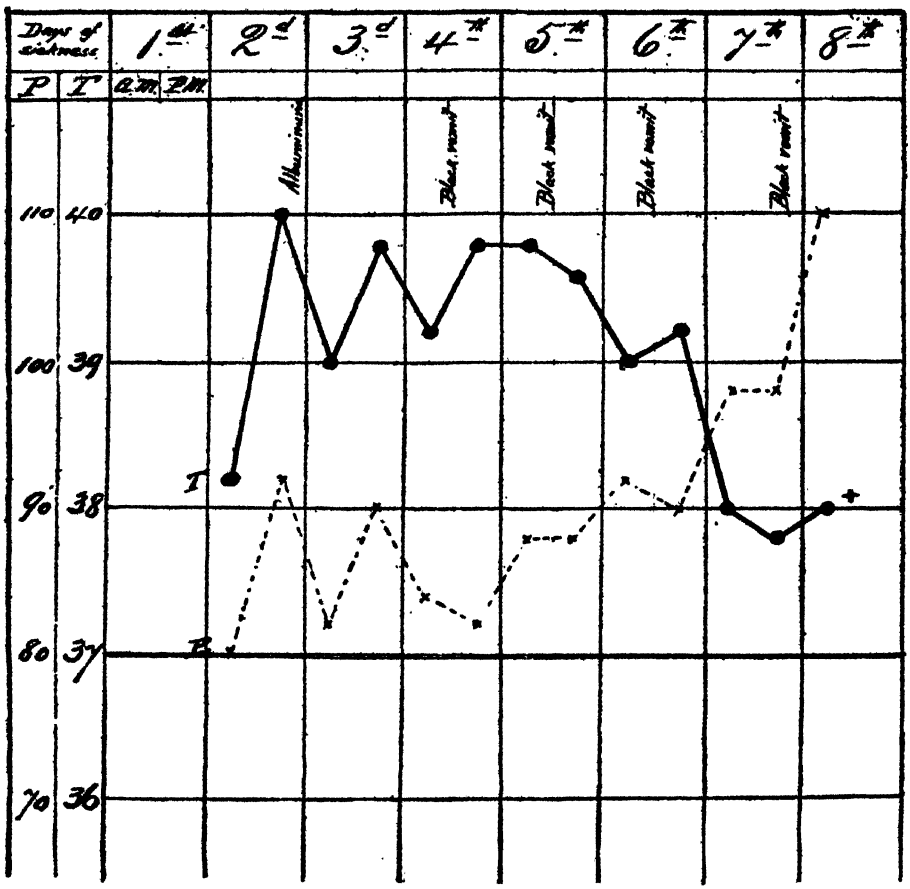


FIG. 5.—CHART IN CASE OF YELLOW FEVER OF GREAT INTENSITY (FATAL).

careful observers, and there is no reason why an ill-advised treatment might not excite it.

The extravasation of blood from the genito-urinary tract is seen only in very severe cases and chiefly among females (metrorrhagia, etc.).

Bleeding into the skin, purpura, in varying degrees of intensity, from disseminated petechial spots to veritable echymotic areas, is sometimes seen. More often it is only a discrete petechial eruption that is found.

The heart action corresponds generally to the intensity of the

and the degree of toxemia developed in each particular case. In the early days of the disease (first to third), the pulse is generally strong, bounding, and from 80 to 110 beats per minute. During the secondary fever, however, the pulse rate does not usually keep up in correlation with the temperature and the chart often shows a distinct separation of the

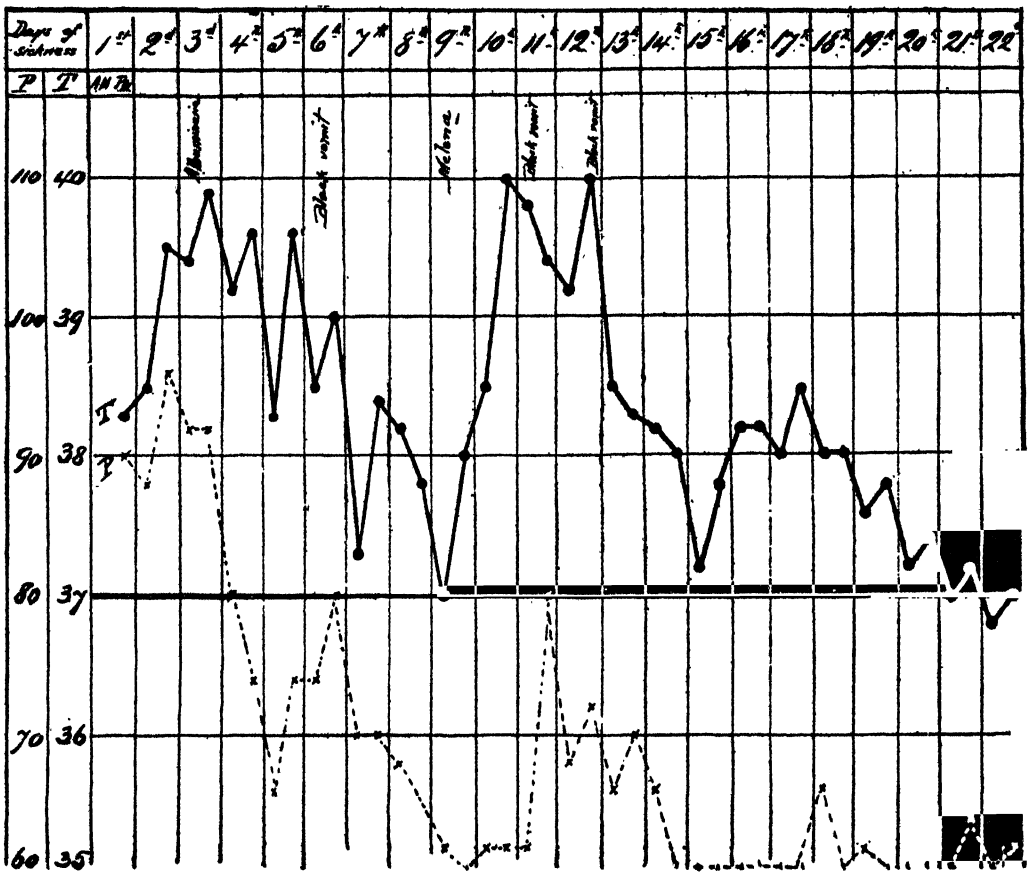


FIG. 6.—CHART IN CASE OF YELLOW FEVER. VERY SEVERE, PROTRACTED CASE; LATE REMISSION (RECOVERY).

respective lines, that is, rising temperature with lowering pulse rate (Faget's sign). This symptom is quite constant and may be relied upon as diagnostic. This condition, which is also met with in cases of malignant jaundice, in yellow fever is not dependent upon the intensity of the icterus, but may be seen even in mild cases where the yellow pigmentation becomes marked only at the end of the disease.

The slowing of the pulse irrespective of the rise of temperature is often misleading and must not be taken as a sign of improvement. In

the grave cases, this phenomenon is accompanied by signs of cardiac depression, shallow breathing, cyanosis of face or lips, cold extremities, etc. Cardiac failure as a result of extreme toxemia is the most common termination of the fatal cases.

The blood itself, bearer of the infective germ, is peculiarly unaffected in yellow fever. The absence of leukocytosis and the high hemoglobin rating may be considered as pathognomonic in this disease. Considering the repeated hemorrhages we encounter and the evidently toxemic character of the specific poison, it is remarkable to note that a hemoglobin percentage is often met with during the first five or six days, even higher than normal, while the specific gravity of the blood is not altered. Unlike other acute infectious diseases, the hemoglobin test rarely shows below 90 per cent., and in some cases it registers as high as 105 per cent.

At the same time that an increase in the number of blood platelets may be demonstrated, a normal red blood cell count will be found. The leukocytes will be diminished in number, while keeping their relative proportions as regards their varieties.

A leukocytosis or hyperleukocytosis is present only in cases with complications or just before death takes place.

Digestive System.—From the earliest stages of yellow fever, symptoms are referred to the digestive organs. At the beginning, as the fever rises, intense thirst is usually felt, the tongue becomes dry, red at the tip, or slightly coated along its center. The gums are sometimes found swollen and bleed readily, at the second to fourth day, but this sign cannot be relied upon except in cases where the teeth had been carefully attended to before the attack; bleeding gums are frequently met with as the result of local conditions in the mouth, irrespective of the yellow fever infection.

After the first or second day, attention is directed to the stomach, patients complaining of a sense of weight or oppression at the epigastrium; this afterwards turns into actual nausea and vomiting takes place sooner or later, consisting at first mainly of the liquids that may have been ingested.

After a time, the drinks being suspended, the substances vomited will be made up of glairy mucus and acrid gastric juice, more or less bile-tinted. At the fourth or fifth day, in ordinary cases, the presence of blood in the stomach contents may be demonstrated. It will appear, perhaps, in the shape of light streaks of fresh blood, or in specks, suspended in the vomitus (the "fly-wing" specks), and these will increase gradually in quantity, until the matter thrown up becomes composed chiefly of the "coffee-ground" material of the classics. When the vomited substance is made up of pure blood, more or less disintegrated by the action of the gastric juices as a result of copious hemorrhage, we have the characteristic tarry or "black vomit."

This symptom does not constitute a fatal sign, as has been estimated by many writers, and, in fact, it is remarkable the amount of blood or

"black vomit" that may be emitted and the patients still go on to complete recovery.

The intestinal tract is not particularly affected in yellow fever. When found, melena is rarely the result of hemorrhage from the intestines; more often it comes from the passage of the so-called "black vomit" beyond the stomach, into the duodenum.

Diarrhea during yellow fever is as a rule caused only by untoward purgation; it is not present in uncomplicated cases.

The liver, in spite of the profound lesion which it develops in the course of this disease, gives but little sign of the important rôle it always plays. There is no appreciable enlargement or atrophy; it may appear slightly tender on pressure during the first few days. The jaundice, which is evident in the conjunctivæ from the third or fourth day, progresses in parallel lines with the general course of the disease and seems, as pointed out, "incident to the pressure of swollen degenerating liver cells on the bile capillaries."

The absence of gastro-intestinal symptoms (aside from the intense gastric irritation, causing the characteristic vomiting), is remarkable and fails to excuse in a logical manner those who, until a comparatively recent date, insisted upon placing yellow fever among the gastro-intestinal infections; there is no distinct abdominal pain, no constipation, no diarrhea, no tympanites, etc.

An inflammation of the salivary glands, particularly the parotids, has been met with repeatedly as a complication.

Genito-urinary System.—It cannot be said that the genital organs in yellow fever suffer such disturbance in their function as to constitute any symptom of the disease. It is true that pregnant women usually abort when in their second or third month of gestation, but we see the same take place in cases of other high fevers and acute depressing conditions.

Hemorrhage from the uterus is frequent, however, more particularly when the yellow fever attack occurs during or just before the menstrual period.

The urinary apparatus, on the other hand, and specially the kidneys, is early affected and its function very decidedly impaired. The renal congestion in the early part of the disease is made evident by the appearance of albumin in the urine, sometimes as early as the second day, most frequently at the third day. The absence of albuminuria is such a rare thing in yellow fever, that many students of this disease, the writer among them, are prone to discredit the diagnosis of non-albuminuric yellow fever and to attribute such to an error of observation or faulty technic in the urinalysis.

The amount of albumin present may be only the faintest trace; indeed, such is the way in the mildest cases, where it then tends to disappear very soon, leaving the urine with its normal constituents only. In most cases, however, the albumin tends to increase during the second stage of the disease and casts may appear in the sediment. Urea and

chlorids tend to diminish in quantity regardless of the severity of the disease.

When the jaundice is particularly marked, bile pigments not infrequently appear in the urine and several authors have reported the presence of leucin crystals in these cases.

Bleeding from the urinary tract is very rare and hemoglobinuria is present only in complicated cases, in old malarial subjects, etc.

Ehrlich's diazo-reaction has been found absent in yellow fever urine and its presence may be considered of sufficient value to exclude such diagnosis; some writers claim to have observed this reaction in yellow fever, but rather imperfect and lasting a very short period only.

The casts found in the urine are usually of the hyaline variety, often bile-tinted, or they may be granular or epithelial; their presence does not signify particularly in regard to the prognosis, and at least the hyaline and granular types are seen to disappear very rapidly, as soon as convalescence is established, sometimes even before complete defervescence has taken place.

Fatal cases often present renal involvement; the urine becomes albuminous from the beginning and reaches a very high percentage at a period comparatively early in the disease; granular and epithelial casts soon follow with diminution in the amount of urine voided; signs of uremia, or rather ammoniemia, become evident and the patient dies in total or partial anuria.

The bladder is rarely affected, and only as a complication in old men with prostatic enlargement, or urethral strictures, etc., when retention may give rise to the decomposition of the urine, followed or accompanied by cystitis.

Nervous System.—From the very onset of the disease, patients infected with yellow fever show decided involvement of the central nervous system. In the early stages they appear drowsy and to be suffering great lassitude, yet upon being roused they become quickly alert, the eyes shine brightly with the fever, they look about with surprise or suspicion upon what goes about them.

They complain of intense headache, sometimes frontal, over the orbits, intra-orbital, or extending to the temples; later on, the headache is said to be intense at the occipital region, or the cranial vault. With the lowering of the temperature the headache is materially improved. In some few cases an intense, almost unbearable, hemicrania has been observed.

An early symptom is lumbar pain, rather severe, often the "coup de barre" described also for dengue, influenza and some other infections; it lasts with more or less intensity during the first and second febrile stages: sometimes the pain extends upward to the back of the neck, along the whole spinal column.

Later in the disease, signs of more marked involvement of the nervous system appear in the form of delirium, tremors or subsultus tendinum, a typhoid state with coma and even paralysis of involuntary muscles; or, exceptionally, the patients show great excitability and rest-

lessness with tendency to jump out of bed, run away or fight those who may try to restrain them. During the Santiago, Cuba, epidemic in 1899, several ran out of the hospital ward and jumped into the sea, a few yards away, where, however, they were quickly captured. It became necessary to fence in that particular side of the ward.

In yellow fever, no real paralysis takes place and it is only in the worst cases that we find such vital depression as to produce incontinence of feces or urine. Such a condition has always been considered as indicating a fatal and early termination.

Respiratory System.—Nothing of special interest is referred to the air passages in yellow fever. The autopsy findings seem to indicate that those organs are not much concerned in the pathologic process of this infection.

As a complication, pneumonia has been met with a few times and during the active secondary febrile paroxysm, with the rise in temperature, the rapid respiration, anxious, often shallow, there is sighing and sometimes hiccough.

Objective Symptoms.—The facies in yellow fever has been often described as peculiar to this disease; the fact is that with regard to facial expression and appearance, at the very beginning, the subjects conform to what we are accustomed to see in most acute febrile conditions. The congested conjuctivæ with suffused cheeks and intensely red lips and the semi-wild look on being awakened cannot be said to be peculiar to this disease.

Later on, sometimes even at the second day, if the patient is a white man (and better if a blond one), a faint yellowish tint may be perceived upon the conjunctivæ. The jaundice will be seen to increase apace with the course of the disease, but very gradually; it will later become clearly evident upon the chest and abdomen, the arms, legs, etc. The icterus during the development of the disease is never as intense as we see it in malignant jaundice or in acute yellow atrophy of the liver, but great intensity is usually observed at the termination of the infection by death or recovery. It is only at the acme of the jaundice that we find the urine bile-stained and very exceptionally is there such a degree of acholia as to leave the stools clay colored.

Yellow fever patients when kept in clean bedding and repeatedly bathed, as is done in properly equipped hospitals, fail to give off the peculiar odor that has been ascribed to them by the early writers, and some contemporary practitioners as well. The writer has had occasion to appreciate the difference between pboorly ventilated barracks and clean, modern hospital wards, and there certainly seems to be a distinct odor in the former, but not distinctive of yellow fever, only such as emanates from dry, acrid sweat and lack of cleanliness, one that is met under the same unfavorable conditions, regardless of the class of patients in the wards.

The epigastrium will be found tender on pressure even in mild cases where no nausea or other gastric symptom is manifest; there will be no swelling; later it will be impossible to press upon the abdominal wall

without provoking nausea or emesis; rarely we see some degree of tympanites, but it has no diagnostic significance.

The character of the pulse, besides the lack of correlation with the temperature already referred to, is rather interesting. At the onset, the pulse as may be expected is both rapid and bounding; before the expiration of the first febrile paroxysm it will be seen to decrease in frequency and tension so that during the so-called stage of calm, which usually corresponds to the remission and the end of the second or third day, it will be found full and normal in rate. This low rate (70 to 80) will continue, rising perhaps a little with the fever, until the end of the disease. If the patient recovers, the pulse may come down even to 46 or 50 during convalescence; if the case is to be fatal, however, the pulse and temperature lines will be seen to cross on the chart, the pulse rising rapidly while the temperature seems to descend.

Reference has already been made to the course of the fever and the conditions of the urine in this disease.

Diagnosis.—A combination of symptoms occurring at a stated time is often sufficient evidence upon which to base a diagnosis.

If the patient is seen within the first two days, it is very difficult to fix the guilt upon yellow fever. One may dare to do so if in the midst of an epidemic, but even then, though the chances of error will be less, the disease at this period presents nothing characteristic or what may not occur as well in some other infection. If, however, there are signs of gastric involvement or a slight conjunctival icterus, concomitant with the rachialgia, fever and headache, it may be safe to make diagnosis of yellow fever at such early date.

At the third day of the disease, albuminuria will be found present, even though the disease may be in the period of "calm," and after that date the icterus, albuminuria and fever will serve to make a positive diagnosis, particularly if Faget's sign is observed.

After the fourth day, cases will present more or less vomiting, with specks, or blood will appear in quantity with the stomach contents—"black vomit." The diagnosis is not difficult at this stage of the disease, presenting a very clear and unmistakable picture.

The very mild cases are usually overlooked, or mistaken for some passing febrile condition; they are seldom diagnosed as yellow fever, very few of them being, therefore, recorded.

Differential Diagnosis.—It is very difficult to differentiate most of the infectious diseases at their beginning, still, yellow fever must be diagnosed within a very few days, not only for the patient's good, but also for the public health, since an early diagnosis, particularly of the first cases of an epidemic, is, from that standpoint, of the greatest importance.

In the first two days, yellow fever may simulate dengue, influenza or the eruptive fevers, but at the third or fourth day a definite diagnosis should be arrived at.

In *dengue fever,* we have the same onset, rachialgia and fever, but the headache is more intense, a rash may be discovered or not, since it

often is quite ephemeral, and the albuminuria will be but slight, though quite frequent in this disease; there will be no jaundice whatever, nor bleeding from the gums or elsewhere, nor any distinct gastric symptom during the disease. A great drop in the pulse rate in dengue occurs only during convalescence.

In *influenza,* some catarrhal condition of the mucosæ will be evident, a rare thing in yellow fever; the onset is more gradual and, as in dengue fever, the pains are more articular and muscular than spinal. Pfeiffer's bacillus in the sputum of influenza serves to make an early diagnosis. The albuminuria of influenza appears later in the disease than in yellow fever, seldom acquiring such intensity as we see in the latter. There will be no jaundice, nor hemorrhages, nor gastric symptoms, and Faget's sign will be absent in all cases of influenza.

In the *eruptive fevers* we find intense catarrhal conditions (particularly in measles and scarlet fever), which are seen in yellow fever only as complications and not frequently at that. In small-pox, the vomiting with fever of the early period may be confounded, but that only during an epidemic of yellow fever, since there will be no remission of the fever in small-pox and the icterus will be entirely absent. Other exanthemata are not to be considered as a source of error.

In *malaria,* an early and careful examination of the blood before the administration of quinin ought to settle the question by revealing the malarial parasite. If the case has been treated, there may be grounds for doubt, but in malaria we have the marked fluctuations in temperature from the beginning, occurring even in the absence of any therapeutic measures. The albuminuria, if present in malaria, comes only after a period of many days of fever, while in yellow fever it is a regular and early manifestation. In the severe estivo-autumnal forms of malaria, we may find the albuminuria and even some degree of jaundice, but such grave cases, if they were yellow fever, would also present distinct hemorrhagic tendency, if not "black vomit" as well.

The *bilious remittent* (malarial) *fever* of the early writers, which was said to have been so frequently mistaken for yellow fever, was probably not malarial at all, but a name given to yellow fever itself when observed in the natives or supposed acclimated individuals. We have never seen this form of malaria and other contemporary observers report the same experience. Signs and symptoms common in malarial infection, not found in uncomplicated yellow fever, are enlarged liver and spleen, sudden drops of temperature without accompanying hemoglobin percentage. Hemoglobinuria is a symptom of malaria and not of yellow fever; in the latter we are more likely to have hematuria instead. Jaundice, if present, is liable to be very intense in malarial infection, and is accompanied by distinct symptoms of liver involvement, tenderness, enlargement, etc. Vomiting of blood is rare in malaria, even though of great intensity otherwise.

Malarial cases may be, and in fact often are, infected with yellow fever, and the diagnosis then becomes rather difficult, unless this contingency be kept in mind. There are two distinct forms of this sym-

biosis. (1) In one, the yellow fever infection seems to prevail, the patient going on with the symptoms of this disease, only that every second or third day there is a sudden rise of the fever to 40° C. (104° F.) or more. The malarial parasite will probably disappear from the peripheral circulation to reappear again when the yellow fever symptoms subside, after eight or ten days. Then a sudden rise, apparently without reason, with chill, sweating, etc., will reveal the renewal of the malarial attack. (2) The other type of this combination gives the signs of malaria, not much albuminuria, severe spleen and liver involvement, no Faget's sign. There may be bleeding from gums or even an occasional "black vomit," the malarial parasite being present in the blood all the time. It must be remembered that this condition is not one of either disease being complicated by the other, but simply the infection of a malarial subject by the yellow fever germ, and that while malaria is a disease that may last for weeks or months, as it often does in tropical countries, the duration of yellow fever must be counted in days.

In *typhoid fever,* it is only during the first days that any doubt can exist, at least with regards to yellow fever. If a blood culture has not been made during the first days, a Widal agglutinating test will usually clear up the diagnosis after the tenth day. This is more feasible, inasmuch as typhoid cases are seldom seen before the end of the first week of the disease. If positive diagnosis cannot be made through the blood tests, however, there are many signs which preclude the probability of confounding typhoid fever with yellow fever and *vice versa.* The onset in typhoid is gradual, the coated red-bordered tongue is quite typical, absence of gastric symptoms is the rule, there is no jaundice, no albuminuria. Absence of Faget's sign with low hemoglobin percentage is characteristic of typhoid fever. If there is bleeding, it will be only from the nose, appearing in the stools much later; if there is any albuminuria, it will appear later, after the first week in typhoid fever, and is never, in uncomplicated cases, as marked as in yellow fever. One must look for enlargement of the spleen, never present in yellow fever. The diazo-reaction of the urine, so constant in typhoid fever, is not found in yellow fever. Such a temperature as 40° C. (104° F.), common in typhoid fever for so many days, in yellow fever would imply such degree of severity as to present other unmistakable signs of this infection, particularly gastric and hemorrhagic.

At a certain stage of the disease known as *infectious jaundice, or Weil's disease,* there may arise a suspicion of yellow fever, when first observed. But in that disease the onset is not as sudden, patients suffering from fever and bilious symptoms for several days before the jaundice, which progresses very rapidly, shows itself. The jaundice is peculiarly marked, giving a mahogany tint to the skin of dark people, entirely different from the light yellow of yellow fever. The hemorrhagic tendency becomes evident much later in yellow fever, the urine soon becomes highly colored and the feces very pale, until the stools are clay colored. The pulse follows parallel with the temperature throughout

the disease. Search must be made for the parasite, *Spirochæta icterohemorrhagica,* described by the Japanese investigators.[21]

In *malignant jaundice* (acute yellow atrophy of the liver), the onset is very slow; there is no distinct fever with congestive signs. The liver is soon diminished in size, the feces lose their color. Early in the disease there is a great prostration with a low percentage of hemoglobin; pallor and edema appear in various parts of the body never seen in yellow fever. In acute yellow atrophy, tyrosin and leucin soon appear in the urine and the amount of urea is greatly diminished.

It sometimes happens that cases are seen from which little if any previous history may be obtained (perhaps only a few hours before death), where the presence of jaundice and fever give suspicions of yellow fever. In such cases investigation of the stomach contents will usually decide, since it would be very exceptional to find a case of yellow fever sufficiently advanced as regards fever and jaundice but devoid of blood in the stomach contents.

To judge from the literature on the subject, the forms of *endemic jaundice* that have been observed in Smyrna and Alexandria[22] bear a certain similarity to yellow fever, but in them the fever is more prolonged and hematemesis seems to be no feature of the disease.

From the so-called "gastric fever," bilious fever or "febrile gastritis" yellow fever can be readily distinguished, particularly by the character of the vomitus, the history of the gradual onset, the rapid pulse rate, absence of albuminuria, possible diazo-reaction, etc., in those conditions.

Simple catarrhal jaundice or obstructive jaundice can hardly be confounded with yellow fever, if a history of the case is obtainable; otherwise, it is well to remember that discolored stools are the rule in obstructive jaundice and the exception in yellow fever, and the urine will contain albumin in the latter while it is not likely to in the former. The course of the fever will constitute a fair guide in either case.

Complications.—It cannot be said of yellow fever, as regards other infective diseases, that it is frequently accompanied by conditions which in justice might be called complications. Individuals who lead rather dissolute lives, when infected with the germ of yellow fever will suffer as a result of the particularly weakened condition of certain organs or apparatus, and thus the disease becomes complicated, rarely otherwise.

More frequently we see the *kidneys* as the seat of parenchymatous nephritis, in alcoholic patients. Here we find that the disease beginning in an apparently mild form, suddenly assumes unexpected severity, the symptoms pointing to the renal complication. The urine will become loaded with albumin, casts of all varieties will shortly appear, and while the characteristic hemorrhages and jaundice may not be very pronounced, phenomena of uremia begin to manifest themselves, with diminution in quantity of the urine or the total suppression of it.

Cardiac complications are infrequent though not rare; these are usually due to secondary infections and appear late in the disease (sixth to eighth day), in the form of endocarditis, rarely as pericarditis.

Chronic cardiac cases do very badly with yellow fever, unless they suffer a very mild attack.

Pulmonary complications are very rare. Cases of yellow fever may be observed which develop a bronchitis during the disease, or even a bronchopneumonia. The condition is one of secondary infection and occurs only in very old individuals.

A condition of almost *hemophilia* is sometimes observed, that may be considered as a not infrequent complication in yellow fever.

The hemolytic action of the unknown poison is evident, not only in the profuse hemorrhages from nose, mouth, stomach and intestines, but also by extravasations of blood into the skin and deeper tissues. In a lesser degree a form of purpura may be observed, particularly in prolonged cases.

Sequelæ.—Of all the acute infectious diseases, perhaps yellow fever is the least followed by the development of conditions in any way attributable to this infection.

Amongst those that have been observed with any degree of frequency may be mentioned parotitis. The swelling, accompanied by pain and even fever, of one parotid gland, during convalescence, sometimes goes no further and ceases with the ordinary antiphlogistic treatment; at other times, the inflammation has continued for several days, going on to suppuration, an abscess developing with all its attendant discomforts.

In certain epidemics, the prevalence of local small skin abscesses has been observed, if not a veritable furunculosis; convalescent cases complain of "boils," never having suffered from them before their illness.

Cutaneous gangrene and ulceration of the scrotum, not very serious in character, have been reported; this has taken place, generally, in cases that have been rather protracted, with specially marked toxic symptoms.

Diarrhea (enteritis) has taken place in convalescence, without any clearly apparent reason, except that it occurred whenever an attempt was made to increase or modify the diet. Much care has to be taken with these patients to avoid this disorder from becoming chronic after chronic indigestion, at other times it is manifest only regarding certain their attack of yellow fever.

A peculiarly sensitive condition of the digestive tract has been observed after a particularly severe attack of yellow fever, the patients being unable to take care of the ordinary food, even after a long period has elapsed from the height of the disease. Sometimes it is a state of food, such as meat, eggs or fatty substances.

Mixed Infection.—Reference has been made to the fact that yellow fever is sometimes coexistent with malaria and that the latter's parasite may be demonstrated in cases which otherwise give all the symptoms of yellow fever. (*See* Differential Diagnosis.)

There is no doubt in the minds of many investigators of this disease that some of the symptoms and signs are due to a secondary infection, probably bacterial in character, which takes place in the secondary stage of the fever, producing or intensifying the hemorrhagic feature of the

yellow fever infection. The hemorrhagic group of bacteria, to which *Bacillus dysenteriæ* (Flexner's, Shiga's) and *Bacillus icteroides* (Sanarelli) belong, may play a prominent part in the more severe and fatal cases that occur.

Treatment.—PROPHYLAXIS.—The prevention of yellow fever, as practiced to-day, will finally and decisively exterminate the disease, even if applied without any great stress, so long as the fundamental principles are not lost sight of and the method employed be persisted in unceasingly. It may be divided into two parts: maritime and terrestrial prophylaxis; these in turn will have to differ according to the local conditions and the period in which they are established.

(1) *Maritime Prophylaxis.*—This entails the application of means that will prevent the introduction of yellow fever through any of the ports to which vessels coming from infected foci arrive. In this connection the vessel, on the one hand, and the crew and passengers, on the other, have to be considered separately, besides the distance of the port of departure, the local conditions there at that time and the health of the personnel during the voyage.

The regulations (so-called quarantine regulations) by which control is maintained upon vessels from infected ports, must necessarily be based upon the facts so far demonstrated regarding the etiology of the disease; otherwise they are liable to be unnecessarily irksome if not unjustified. Full confidence in the truth of the mosquito doctrine with regard to the transmission of the disease and knowledge of the insects' habits and their means of development, will enable the quarantine officer to carry out his duties to a successful issue.

The proven fact that no infection can be carried by "fomites" has made this work very much less expensive than in former times and also less onerous and inconvenient to commerce, since the disinfection of baggage, clothing, etc., has been entirely done away with.

At the very outset we are met with the difficulty of determining when a port may be considered infected or suspected, but that should be decided by the governments involved.

When a ship arrives from an infected port, not having had sickness on board in spite of the presence of non-immune crew and passengers, if the voyage has extended beyond eighteen days, the chances are that no infected mosquitoes are on board and therefore the ship should not be held under suspicion. If the duration of the voyage is less than that, the ship should be either held for fumigation or until the 18 days are completed, under observation. If a case of yellow fever has developed during the voyage, the ship must be considered as infected and infective.

Precautions may be taken to insure the safety of the vessel from infection by the application of certain rules while the ships are lying in the ports infected or suspected of being infected with yellow fever. (*See* Public Health Reports, U. S. Public Health Service, XXVI, April, 1911, pp. 570-573.)

It is generally believed that certain cargoes are more likely to carry

mosquitoes than others. In this connection, fruit vessels have been looked upon with greater suspicion and perhaps do harbor more mosquitoes than is usually the case, but there is no direct evidence to show that they are particularly infective, where other conditions do not make them so. In New York, for instance, fruit ships coming from infected ports have never produced a case of yellow fever and they have been unloaded by non-immune men who went into their holds, taking no precaution whatever, even long before the mosquito's rôle had been discovered.

When after a short trip a vessel arrives from an infected port, it cannot be given free pratique until the usual period of incubation of yellow fever has transpired, if no case of sickness has occurred on board since the day of departure. Otherwise, the crew and passengers must be taken off and subjected to observation, while the living quarters of the vessel are thoroughly fumigated. This is intended to kill all the mosquitoes that may be found there, and, after unloading, the rest of the ship's compartments should be fumigated, to insure the destruction of all the insects on board. If the character of the cargo allows the fumigation of the vessel before unloading, this should be performed by all means.

Ships arriving with cases or history of yellow fever on board must be placed immediately under quarantine. The crew and passengers should be removed for observation, then nothing but a thorough fumigation can render the ship free of the infection. If this is done in the manner hereafter described, the vessel is at once rendered absolutely safe.

It is not wise to place much confidence in the certificates of immunity often presented by passengers coming from infected ports; experience has demonstrated their frequent worthlessness.

Lighters should not be allowed to come alongside suspected vessels, as they may be the means of transporting infected mosquitoes ashore.

Observation quarters for passengers or crew of vessels under surveillance should be properly screened by wire gauze that will keep them free of mosquitoes, so that if a case develops, there will be no danger of its contaminating any local insects.

When the sick must be removed from a recently arrived ship, it should be done by placing the patients, each under a mosquito-bar, firmly fixed around the edge of the litter in which he may be carried, and so taken into the ambulance or launch, as the case may be, all the way to the screen-protected hospital wards. These precautions are not so important after the fourth day of the disease, but if possible should always be taken.

The quarantine regulations should be of such a character that, while insuring the various countries against invasion, one from the other, at the same time will interfere as little as possible with the usual commercial intercourse. Bearing this in mind, international sanitary agreements have been entered into, the reader being referred to the Articles

of the last International Sanitary Conference, held in Paris, 1912, for a complete and detailed information upon the matter.

Fumigation of Ships.—The best insecticide gases and the least harmful are sulphur dioxid and hydrocyanic acid gas. They are generally introduced into the holds of the ships that are to be treated, through canvas hose, the gas being generated in a tug-boat or launch that is placed alongside the infected vessel. Sulphur monoxid is not so good an insecticide and is therefore used principally for the killing of rats on board vessels. Several ingenious devices have been used for utilizing the steamers' own fires in producing this gas. Where no such contrivance exists, the fumigation is done by burning sulphur, with due precautions to avoid causing a fire, after tightly shutting the hatches and sealing all openings, etc. If hydrocyanic acid gas be preferred, it is obtained by the action of dilute sulphuric acid upon cyanide of potassium. The detailed method employed in both cases is mainly the same as followed in the fumigation of houses which is explained in detail in the corresponding part of this writing, to which the reader is referred.

(2) *Terrestrial Prophylaxis.*—This may be better divided into three parts: (1) measures intended to prevent the introduction of yellow fever (aside from maritime or quarantine regulations); (2) measures to prevent its propagation, if introduced, and (3) measures tending to eradicate the disease from a given locality.

If the infected country, from which it becomes necessary to protect ourselves, is one directly on the boundary line, no quarantine regulations are applicable, but such measures may be resorted to as will prevent the introduction of the disease. Every effort should be directed against the importation of infected mosquitoes, cases of yellow fever, or persons in the incubation period of the disease.

No stage, wagon, railway-cars or any other covered vehicle from the infected zone should be allowed to approach within two hundred yards of the boundary line. If possible, all such vehicles should be fumigated before returning to their respective stables, at least upon each trip. Although merchandise, baggage, etc., cannot be considered as carrying infection, articles such as boxes, crates, etc., capable of harboring mosquitoes, may well be subjected to the action of insecticide gases. If railway cars must cross the line, they should be fumigated every time they arrive from the infected localities, although they may be allowed to go untreated, if the cars only passed, without stopping, through that section or town.

A number of observation stations should be established, through which intercourse with the infected neighboring country can only be maintained. At these stations the above means will be applied, but every non-immune will also be held, if from the infected zone, for a period not less than six days after arrival, before he is allowed to proceed on his way.

A hospital should be established, ready at hand, where any cases developing at the observation or detention stations may be treated. The

doors and windows of this hospital, as well as those of the observation stations, it seems needless to say, must be protected by wire gauze of sufficiently fine mesh as will prevent the entrance of mosquitoes (16 wires to the square inch); also the surroundings of these establishments must be daily inspected, so as to do away with all their breeding places.

Every person coming from the infected area must be subjected to the most careful investigation; in every case, the thermometer should be used to determine the presence of fever and all such are to be kept under observation.

Immunes, for sanitary purposes, are only those who have suffered an attack of yellow fever or who have lived for at least ten years in recognized endemic foci. For this reason, all children under ten years of age must be held as non-immunes, regardless whether their parents are positively protected, unless said children show evidence of having had yellow fever themselves.

The above, in a brief way, are the means readily applicable to prevent the introduction of yellow fever from another country. If the measures are instituted in time, the bar to infection which they constitute has always been effective.

Once yellow fever has invaded a town or a community, the first care is to prevent its propagation.

Immediate notification of every case of fever, and its protection by mosquito net, must be insisted upon; cases which after twenty-four hours cannot be declared negative, should be considered, from a sanitary standpoint, as cases of yellow fever and treated accordingly. The prompt screening of cases will aid greatly in the effort to suppress the epidemic and if the sleeping quarters of all cases of yellow fever are so treated, it will serve to hold the mosquitoes that may have become infected ready for their early destruction by fumigation. If the patient can be removed to the hospital, this is always the best procedure, otherwise the fumigation of the house and the ones on either side of it, if closely placed, as is usually in towns in Southern countries, becomes difficult if not impossible, particularly because of the objectionable odor of sulphur even when it is not unbearably irritating.

Fumigation should be carried out in a thorough and scientific manner; the authorities should meet with intelligence the many little obstacles that come up with every particular case, keeping in mind that in preparing a house for fumigation, the least noise or disturbance possible should be made, so as not to frighten the insects out of their resting-places on the walls, ceilings, corners, closets, etc.

For shutting up porches, small court-yards, etc., heavy sail-cloth is the best material. It is carefully tacked along the edge of the wall, with paper pasted over the joints to make it absolutely tight, and every joint should be so treated. Small isolated wooden buildings should in all instances be entirely covered with sail-cloth, as it is impossible to make them gas-tight otherwise.

In cities where the houses are placed one next to the other, the two adjoining houses should be prepared at the same time as the supposedly

infected one, and the fumigation started simultaneously in all three; this will insure the destruction of mosquitoes which might attempt to escape from the infected house.

If this is carried out promptly and thoroughly, the chances are that the particular case in hand will not produce any secondary cases and the disease will therefore be confined within very narrow limits.

In setting forth in detail the work of fumigation, the writer wishes to quote from an article prepared upon the subject that needs but little rectification.[16]

The work of fumigation may be divided into two parts: first, the preparation of the building, and second, the process of fumigation properly speaking.

Preparation of the Buildings for Fumigation.—The first thing to be done upon beginning the fumigation of a house is to close all the doors and windows which communicate with the outside, leaving only one door for the men to go in and out of the building. If the house has porches, these should be covered with canvas or sail-cloth. After this has been done, paper is pasted over all the crevices and fissures, first around the exterior doors and windows, afterwards around the interior ones. The house should be divided into different isolated rooms or compartments, for the purpose of fumigation. After this has been done, the apparatus necessary for the fumigation is introduced into the building and placed at the most convenient spots. All the drawers, presses, trunks, etc., should be then opened and the furniture separated about one foot from the walls of the different apartments. Following this, the fumigators (pans containing sulphur and alcohol) should be serially lighted, the operator retreating in the direction of the one door of exit, taking care to cover all crevices around the doors of the different compartments as the fumigation proceeds. After having sealed the door of exit, the fumigation of the covered porches is started, the operator taking care that the canvas or tarpaulin which surrounds them is hermetically closed.

Metallic gauze cages containing mosquitoes should be placed in different parts of the house to test the efficacy of the fumigation.

When for some reason it is not advisable to leave the drawers, presses, etc., open, their contents should be taken out and shaken before being returned to their places, so that no mosquito may remain in the interior of the furniture.

It is frequently necessary for the sanitary authorities to treat in this manner barracks with badly adjusted walls and roofs, huts, wooden buildings, etc. In such cases it becomes necessary to cover the building completely with canvas, as suggested before, adjusting the borders tightly and pasting strips of heavy paper over them. The procedure is otherwise the same as that already indicated.

The Process of Fumigation.—For the destruction of mosquitoes, *sulphur dioxid,* obtained by the combustion of sulphur in the proportion of two pounds for every one thousand cubic feet, is one of the most efficient gases employed. After three or four hours' exposure, it causes

the death of all the mosquitoes in the apartment. The principal objection to the use of sulphur is that it attacks certain tissues, pictures and metals, but seldom in an irreparable manner. Metals may be protected by covering them with a thin layer of vaselin. For fumigation, the sulphur in powder is placed on frying-pans or other flat vessels, each of these within other receptacles containing water, into which the burning sulphur, that sputters during the fumigation, may fall. A small quantity of alcohol is poured over the sulphur to start the combustion and it is lighted at the moment of leaving the apartment. At the expiration of four hours, the outer doors are opened first, and progressively the interior ones, to allow the vapors of the sulphurous acid to escape.

Although many other insecticide gases have been recommended, the writer and his associates have employed sulphur dioxid exclusively in dealing with mosquitoes, and with the best results.

Since the invasion of bubonic plague in America occurred, and the necessity of fighting it by means of muricide as well as insecticide gases, the use of *hydrocyanic acid gas* in extensive fumigations became rather popular in Cuba, though certainly not the best means for an antiplague campaign. Its powerful insecticide properties have been known for a long time, but the danger it carries to human life, having been so much exaggerated, prevented any great use of it until recently.

Ordinary precautions, easily taken, have made the employment of this agent absolutely safe, no accidents having been recorded in Cuba, where, during an intense campaign against plague, hundreds of thousands of cubic feet of space have been so treated.

The houses are prepared in the same way as recommended for sulphur fumigation, though greater care should be taken in making them gas-tight, as hydrocyanic acid gas is more diffusible than the sulphur dioxid. The production of hydrocyanic acid is brought about by the action of dilute sulphuric acid (25 per cent.) upon cyanid of potassium. When it is only one compartment that has to be fumigated, a generating apparatus may be used from the outside, carrying in the gas through rubber hose, as is done in the fumigation of fruit trees after covering them with canvas. Otherwise, the following method is to be recommended.

Into each compartment to be treated, a wooden, earthenware, or lead-lined vessel is placed, containing the sulphuric acid solution, in sufficient quantity to dissolve the cyanid of potassium (about three times its volume or more); then the proper amount of the salt, in proportion to the size of the room, is wrapped in paper. This is then dropped into each vessel of the acid in turn, the reaction being delayed by the paper wrapper, so that the operator has time to retire and seal the compartment from the outside. Ten to fifteen grams of cyanid of potassium should be used for each one thousand cubic feet of space.

After three or four hours' exposure to the gas, the house is ready to be opened. The doors and windows of the house must be opened *from the outside,* the operator not entering the building until free cir-

culation of air has been established and all the gas has presumably diffused into the atmosphere.

When an epidemic of yellow fever is once developed, the above methods alone are not sufficient to eradicate the disease from a city or district, and the campaign against the infection must be carried out upon more extensive and somewhat different lines.

In the first place and of great importance, if the disease has been more or less endemic in the country or town, a *census* of the non-immune population should be made, that will allow proper surveillance of the inhabitants and the prompt recognition and segregation of cases. Where the disease appears for the first time, this census cannot be of any advantage, since all, or nearly all, the population will be susceptible.

Every government employee, policeman, etc., besides those regularly appointed for the purpose, must be instructed *to report* at once, to the sanitary authorities, all cases of illness that should come to his knowledge, and physicians should be expected to report as yellow fever all cases whose cause is not absolutely clear from the beginning.

A *campaign of education,* carried out by all means available, that will make evident to the people the relation of mosquitoes to the spread of yellow fever, the ways to kill their larvæ, etc., will go far towards checking any epidemic, as it was demonstrated in New Orleans in 1905.

"Mosquito-larvæ hunts" and *"fumigation days"* by blocks or wards, undertaken in the city, will always prove a powerful aid, tending to the more rapid stamping out of the disease.

A knowledge of the life-habits of *Aëdes colopus* (*Stegomyia fasciata*) is necessary to accomplish better the destruction of its larvæ and to prevent the breeding of the insects in the cities where they are known to thrive.

This part of the campaign must be worked out upon the following lines. A *house to house inspection* at intervals not greater than ten days must be arranged by having a sufficiently large corps of trained inspectors. They are to discover mosquito breeding places and the presence of larvæ wherever they may occur, instructing the tenants how to avoid the repetition of what, during an epidemic of yellow fever, ought to be considered a punishable offense. To do away with breeding places, all tin cans, bottles, etc., must be carefully collected from the empty lots and fields around the city and measures taken to prevent their again accumulating.

Where the *water supply* is derived from a reservoir, the destruction and prevention of breeding places becomes less difficult than where well-water is used or house cisterns or other deposits are necessary for ordinary domestic purposes. Here a special inspection of the containers becomes imperative, to see that they are protected from the insects by means of a tight cover or by wire gauze, and that the protection is maintained in perfect condition.

Where a great number of containers must be kept or large tanks used for the purpose, the expense of covering them may be too great; in such cases a simple expedient may be resorted to. The writer refers to

the introduction of the small fresh-water fish known as *minnows* (*Gambusiæ*, etc.), which thrive under most conditions and will keep the water free from larvæ. Two or three fish will be enough for as many cubic yards of water, and need no special care.

Finally, *the surface soil* must be kept well drained by means of slanting ditches that will prevent the rain-water from collecting. The outskirts of cities should be treated in the same way, and at the same time crude petroleum should be poured upon the surface of stagnant pools that for any reason cannot be drained. Petroleum kills the larvæ of mosquitoes by obstructing their respiratory tubes, since they must come to the surface to breathe, and one cubic centimeter is usually sufficient to cover one square meter, if protected from the wind, as in caves, etc. Otherwise, a greater quantity of oil is necessary, and even a large quantity is not enough when exposed to the action of the winds.

By keeping the soil of lowlands or stream-beds often sprinkled with petroleum, at regular intervals, any collection of water that may form will have the protective film of oil upon it; besides this, it has been noticed that mosquitoes are kept away to a great extent by the odor of the crude oil.

A prophylactic campaign, based upon the principles here noted and carried out mainly upon these lines, has been the means of stamping out yellow fever, as has been stated, and even though no greater impulse be given to this work, as performed at present in several countries, there is no reason to doubt but that it is only a question of time before this dreaded disease is finally eradicated in America.

CURATIVE TREATMENT.—A rational treatment of yellow fever cannot be that which, as recommended by most authors, is purely symptomatic. The main fact of its etiology must be kept in mind, the fact that it is a *blood infection* and that the symptoms are but the signs of a more or less severe *toxemia*. It is when we lose sight of this that we are liable to fall into the error so often committed by our predecessors who treated the disease by violent purging, or bleeding, or sweating, or what not.

It may be said at the beginning that no violent measures of any kind should be attempted in yellow fever; **quiet surroundings,** soothing drinks and easy ways go further than any active interference toward a favorable termination.

The greatest benefit can be obtained in cases seen in the early stages; in fact, the writer believes the prognosis often rests upon the stage of the case when first seen and diagnosed. When one is fortunate enough to take hold of a case during the first three days, the chances are usually in the patient's favor. Some, however, are of such degree of severity, that one may predict an early and fatal termination from the very outset, no remedial measures meeting with the slightest success.

All efforts should be directed toward (1) sustaining the natural vital forces of the individual and (2) eliminating from his body the greatest quantity of the specific toxin, whichever it may be, taking care that, in endeavoring to obtain this end, the normal resistance or the reparative powers be not diminished by our efforts.

The best results are secured when the proper **nursing** is at hand, for in no other disease are certain details of management and observation of greater importance and utility. When careful and painstaking nurses cannot be obtained, a detailed account of the necessary points must be written out for the untrained assistant, for a clinical history, with accompanying chart, is the best guide in carrying out a common sense treatment in this disease. Even when a temperature curve cannot be traced upon a chart, the thermometer must be used, nevertheless, every three hours, and its marking recorded, as well as the frequency and, if possible, the character of the pulse. The appearance of new symptoms must be set down, the hour when observed, the increasing or diminishing intensity of each one, etc. The frequency and character of the stools and the amount of urine (which should be measured, not guessed at) every twenty-four hours, the presence of albumin, etc., should all be written upon a daily sheet for the physician's information and guidance.

Cases never do as well when treated at home as when the advantages of a well-conducted **hospital** are at hand. For this reason the patient should be removed as early as possible with the least disturbance, taking care to surround the procedure with all the necessary safeguards that will insure the health of the community against the possibility of infecting mosquitoes during the transportation. When it becomes imperative to treat the patient **at his home,** he must be isolated in a room by himself, where the doors and windows will be protected by wire gauze, that they may remain open without giving access to mosquitoes. After the fourth day of the disease, the wire screens may be removed without danger to the public health, thus obtaining better ventilation for the room. Once the patient is isolated, the room from which he was removed, as well as the others of the house, may be fumigated without causing him any disturbance.

During epidemics it has been necessary to place yellow fever cases **in tents,** with two or more beds each, according to capacity. Patients do very well under these circumstances, sufficient ventilation being obtained by raising the side walls, while the patients remain under individual mosquito-nettings, kept in good repair and well tucked in under the edge of the mattress, thus securing absolute safety from infecting any insects.

It has been the writer's custom to **refrain from all internal medication** during the first three days of the disease; much harm has been done in former years by needless therapeutics in yellow fever, usually causing a more irritable condition of the stomach without any good whatever. Many authors, even to this day, recommend an initial **cathartic,** the justice of which can hardly be sustained. Such practice is not followed in other infectious blood diseases and the vast amount of evidence gathered so far has failed to show that cases do any better by virtue of this preliminary purging. Of course when the patient is one who suffers from chronic constipation, or who reports not having had a movement for two or three days previous to the physician's visit, it is obvious

that an attempt should be made to clear the bowels, regardless of the nature of the disease which calls for attention. The choice of a cathartic at this time must rest with the individual practitioner and bear relation to the condition of the patient, the age, constitution, etc., but **calomel** in some form has been found particularly useful. Administered in repeated small doses, it acts both as a cholagogue and as an antiseptic; it should be followed by a fair dose of one of the milder **mineral waters** (Pluto, Carabaña, Rubinat). Sometimes a copious **enema,** preferably containing **sulphate of soda,** in the proportion of a tablespoonful to a quart of water, will bring down much fecal matter from the rectum and stimulate further discharge from the large intestine; this measure is very useful in cases where the gastric irritation is already apparent at the first visit.

A cleansing **bath** should be followed by absolute **rest in bed** during the whole course of the disease, the physician insisting upon this even when the patients may declare marked general improvement. They should not be allowed to get up for any purpose whatsoever: a bed-pan must be provided and the recumbent position maintained during the act of emptying the bowels or bladder; a feeding-cup or tube will allow the patient to drink while lying down. Efforts to sit up or move around are conducive to disastrous results and the great importance of this enforced quiet is recognized by all who have had extensive experience in the management of yellow fever.

No **food,** that may be called such, is allowed during the first three or four days, and it must be withheld even further if such unfavorable signs as continued high fever or vomiting be present. If the thirst becomes unbearably intense, cold **alkaline waters** may be allowed, no great quantity at any time, but sipped slowly or sucked through a glass tube; for this purpose, Vichy (Celestin), Mondariz and other lightly charged waters are excellent, or else a very weak lemonade, iced, taken at stated intervals, may be substituted. Regarding the suppression of all food, we have had occasion to use **rectal feeding** with seemingly favorable results. This is continued for three or four days only, according to the behavior of the rectum, then suspended for two days and renewed. It is seldom that this method has to be repeated more than twice, as the duration of the disease will rarely warrant its repetition. As may be readily understood, the object of stopping all food by mouth is to relieve the stomach from all function, suppressing a source of irritation from an organ that is naturally irritable in yellow fever; in so doing, the chances of "black vomit" are also lessened to a remarkable degree.

Later in the disease, if gastric intolerance is improved or relieved, and the temperature is not above 39° C. (102° F.), a moderate amount of milk may be allowed in small quantities, repeated at intervals and slowly sipped; it may best be mixed with lime-water or Vichy. Other excellent substitutes for milk or other food are toast-water, barley or oatmeal-water. Later, frozen cream, in small quantities each time, and

gelatin, plain or wine-jelly, may be given. All strong beef-extracts must be avoided, as well as alcoholic beverages.

No active **eliminative treatment** should be instituted: by no means should **diaphoretics** or **diuretics** be employed, just as we do not recommend the use of purgatives. Such methods would entail the unwarranted stimulation of organs already weakened by the disease itself, which would be at least unwise to irritate. Besides, our present knowledge of the final destination of the toxins in the body does not seem to bear out the old theories of elimination through the natural channels. Guiteras, who has enjoyed unusual advantages in the study of this disease, holds views against eliminative treatment in yellow fever, believing that we must rely to a certain extent upon neutralizing the toxins in the body of our patients, since we do not know how or when they are eliminated. In this connection, however, he seems inconsistent —he recommends the administration of large amounts of water "even up to eighty ounces in twenty-four hours," as well as calomel and jalap or castor oil at the beginning of treatment.

External applications are wonderfully efficient in relieving subjective symptoms at the early stages of the disease. The **ice-cap** placed upon the head or at the back of the neck, or even **ice-water compresses** to the forehead, will usually rob the headache of its torturing intensity. The lumbar pains are best treated by **hot fomentations, dry-cupping** of the region, **mustard plasters** directly on the lumbar vertebræ, gentle **massage** of the muscles or rubbing with the hands adding some soothing lotion.

The anuria must be met by the use of **warm mustard baths, hot air baths, hypodermic administration of urea,** even to 15-grain (1.0 gram) doses (Carroll). **Goats' renal vein blood serum** has been used with success and enabled the patient to bridge over a particularly dangerous crisis.

When the quantity of the urinary secretion can be kept up in yellow fever, the changes are in favor of recovery; in fact, the more urine voided during the twenty-four hours, the more favorable will be the prognosis. Experience has shown that cases with anuria are uniformly fatal, and those which show a defective action of the kidneys from the early stages of the disease usually have a fatal termination as well. The permeability of the kidneys seems to be of greater importance than the degree of damage that may result to the kidney cells, inasmuch as cases with abundant albumin and casts of all kinds often recover, if the quantity of urine is sustained, while others with very little albumin succumb, if the secretion is very much diminished.

An expedient which has proved very useful in this connection, when we cannot resort to medicine by mouth, is the administration of **cold enemata of normal salt solution,** which tend to increase the urinary secretion and to lower the temperature at the same time. Through a long rectal tube, one pint to one quart is allowed to flow in, very slowly, so as to secure its retention. When rectal feedings are also being resorted to, they must be prepared with an excess of salt solution each time, instead of the latter being injected separately.

After severe hematemesis, constant **rectal irrigation** is very beneficial, and may be carried out by the Murphy drop method, as in typhoid and other wasting fevers.

The nausea and vomiting are perhaps the most annoying symptoms and at the same time the most difficult to ameliorate. If the absolute **suppression of food** does not control the retching or vomiting, it may be well to try **effervescing drinks** of various kinds, or, by administering spoonful doses of the separate solutions of **Seidlitz powders**, obtain the effervescence in the stomach. Iced dry **champagne** and small sips of **ginger ale** are also useful. The filling up of the stomach with any liquid whatever will produce vomiting and so the greatest care and judgment must be exercised, even to the extent of measuring the amount of liquid allowed, particularly when cracked ice is given.

The **ice-bag** placed upon the epigastrium or over the trachea at the root of the neck often relieves the condition of nausea.

When the small particles of blood begin to appear in the vomitus, something more than the measures above outlined must be undertaken. A good method has been to administer five drops of the **tincture of chlorid of iron** every two or three hours, dissolved in a small quantity of lime-juice and glycerin. As the ferric chlorid no doubt acts locally upon the damaged mucous membrane, where the hemorrhage was likely to take place, it is well to stop its administration so soon as the specks disappear from the vomited matter or when the signs of gastric irritation become intensified. Other treatments directed towards controlling the gastric hemorrhage have not been particularly satisfactory, nevertheless, hypodermic injections of **adrenalin** or **ergotin** solutions should be tried. Bleeding gums are often improved by the use of local applications of the common **astringents.**

When "black vomit" makes its appearance and the hemorrhages from the stomach continue incessantly, oral feeding or medication must be instantly abandoned and **rectal feeding** definitely resorted to. Not more than eight ounces should be injected at one time, every four hours, carrying out the treatment as above outlined, or on alternate days, so as to give the rectal mucous membrane a period of rest that will in a measure prevent subsequent excessive rectal irritation. The formulæ recommended are rather numerous, but the following has been found quite effective:

Milk	3 ounces (better peptonized) (90 c.c.)
Whisky.....	½ ounce (15 c.c.)
Normal salt solution..	3 ounces (90 c.c.)

It should be administered very slowly and preceded by a cleansing enema of clear water.

To allay the violent uncontrollable vomiting, it may be necessary to use hypodermic injections of **morphin.**

The fever in this disease is one of the symptoms which should least worry the practitioner. Cases of hyperpyrexia are of the rarest occur-

rence and this alone demands but little attention. This notwithstanding, an effort should be made to lower it when it rises above 39.5° C. (103° F.), and this ought to be undertaken without the use of antipyretics. The **coal-tar preparations** are not safe remedies in yellow fever and they should be used with the greatest caution. **Aspirin, antipyrin** and **phenacetin** are the safer ones, but they are better administered in combination with **caffein** to offset their depressing effects upon the heart and more as analgesics than as antipyretics.

Cold water is by far the best antithermic that we can employ, since it not only lowers the temperature as often as we may wish to apply it, but it also promotes leukocytosis, relieves congestion and gives a sense of well-being after its application. The water should be at a temperature not lower than 21° C. (70° F.) except when the fever keeps high in spite of repeated sponging, when the water may be used at 16° C. (61° F.) or even 10° C. (50° F.). Sponging at four-hour intervals may be found sufficient; no tubbing must be tried, remembering that the greatest quiet is the best for the patient.

The use of various substances in the water for the bath, such as **alcohol, bay-rum, vinegar,** etc., is of secondary importance.

Many conditions, some derived from the yellow fever itself, others as a result of complications or appearing in subjects who were much below par before their present attack, will have to be met during the course of the disease. Many cases will require at some stage of their attack more or less cardiac stimulation; this is best obtained with **strychnin** or **digitalin,** used hypodermically. The use of the latter drug is quite advantageous, since it increases the urine at the same time; for this purpose alone, however, it should never be used. **Alcohol,** though contra-indicated in marked kidney involvement, is an excellent heart stimulant, especially in persons accustomed to its use, but it must be administered in enemata, very cautiously at first. For oral administration, iced **champagne** should be preferred to any other alcoholic concoction.

For impending heart failure or syncope, hypodermic injections of **camphor,** dissolved in oil or ether, must be given; pure ether may be used at an emergency.

The nervous symptoms, restlessness, insomnia, etc., are better met by **hydrotherapeutic measures**; the giving of drugs for such conditions, except opiates in hypodermic form, must be avoided.

Attempts to treat yellow fever with **specific antitoxins** (Sanarelli) or **vaccines** (Freire), etc., have demonstrated their utter worthlessness, and the use of human serum in this connection has not gone beyond the experimental stage; from a practical standpoint, these means of treatment have nothing to recommend them.

TREATMENT OF CONVALESCENCE.—Most cases of yellow fever have a rapid and uninterrupted convalescence. There are some, however, who have poor recuperative powers after the infection has entirely waned and they seem to pick up strength very slowly and laboriously. While many of our patients are up and about in a fortnight after their initial

chill, some of those who may have suffered from abundant hemorrhages or had been in a typhoid state, will have the greatest trouble to regain their wasted powers. They often suffer from a condition of indigestion or impaired functional digestive power, which, though not particularly dangerous, proves most taxing to the physician in charge. Too early an allowance of **food**, if solid or too highly seasoned, may bring about serious consequences. Sometimes patients have to be kept upon liquid diet for a considerable time.

A good index will be the condition of the kidneys, that will point when a more varied diet than milk and gruel may be allowed. After the albumin has decreased considerably and shows a tendency to continue diminishing, the patients may be allowed gelatins, made with beef or mutton broth, corn starch, custard, etc., the food being increased and varied with the greatest care.

Jaundice often becomes marked during convalescence and persists for many weeks even after the patient is about his ordinary calling.

The administration of **tonics**, by mouth or hypodermically, is very beneficial when the digestive system is in a condition to meet the demands of the renewed or increased appetite, which is to be expected from their use.

Prognosis.—In uncomplicated yellow fever, that is, in cases that were not primarily affected by syphilis, hepatic, renal or cardiac disease, the prognosis, all other things being equal, is not as uniformly bad as it was formerly estimated.

In a general way, it may be stated that it is quite favorable in the case of children, though we have seen a few of them terminate fatally; patients over 50 years of age do badly, also drunkards, drug addicts and those who have been weakened by excesses of any kind or by extreme fatigue, after long marches, etc.

The character of the fever and the amount of kidney involvement the author considers among the best signs upon which to base a prognosis. Cases where the temperature persistently reaches above 40° C. (104° F.) are generally fatal, or suffer grave inconvenience during convalescence. When the temperature remains around 39° C. (102° F.), it is a favorable sign, especially if a remission takes place during the first three days. Cases of continued high fever, in which there appears no distinct remission in the early days, always do badly and often terminate fatally in spite of treatment. A rising pulse rate, with lowering of the temperature, is a very unfavorable sign. A marked diminution in the quantity of urine voided, or total suppression, is invariably unfavorable to the patient.

The development of a typhoid state is not necessarily fatal, but it must be looked upon as an unfavorable sign; extreme nervous irritability is also unfavorable. Profound icterus, from the early stages, is very unfavorable.

When the gastric irritation is not marked and the kidney signs keep in abeyance, a favorable prognosis may usually be made with some assurance. There are some cases which do not respond to the

therapeutic measures employed and from the very beginning of their attack show such unmistakable signs of severity that an unfavorable termination must be looked forward to. No doubt the pathological process in these cases is of such a nature and rapidity that the resulting lesions quickly place the organs in a condition beyond repair. In these cases, delirium, "black vomit" and anuria soon develop.

RELAPSES.—It has been claimed that relapses are more frequent in some epidemics than in others; however, they are comparatively rare in this infection. When they occur, it is usually one or two weeks after the disappearance of the fever. They are induced by excesses, either of food or drink, and are seldom accompanied by all the symptoms of yellow fever, so that it is difficult to assert that an actual relapse has taken place and not a condition of indigestion developed. This notwithstanding, even a recurrence of albumin and gastric intolerance has been observed in several cases.

Atypical cases have shown a sudden rise of temperature and a second or third period of fever taking place when the primary attack is about to terminate, the temperature continuing so for three or four days, before definitely coming down to normal or subnormal; but this, which might well be thought of as an unusual exacerbation of the original attack, cannot in justice be called or considered a relapse.

Pathology.—It may be said at once that yellow fever has no pathognomonic lesion; the changes in the various organs are such as we may meet in many other infectious diseases of the same severity. Yet, there is a certain group of lesions which, when occurring in cases of jaundice may safely be considered diagnostic; this group is to be found consisting of the skin, liver, stomach and kidney lesions.

Yellow fever cadavers uniformly present the peculiar yellow tinged *skin and conjunctivæ.* Only in the most severe and prolonged cases (that may have lasted ten or more days), do we see a very intense jaundice, such as is met with in acute yellow atrophy of the liver; the post-mortem jaundice in yellow fever is always quite evident but not pronounced. Besides jaundice, there may be some degree of emaciation; but this is often absent, owing to the short duration of the disease, and is present mainly in cases that have died during convalescence from some intercurrent disease, or after ten days or a fortnight as the result of complications in the course of their yellow fever attack.

The skin will also show ecchymotic areas, particularly upon the dependent parts of the body. This is more often seen in very severe cases and several hours after death; small petechiæ are very common about the feet and abdomen.

The same yellow discoloration of the skin is evident upon cutting the body. The serous membranes and their liquid contents, as well as the adipose tissue layers, will be found more or less tinted. This condition, however, is present in almost all cases of jaundice.

The lesions generally found in the principal organs are as follows:

The liver is usually of normal size—sometimes slightly decreased in size. The consistency does not change, though in protracted cases

it has been found rather friable. The color, that of chamois skin, or a little darker, is the rule, but sometimes, and particularly in cases rapidly fatal, the yellow color is streaked with dark gray or purplish lines, or mottled, the yellow tint always predominating. A dark-colored liver has been found exceptionally in chronic malarial subjects.

On section, the organ will present the same appearance, but the anatomical details will become prominent. Some degree of injection may be observed with little or no bleeding of the cut surface. Subserous hemorrhages upon the surface may occur in small patches, its extension depending upon the intensity of the case.

Histological sections of yellow fever livers give a most diversified picture in some points, while in others there is considerable uniformity. The writer believes the difference of opinion among various observers is due mainly to their having examined or prepared the tissues under varying conditions. He had opportunity to work with absolutely fresh material, that is, from autopsies made soon after death, and has thus been enabled to appreciate greater uniformity in many microscopical characters. Their interpretation, as regards pathogenesis, is a question still open to discussion and need not be dwelt upon here very extensively.

There is a distinct fatty change in the liver cells, most of which will be found to contain numbers of minute droplets, disseminated in the protoplasm, which is never or rarely supplanted: the nucleus remains practically unaffected.

In some specimens, necrobiotic areas are found, principally in the intermediary zone, while the marked fatty changes are more prominent in the peripheral and central zones of the lobules. Both fatty cells and necrosis of single cells may be found throughout the lobule, but distributed in the manner indicated. Rocha-Lima [17] lays great stress upon this common feature and considers it of special diagnostic significance. This, of course, cannot be granted until a sufficient number of specimens, derived from other diseases, are examined. It may also be noted that the variations as to the proportional changes in the liver cells occur not only in different livers but in different parts of the same organ.

No "general disorganization" of the parenchyma, as claimed by Azevedo Soudre and Couto,[18] can be demonstrated, though upon first notice such may appear to be the case. In the necrotic regions referred to, the trabeculæ may indeed be found to have been destroyed as well, but this fact cannot be considered either typical of yellow fever or endowed with special significance.

Although the nuclei of even the very fatty liver cells are as a rule but little affected, still a close investigation will reveal here and there certain changes that have been extensively dealt with by various authors, but which really cannot be admitted as being pathognomonic, nor unlike what is met with in other conditions of a marked degenerative process. Evidence of regeneration also, karyokinesis, etc., may be frequently found in liver cell nuclei.

In some areas of the liver, small zones of distinct hyperemia will be observed; the capillaries as well as the central veins are injected though not distended; on the other hand, anemia of the organ is a very constant and marked character, particularly towards the periphery of the lobules.

Hemorrhages are very common, in some instances of sufficient importance as to affect the tissues in their immediate neighborhood. White cell infiltration, more so of the necrotic areas, may be observed.

In the endothelial cells of the capillaries, Seidelin[19] particularly has found a peculiar fat-containing pigment. The author has observed such a substance, but generally occurring in the liver cells themselves; its main characteristic is its insolubility in fat-dissolving reagents "and stains with sudan III even after treatment with alcohol and xylol, etc." Bile pigment is not found as a regular content of the liver parenchyma; there is no real jaundice of the liver in this disease and the bile capillaries are intact except in the necrotic patches above mentioned.

The connective tissue around the portal veins is usually normal. In some specimens slight cell infiltration or edema may be observed; otherwise, the stroma of the liver is neither increased in volume nor in any other way affected.

The gall-bladder is generally distended with clear bile, though sometimes it is found almost empty; its walls are normal.

The kidney is regularly involved in this disease. Microscopically it will appear, wrapped in a certain amount of yellow adipose tissue, normal in size, a little darker in color, the capsule smooth, shiny, perhaps a little more adherent than normal, with a few subcapsular hemorrhagic spots. Upon section, it will be found dry, swollen and often with clear evidences of fatty changes in patches. Microscopically, the cells often contain fat droplets in great quantities, diffusely distributed throughout the organ, but more compactly arranged upon the yellowish spots. Necrotic changes are less frequent; more common than any other process is a granular degeneration of the renal epithelium, particularly of the straight tubules. Cloudy swelling is the most common kidney lesion in yellow fever; less frequently do we see a real acute nephritis.

More profound changes in the kidney are usually due to previous condition of the organ and not to the yellow fever infection itself.

The stomach, of normal size, with perhaps a few subperitoneal hemorrhages, invariably contains a certain amount of blood as such, or as "coffee-ground" material. It is of the utmost rarity to find a stomach in yellow fever autopsies that has not suffered a more or less extensive hemorrhage. Sometimes the liquid is made up of the normal gastric contents mixed with flecks of blood in suspension, the classical "fly-wing" vomit, or only a bloody slime, covering the mucous membrane of the stomach, may be found. These different aspects depend, naturally, upon the amount of blood extruded and the time when it took place. It is reported that in rare instances no blood may be found in the stomach, but the writer has yet to see a case of yellow fever that ended in death without this characteristic sign.

The wall of the stomach is thickened, the mucous membrane edematous, showing upon its surface the site of ruptured blood vessels or under it, the presence of extravasated blood. Erosions the author considers to be usually of post mortem occurrence and ulcerations are rare, developing, no doubt, at the seat of hemorrhage in protracted cases. There are no more definite microscopic changes worth noting.

The duodenum will regularly present the same characteristic picture as the stomach mucosa, and the hyperemia will be found diminishing gradually as we advance along the intestinal tract; it often contains bile in quantity. The intestinal contents are always bile-stained; there are no clay-colored stools in yellow fever, no matter how intense the degree of jaundice may be in the particular case. The conditions mentioned as existing in the liver, kidney and stomach may be deemed sufficient upon which to base a diagnosis; there is no other disease in which these organs are so uniformly affected in that way, at the same time.

The heart is found most often in diastole, flabby and soft, enveloped in more or less fat; its size is generally normal, no organic lesion found may be attributed to yellow fever. The pericardium may contain a little more fluid than usual and slight hemorrhages may be present. The color of the heart muscle is pale and yellow streaked. The endocardium is also yellowish and may show small hemorrhages under it. There is no endocarditis in uncomplicated yellow fever.

Microscopical examination only shows a degree of fatty degeneration of the muscle fiber.

The endothelium of arteries and veins, as may be expected, is also tinged with yellow, but no special changes are apparent.

The spleen is usually of normal size; exceptionally it may be found slightly enlarged; of normal color and consistency; there may be injection of the blood vessels. As a rule, the spleen is found enlarged only in malarial individuals or in cases of yellow fever complicated with other diseases.

The pancreas is regularly enlarged; of pale color, somewhat softer than normal. The epithelium will appear in different portions of the organ with fatty changes or necrosed. No other marked changes can be observed though it is reported that some alteration has been observed in the islands of Langerhans.

The central nervous system is not particularly affected. *The brain* microscopically shows slight hyperemia of the cortex. Hemorrhages are rare, though they have been observed; usually of limited extent. Microscopically no distinct lesion can be demonstrated. The meninges are as often hyperemic and in a general way the signs of congestion may be found of no diagnostic value.

The respiratory organs have nothing distinctive, though in the *pleuræ* small subserous hemorrhages are very frequent. The *lungs* are often very congested, but no real pneumonia can be shown upon microscopical investigation. Post-mortem infiltration and hypostatic congestion are common.

The *uterine mucosa* is nearly always found much congested and frequently blood is found in the uterine cavity. Under the microscope the muscle fibers will be seen affected with fatty changes. The same are found sometimes in the *ovaries* or *testicles,* which microscopically show no lesion whatever.

History.—Whether yellow fever was originally an American or an African disease is a mooted question. It cannot be denied that the earliest positive knowledge of its existence is derived from American sources, but recent investigations seem to indicate that the disease has been endemic in the West Coast of Africa for more than a century, certainly, without causing much havoc or attracting very particularly the attention of the European rulers of that part of the world. Hence there is some justification in the theory that, exactly as malaria and other tropical diseases, it may have been no less prevalent there at the time that slavery was introduced in America, and unknowingly being brought, together with it, to this side of the Atlantic.

In connection with this, it is interesting to note the reference made by one of the earliest writers concerning the West India Islands. In speaking of the malignant fevers, he says: "The bad air was brought there by some ships which came from the coast of Africa, etc."[1]

On the other hand, it is difficult to explain why, if prevalent, or endemic, in West Africa, it did not invade European countries even before the discovery of America, or immediately after, when a veritable fever of exploration and conquest took hold of most of the civilized nations during the sixteenth century.

Epidemics of this disease occurred during the eighteenth and nineteenth centuries, causing a loss of life that was really appalling, principally in America, and invading coast cities from Portsmouth, N. H., to Montevideo in Uruguay, along the Atlantic, including the West Indies, Mexico and the Isthmus of Panama.

The Boston expedition of 1693, which brought the disease from the Island of Martinique, is perhaps the earliest authentic record in the United States. The last epidemic occurred in this country at New Orleans in 1905, when more than 3,000 cases developed. Between these two events, all the Atlantic Coast and the Gulf States were invaded at one time or another, as may be readily seen by a perusal of the very complete history of the disease prepared by the late Gen. Geo. M. Sternberg, for the "Reference Handbook of the Medical Sciences," which, of course, does not contain reference to the later epidemics at Laredo, Texas, and New Orleans and adjacent territory. No epidemic, perhaps, was so widely extended nor caused such a death-rate as that which invaded the United States in 1878, spreading from New Orleans as far north as Missouri, embracing 132 towns in eight states and resulting in 15,934 deaths, having developed more than 74,000 cases. In view of the present knowledge regarding the epidemiology of yellow fever, another such epidemic is never again likely to occur.

In the meantime, as pointed out before, and mainly as the result of infection being carried out from America, several ports of Europe,

principally of France, Spain and Portugal, suffered outbreaks of yellow fever, of greater or lesser intensity; the sources in every instance were traced to vessels arriving from some of the well-known foci on this side of the Atlantic. Europe has now been free for many years from epidemics of this disease, and the probabilities are, in spite of the West African endemicity, that no recurrence of yellow fever in any of its ports will be the cause of any great alarm from an epidemiologic standpoint.

Since 1905, the disease has been gradually disappearing from its former haunts, and although appearing in various new localities, such as in Tocopilla, Chile, and lately in Buenaventura, Colombia, the fact is that it is being very decidedly stamped out in America, even by the half-hearted measures implanted in many of the countries most concerned; these results are, no doubt, due to the employment of rational, not to say scientific, means of defense, which are directed to its final extinction.

Present Geographical Distribution.—At the present writing (July, 1918), yellow fever infection as a world menace may well be considered a negligible quantity. There is no longer such a focus as Havana, Rio de Janeiro or Vera Cruz were before 1901, when the methods of propagation by mosquitoes were definitely demonstrated by the United States Army Commission.[2] We may safely say that the disease probably lurks only in the by-ways of the northern South American republics, since it has been extinguished in the principal ports and is but latent in such as Guayaquil and Bahia. This excellent state of affairs may be readily appreciated by a study of the reports issued by the U. S. Public Health Service. Its sources of information may be thoroughly relied upon regarding those places where the Service maintains trained representatives, but the consular reports are usually based upon knowledge derived from the local authorities and it may be best not to take them at their full value.

Thus we see that, in 1917, yellow fever showed itself as follows:

1917

Brazil		
Espirito Santo, State	18	cases
Pernambuco	1	"
Ecuador		
Babahoyo	3	"
Chobo	1	"
Guayaquil	98	"
Milagro	4	"
Naranjito	2	"
Yaguachi	1	"
Mexico		
Yucatan, State	18	"
Campeche, State	2	"

Honduras

Tegucigalpa ..... 1 case

Venezuela

Coro ..... present

Thus we may readily see that Ecuador seems to be holding the record, particularly the city of Guayaquil. The conditions at this port are such that the Rockefeller Institution has decided to make an attempt towards their betterment, going to the extent of sending a commission there for the purpose.

On the other side of the Atlantic, official reports indicate that the disease is certainly endemic on the West African coast.[3,4] It is ascertained that the disease constitutes there an endemic focus, or rather several foci, of "maladie habituelle," attacking both white and black population, though in different intensity. The problem of its eradication, in such semi-civilized communities, is more difficult to solve than it is with us, but there is no reason to doubt that with the termination of the present European conflict, when attention may be given to the question of colonial sanitation with the interest it deserves, the infection, even there, will not be a source of much worry to the civilized world.

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CHAPTER XXI

ASIATIC CHOLERA

By Eugene R. Whitmore, B.S., M.D.

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Synonym.—Cholera.

Definition.—Cholera is an acute specific disease, caused by the *Spirillum choleræ asiaticæ*, discovered by Koch in 1883, and characterized clinically by a profuse painless diarrhea, vomiting, rapid collapse, muscular cramps, and suppression of urine.

Etiology.—Predisposing Causes.—There appears to be no difference in sex or age susceptibility. Overcrowding and bad ventilation are predisposing causes; as are worry, underfeeding, acute infectious diseases, overexertion and alcoholism. One of the most important predisposing causes is gastro-intestinal disturbance; and, in the Philippines we expected an increase in the number of cases of cholera after a flight of locusts, on account of the gastro-intestinal disturbance resulting from the eating of the locusts. Healthy persons, carrying the cholera vibrio in their intestine, may develop an attack of cholera after a cathartic, or after some gastro-intestinal disturbance; and it is not uncommon to see a return of the symptoms in a cholera convalescent after some indiscretion of diet.

Exciting Cause: The Organism.—In 1883 Koch discovered the specific cause of cholera, first in Egypt, and later in India. The *Spirillum choleræ asiaticæ* is a short, slightly curved rod, about 1.5 microns long, with a single flagellum at one end, and actively motile. It grows well on all ordinary culture media, and its ability to grow in alkaline media is taken advantage of in developing various special media for its growth.

The El Tor strains of the cholera vibrio produce hemolysis in fluid blood media, while the genuine strains of the cholera vibrio do not produce hemolysis in such media. Both types produce a clear zone around the colony on blood agar; but this is not due to hemolysis in both cases:

the genuine cholera vibrios produce this zone as a result of their digestive action on the blood-cells.

A number of laboratory workers have taken cultures into the stomach, partly by accident and partly by intention. In some cases where old cultures were taken there were no symptoms. In a number of accidental laboratory infections there have been all degrees of severity of the infection, from mild diarrhea to rapidly fatal cholera. One of the most interesting experiments is that of Pettenkoffer and Emmerich, who took cholera cultures with the intention of testing whether the cholera vibrio caused cholera. They took some alkali to neutralize the gastric juice, and then drank water to which they had added small amounts of a fresh culture of the cholera vibrio. Pettenkoffer developed a mild diarrhea; but Emmerich developed a severe attack of cholera which came near to costing him his life.

The cholera vibrio does not form spores or any resistant form. Healthy persons, who have not had cholera or diarrhea, may pass cholera vibrios in their stools for a month or two. Following cholera, the vibrios usually disappear from the stools in eight to ten days; but they may persist for over sixty days. Dunbar found living cholera vibrios in stools after being kept at room temperature and on ice for one hundred and sixty-three days. The vibrios stand temperatures well below freezing, and they will stand alternate freezing and thawing. The cholera vibrios die quickly after the death of the patient, and there is no contamination of the ground in which the body is buried. The vibrios die in guinea pigs, fifteen to twenty days after burial.

The behavior of the cholera vibrio in water is of special importance, as cholera is commonly a water-borne disease. In some waters, the vibrios die very quickly, while they live and multiply in other waters. In sterile water the vibrios will live for a year; and they have frequently been isolated from water in rivers, wells and tanks. In view of the large number of cholera-like vibrios which are found in waters, fish, and in the stools of healthy persons, it is very important to make a complete determination of all vibrios isolated, before concluding that one is dealing with a cholera vibrio. The cholera vibrio does not live more than five or six days on food, and it does not live long in unsterilized milk, on account of the acidity of the milk as soon as it begins to sour. There is danger of infection from green vegetables that have been fertilized with human feces.

The cholera vibrio does not stand drying, and it dies in a few days on clothing kept under ordinary conditions. There is no danger of infection from dust. It resists sunlight for some time, but is killed by 10 minutes' exposure to a temperature of 50° C. (122° F.). It is readily killed by all of the ordinary disinfectants.

Epidemiology.—(a) Source of Infection.—The source of infection in cholera is man.

In the *clinical case* of cholera, the vibrios are passed in enormous numbers in the stools, and are at times present in the vomitus. Greig found cholera vibrios in the urine of 8 of 55 cases of cholera. He also cultivated

the cholera vibrio from the lung of a case of cholera with pneumonia, and he suggested the possibility of spread through the sputum in such cases.

Mild cases of cholera, amounting to little more than a simple diarrhea, are important sources of infection. Convalescent cases rarely excrete the vibrios in the stools for longer than seven to ten days, though they may continue to excrete the vibrios for as long as sixty-five days.

Vibrio carriers are numerous in epidemic centers, and it is very common to find one or more vibrio carriers in a house where a case of cholera has developed. In Manila, six to seven per cent. of the healthy persons in some of the infected neighborhoods were carriers of the cholera vibrio. Heiser reports that of 876 contacts in connection with 72 cases, 40 showed vibrios in the stools, 29 being the cholera vibrio. Munson reports a systematic examination by the Health Stations in Manila: of 29,448 persons examined, 526 (1.78 per cent.) were carriers of the cholera vibrio, this percentage going as high as 2.4 in one health district. None of these persons were cholera suspects. In Bilibid Prison, 5 per cent. of the inmates were carriers of the cholera vibrio. Some of these persons developed cholera after carrying the vibrio for 17 to 18 days, one such case dying within 8 hours after the onset of the illness.

Pottevin examined the feces of 14,158 Egyptian pilgrims at Tor, in the winter of 1912-1913: 13,612 were healthy persons; 480 were sick in the hospital, and 66 were postmortem examinations. Vibrios were found 106 times (7.4 per 1000), 69 (4.8 per 1000) being cholera vibrios. In the 13,612 healthy persons, vibrios were found 40 times (2.8 per 1000); 1.7 per 1000 being cholera vibrios. He also found that persons sick of some other disease than cholera, especially dysentery, were very commonly carriers of the cholera vibrio—the incidence being as high as 79 to 110 per thousand.

Pottevin finds healthy carriers are especially numerous among children. Of 3,173 examinations in St. Petersburg, in 1909-1910, he found 6.6 per cent. of carriers among healthy adults; 9.8 per cent. among children 1 to 15 years old, and 20 per cent. among children less than 1 year old.

It is to be borne in mind that, in the case of carriers, the vibrios may appear in the stools intermittently. For this reason, the Philippine Board of Health insists on repeated examinations of the stools of negative persons in the search for cholera carriers.

Undoubtedly the carriers and the mild cases are of the greatest importance in the spread of the infection in a community and along routes of travel.

There is no evidence that any lower animal harbors the cholera vibrio, or plays a part in its spread to man. In the Philippines, it was suggested that the pig, on account of its special function as a scavenger, might play a part in the spread of the cholera vibrio. Numerous feeding experiments, even to having a part grown pig drink a liter of rice-water stool from a case of cholera, were carried out; but the cholera vibrio was

never found in the rectal contents of the pigs, either before or after feeding material containing cholera vibrios.

(b) Mode of Transmission.—Cholera is spread in the same way as other diseases in which the infectious agent is contained in the feces, and is taken through the mouth.

Water is one of the commonest modes of transmission of the cholera vibrio. The organism lives for a long time in water, and the fecal discharges of cholera patients or carriers, passing into water supplies, may cause an explosive epidemic. An example of the water-borne epidemic of cholera is the Hamburg epidemic in 1892. The water of the river Elbe, infected by the discharges of cholera patients among some immigrants, was distributed throughout the city for drinking, without purification. Beginning with an occasional case over some weeks, there was a sudden outbreak of the disease, this outbreak reaching its height in ten days with 1000 cases in a day, and then gradually subsiding during the next two months. Vegetables washed in contaminated water may convey the infection.

Milk is not so frequently contaminated, probably on account of the acid reaction that develops when milk sours. However, Heim demonstrated living cholera vibrios in milk that had been sour for six days. Milk may be contaminated by the use of contaminated water, in washing the cans or as an adulterant. Milk is not used to any great extent in many of the countries in which cholera is prevalent.

Contact infection is a common mode of transmission of cholera. This is especially apt to be the case where a number of people live in close contact, and eat and drink from a common dish or bowl, not infrequently dipping the fingers into the common food dish. An example of contact infection is an epidemic on a ship that left Naples for Brazil, in 1893, with 1472 deck passengers. Cholera broke out among the passengers on the way, and the ship could not land her passengers in Brazil, but had to return to Italy with them. The round trip from Italy occupied nearly two months, and 141 of the passengers died on the trip. Persons handling the clothing and bedding, soiled with the cholera discharges, are not infrequently infected.

Flies transmit the cholera vibrio, just as they transmit the typhoid bacillus, and in the same way. As the cholera vibrio does not stand drying, it is not so readily transmitted by the feces-soiled legs and body of the fly. The cholera vibrio will live in the intestine of a fly for at least three days; and the feeding habits of flies—feeding on fecal matter and on the carbohydrates of man's food—make them especially adapted to carrying the cholera vibrio from feces to man's food. Moreover, the necessity for the fly to take liquid or semi-liquid food accounts for its habit of regurgitating a drop of fluid from its crop onto the food and then sucking up the drop with the dissolved food. Finally, a fly defecates frequently when feeding. Thus, the fly, after walking on, and feeding on, feces containing cholera vibrios, walks on, regurgitates on, and defecates on, the food of man, in that way carrying the cholera vibrio from the contaminated feces to the food.

As the cholera vibrio does not stand drying, there is little danger of transmission through dust or on articles of furniture. The vibrio will live for some days in clothing and bedding that is rolled up without any special attempt at drying.

Where transmission is by contact or by flies, there is not the explosive outbreak that is seen when the transmission is by water. Instead, the so-called "cholera nests" appear about the point where a case develops; and it may be difficult to trace the connection between the cases or between the nests. In some of the towns in the Philippines, these "cholera nests" were very clearly developed after the cholera had been going in the town for some time; and these nests of a few houses were widely scattered through the town, without any traceable connection with each other.

(c) Susceptibility.—All races, all ages, and both sexes are susceptible to infection with the cholera vibrio. Overwork, worry, gastro-intestinal disturbances, and alcoholic excesses increase the susceptibility to infection.

(d) Mechanism of the Disease Process.—In a cholera epidemic, not all persons who take the cholera vibrio into the stomach develop cholera. Among those who develop the disease there are all grades of severity, from mild diarrhea to the severe and rapidly fatal cases. The main reason for the difference in severity of these cases would seem to be in great part due to the difference in resistance of the intestinal epithelium and the general resistance of the person. It is known that cholera is more severe in persons who are weakened from any cause. The causes of natural immunity, and of difference of susceptibility in different individuals, are not known.

When a person takes cholera vibrios into the stomach with water or food, many of the vibrios are killed by the acid in the gastric juice. But large masses of food and large amounts of water may protect the vibrios or dilute the gastric juice to such an extent that the vibrios are not killed in the short time they remain in the stomach before being passed on into the small intestine. If the person has some gastro-intestinal disturbance, or worry, there may be a lessened acidity of the gastric juice; and at times and in some persons the gastric juice is low in acid. When the vibrios reach the small intestine, they find the alkaline reaction of the contents suitable for their rapid multiplication. At times there are no symptoms, and the patient is simply a temporary carrier of the cholera vibrio. Frequently there is a mild diarrhea, which is over in a short time. Under such conditions, any indiscretion in diet or any stopping of peristalsis may lower the resistance of the intestinal epithelium, and the patient may develop a sharp attack of cholera. As long as the cholera vibrio develops in the intestinal contents only, there will not be any very severe symptoms, as it does not secrete a soluble toxin. But, when the resistance of the intestinal epithelium is lowered—or perhaps some strains of the cholera vibrio are more invasive than others—the vibrios invade the epithelium. The vibrios are broken down in the epithelial cells and in the lymph spaces

between the epithelial cells; and the toxin thus liberated causes necrosis and desquamation of the epithelium. The toxin is absorbed and causes the acute intoxication of the typical attack of cholera.

The body reacts to the absorption of the toxin by the pouring out of large amounts of fluid into the gastro-intestinal tract. This pouring out of the body fluid causes the dryness and shrinking of the tissues, the concentration of the blood with the resulting low blood pressure, and the suppression of urine. The abundance of albumin and casts in the urine is probably dependent for the most part on the nephritis which develops early in cholera.

The nephritis leads to a marked acidosis in cholera, and it is probable that part of the symptoms are due to this. Thus, the so-called stage of asphyxia and coma may be due to an extreme acidosis. The ammonia excretion is high; the carbon-dioxid content of the blood is diminished; the excretion of acetone bodies is normal. The muscular cramps are usually ascribed to the loss of water from the nerves; but they may be connected with the loss of calcium salts as a result of the great outpouring of fluid into the intestinal tract. The destruction of the intestinal epithelium, and the lowering of the resistance, pave the way for secondary infections.

The cholera vibrio reaches the gall-bladder in a rather large percentage of cases of cholera. Greig found the vibrio in the bile of 80 out of 271 cases of cholera, and in twelve of the cases there were pathological changes in the gall-bladder. In most of the cases in which the cholera vibrio is found in the bile, it is in pure culture.

There is difference of opinion as to the manner in which the cholera vibrio reaches the gall-bladder; and whether there is general infection. Nichols is of the opinion that the gall-bladder infection results from a portal or general septicemia, with elimination of the organism in the bile. Greig is of the opinion that the organism reaches the bile-ducts through the lymph stream and at times goes up the ducts from the duodenum; but that it does not pass through the blood stream. Greig found the cholera vibrio in a lymph gland near the duodenum; in the liver, especially in the region of the gall-bladder; he found it in the exudate in the pulmonary alveoli in cases of cholera with pneumonia, and in the wall of the urinary bladder. This, with the cultivation of the vibrio from the lung and the finding of it in the urine in cases of cholera, leads Greig to the opinion that a septicemia occurs in many cases. Sanarelli, working with young rabbits, was never able to get the cholera vibrio past the stomach; but, when injected subcutaneously or intravenously, the vibrios reached the intestine, and typical cholera occurred. Adult rabbits lost their immunity when the colon bacillus or its products was injected intravenously or into the wall of the appendix. From this, Sanarelli is of the opinion that the cholera vibrio passes through the mucosa of the mouth and the tonsils and reaches the intestine through the blood and lymph channels, first appearing in the region of the ileocecal valve.

Death takes place in the stage of collapse, or later from uremia and

acidosis. In cholera sicca, death is due to the profound toxemia, before diarrhea sets in.

The tendency of the disease is to recovery by the production of antibodies. Immunity following an attack is of short duration, and second attacks of cholera are fairly common.

Symptomatology.—CLINICAL HISTORY.—The period of *incubation* is a few hours to five days—usually about three days—during which time there are no symptoms. The disease *sets in* with a mild diarrhea, which is usually painless, but may be accompanied by colicky pains. At first the stools consist of thin fecal matter of about normal color. The diarrhea rapidly increases, and soon the stools become profuse, colorless and watery, rendered slightly opaque by flocculi of intestinal epithelium, giving the appearance of rice-water or thin gruel. The stools are alkaline in reaction, and have an albuminous odor. The stools are passed without colic or tenesmus, there being rather a feeling of relief as the enormous amount of fluid is passed.

Vomiting sets in at the same time the diarrhea increases. At first the stomach contents are vomited; but very soon the vomitus takes on the character of rice-water. The vomiting is projectile, and the fluid gushes from the mouth and soils everything about.

With this great loss of fluid from the body, the tissues very soon become dry and shriveled: the skin is wrinkled and inelastic, giving rise to the washerwoman's fingers; the eyes are sunken; the nose is pinched; and the cheeks sink, leaving the cheek bones prominent. Painful cramps appear in the muscles of the legs, thighs, arms and abdomen. The voice becomes weak and husky. The secretion of sweat and urine is reduced to a minimum. The respirations are rapid and shallow; the heart sounds are faint, and the pulse is feeble; the blood-pressure falling to 50 to 70 mm., or it may be impossible to measure it. The skin becomes cyanotic, especially about the nails and the lips, and the face assumes a dusky gray hue. There is intense thirst.

The rectal temperature may be 38.9°-40° C. (102°-104° F.); but the surface temperature is subnormal: the skin feels cold and clammy, and may be moist with a sticky perspiration. The reflexes are diminished; the mind is clear, though the patient is apathetic; there is complaint of exhaustion, especially from the profuse stools; there is air-hunger, palpitation of the heart and faintness.

All of these symptoms may increase: the cyanosis increases to a dark gray or violet color; the heart-sounds are weak and irregular; the pulse is lost; respiration is shallow and labored, sometimes giving the name of asphyxial stage to the condition; the vomiting and diarrhea gradually cease; there is total suppression of urine; the patient passes into coma and dies.

Instead of progressing to a fatal termination, the symptoms may become less marked, and the patient enters the stage of reaction. The vomiting ceases; the stools become less numerous and gradually return to normal; the pulse returns; the skin becomes warm and regains its elasticity and fullness; the cyanosis disappears, and the skin and mucous

membranes become normal in color; the secretion of urine returns; and the patient has returned to complete health in a few days.

But, in many cases, with the stage of reaction, temperature remains elevated to 38.3° or 38.9° C. (101° or 102° F.), the cheeks flushed, and the mucous membranes bright pink in color; the pulse is full and bounding, with the blood-pressure as high as 160 to 180 mm.; there is constipation, and complete suppression of urine. The tongue and lips are dry and cracked, and are covered with brownish sordes. There is headache; the patient becomes apathetic, passes into delirium, and dies in coma.

In some cases, instead of reaction setting in, the cyanosis continues; the pulse is soft, with normal or subnormal blood-pressure; the diarrhea continues and may be bloody; the urinary secretion is not established; and the patient dies on the fourth or fifth day.

Soucek saw cholera rashes rather commonly in an epidemic on the eastern front. One-fourth of the rashes were urticarial, the others macular like measles. The urticarial rash generally appeared about the fifth or sixth day; and the macular rash appeared about the ninth to twelfth day. The macular form appeared on the face, and spread over the body in one to three days. The rash lasted three to six days. The appearance of the rash coincided with improvement in the condition; and Soucek suggests that it is anaphylaxis.

Laboratory Findings.—In the stage of collapse, the blood is thick and may not flow when a vein is cut. The thickening of the blood is due to the loss of water from the tissues. While in normal blood the corpuscles are about 45 per cent. of the bulk of the blood, in the stage of collapse in cholera, the corpuscles may be as much as 80 per cent. of the bulk of the blood. The red-cell count, as well as the leukocyte count, is high according to the concentration of the blood, there being no evidence of leukocyte reaction. The carbon-dioxid content of the blood is decreased. As early as nine hours after the onset of symptoms, the urine may contain albumin; and later the scanty urine is loaded with albumin, and hyaline and granular casts. The ammonia in the urine is increased; the urea is diminished; there is no change in the acetone bodies. There is increased tolerance to sodium bicarbonate.

Diagnosis.—Differential Diagnosis on the Clinical History.—During an epidemic, the diagnosis is readily made from the clinical picture of profuse painless diarrhea of rice-water stools, vomiting, cyanosis, rapid shallow respiration and feeble pulse, with suppression of urine and muscular cramps. But various metallic and meat-poisonings may give all the symptoms of cholera, and can be differentiated only by bacteriological examination. Bacillary dysentery may be mistaken for cholera, especially those cases of cholera in which the enteritis continues for some days. Pottevin found that dysentery and cholera were at times combined; and it must be remembered that dysentery patients are very frequently carriers of the cholera vibrio.

Cholera must be differentiated from cases of *Bacillus aertrycke* infection: the abdominal pain, absence of suppression of urine, and ab-

sence of rice-water stools will help; but a definite diagnosis can be made only by a bacteriological examination of the stools.

In children the meningeal symptoms may be marked; and in Manila it was not uncommon at the postmortem table to find cases of cholera which had been clinically diagnosed as meningitis. Pottevin also noted marked meningeal symptoms in children with cholera.

LABORATORY DIAGNOSIS.—The blood-serum of a cholera patient does not usually develop agglutinins early enough to be of assistance in diagnosis. Greig studied the agglutinins in cases of cholera, and found that fatal cases occasionally agglutinated as high as 1:40; but that they usually gave no agglutination. In non-fatal cases, the agglutination increased to the sixth day, and dropped after the twentieth day: high titers—1:400 to 1:1000—were occasionally obtained. Carriers show agglutination for some time, and this may help in tracing them. When cholera-like vibrios were isolated from a stool which also contained cholera vibrios, there were agglutinins for the cholera vibrio only, and none for the cholera-like vibrio. Normal human serum does not agglutinate the cholera vibrio above 1:20, and very rarely above 1:10.

Bacteriological diagnosis is the principal method of laboratory diagnosis of cholera; and, as a bacteriological diagnosis can be made very early in the disease, it is of great importance in the fight against cholera.

It may be possible to make a diagnosis by the direct examination of the stool. A small flake of mucus from the stool is placed on a slide, without spreading; it is allowed to dry, and is stained with a 1:9 dilution of carbolfuchsin. The cholera vibrios appear as typical comma-shaped bacilli, easily distinguished from the other intestinal bacteria. It is necessary to be familiar with the appearance of the normal stool, in order to avoid confusion with the slender spirilla that are common in normal and diarrheal stools.

Dunbar has suggested a method of agglutinating the cholera vibrios directly in the feces. Several shreds of mucus are taken from the stool, and each shred is rubbed up in a drop of peptone water on a cover glass. To some of the cover-glass preparations is added a drop of a 1:50 dilution of normal rabbit serum, and to others is added a drop of a 1:500 dilution of a high titer cholera-agglutinating serum. In the preparations to which the cholera-agglutinating serum has been added, the cholera vibrios soon lose their motility, while in the controls, to which the normal serum has been added, the cholera vibrios are actively motile. This method is of value in cases where the cholera vibrios are present in almost pure culture; but a negative result is not to be considered as of diagnostic value.

Cultures.—The most satisfactory method of bacteriological diagnosis is to make cultures from the stool or intestinal contents, and to study the organisms in those cultures: cultures must always be made, even when the other methods are used. A shred of mucus is placed in a tube of peptone water, and is rubbed up on the side of the tube. The peptone water tubes are incubated for six to eight hours, and then a loopful of fluid from the surface of the tube is examined by smearing it on a slide, drying with

gentle heat, staining with a 1 : 9 dilution of carbolfuchsin, and examining under the microscope. From any tubes which show comma-shaped bacilli, agar plates are streaked, and are incubated for twelve hours. Agar plates may also be streaked directly from the feces, at the time the peptone water tubes are inoculated.

For the plates, 3 per cent. agar must be used, and the surface must be well dried by inverting the plates in the incubator, with the lid off, for half an hour before streaking them. A glass rod, a platinum loop, or a pledget of cotton can be used for streaking the material on the plates; the requirement being that there shall be isolated colonies on the plates. The vibrio colony has a very characteristic appearance on the agar plate: it appears as a pale disk, which is slightly opalescent and iridescent by transmitted light. At times the colonies are clear and transparent; at other times they may have a yellowish-white appearance, somewhat like colonies of the colon bacillus.

A microscopic slide agglutination is made from the characteristic colonies on the agar plates. A loopful of a 1 : 500 dilution of a high titer cholera-agglutinating serum is placed on a slide, and with a platinum needle a small amount of material from one of the characteristic colonies is rubbed up in the loopful of serum. Cholera vibrios will be instantly agglutinated to a curdy appearance, while the cholera-like vibrios and other bacteria will rub up to a milky emulsion. The diagnosis is completed by staining some of the material from the colonies which agglutinate in the cholera serum, and by streaking material from the same colonies on agar tubes and studying them further, especially by testing their agglutinability in a cholera agglutinating serum and by testing them by the Pfeiffer phenomenon. In a large number of cases in Manila, in which a diagnosis of cholera was made from the microscopic slide agglutination, we never found the method in error when the organism was carried through further tests. McLaughlin and Whitmore also studied a number of cholera-like vibrios, isolated from various sources, including the stools of persons in the cholera-infected districts; and they were never able to make any of these cholera-like vibrios take on the characteristics of cholera vibrios, and were never able to show that the microscopic slide agglutination method had failed to differentiate a cholera vibrio from a cholera-like vibrio.

In the Philippines, where it was often necessary to send material some distance to the laboratory, agar slants with a sterile swab were sent out to the various health officers. A swab of fecal material, either from a stool, or from the rectum in case the patient was found dead, was spread over the surface of the agar in the tube, and the tube was sent in to the laboratory. We succeeded in isolating cholera vibrios from such tubes when they had been as long as fifteen days in transit to the laboratory, under the ordinary temperature conditions in the tropics. Panganiban and Schöbl have tested various methods of preserving cholera vibrios in stools. They find that salt solution, in concentration from 0.5 to 5 per cent., will preserve the vibrios for five weeks: stronger solutions of salt were not satisfactory. Bile, as suggested by Ottolenghi, was more satis-

factory than salt solution. When mixed with a salt solution suspension of feces, so the final mixture contained 25 to 50 per cent. of bile, the vibrios were preserved for seven weeks. It is advisable to emulsify the stool in bile or physiological saline solution for sending to a distant laboratory.

Culture Media.—While peptone solution is satisfactory as an enriching medium in general, where the cholera vibrios are scarce some of the other enriching media will give better results. One of the best of these enriching media is Goldberger's egg-peptone solution, which is made as follows: an egg is shaken up with an equal volume of water; this mixture is mixed with an equal volume of a 5 per cent. solution of sodium carbonate, and the mixture is steamed in the Arnold for one hour. One part of this egg mixture is added to nine parts of peptone solution, and the mixture is filtered and sterilized. The egg-peptone solution is used in the same way as is the ordinary peptone solution.

Instead of ordinary agar for plating, a number of selective media have been developed for the detection of the cholera vibrio, all of these media depending for their usefulness on the fact that the cholera vibrio grows well on a medium of such alkalinity that the common intestinal bacteria do not grow on it.

Dieudonne's alkaline blood medium is one of the most commonly used of these selective media. Equal volumes of defibrinated blood and normal potassium hydrate solution are mixed, and the mixture is sterilized in the autoclave. Seven parts of ordinary agar, neutral to litmus, are mixed with three parts of this alkaline blood, and plates are poured. Before use the plates are allowed to stand at 37° C. for twenty-four hours, or at 60° C. for five minutes. The plates must stand for twenty-four hours before they can be used. The reason for this is that a large amount of ammonia is formed from the alkaline blood mixture, and this inhibits the growth of the cholera vibrios. On this medium, the cholera vibrios and cholera-like vibrios grow well, while the colon bacillus and other bacteria are inhibited. In twelve to twenty-four hours the vibrios appear as large, round colonies, light gray in transmitted light and hyaline in reflected light. A disadvantage of Dieudonne's medium is that the cholera colonies grown on this medium are sometimes difficult to emulsify, and this interferes with the agglutination.

Goldberger's medium for plating is prepared as follows: Ordinary meat infusion is neutralized to litmus with 5.3 per cent. solution of anhydrous sodium carbonate, and then 2.5 c.c. of the 5.3 per cent. sodium carbonate solution is added to each 100 c.c. of the medium; the medium is heated in the Arnold for half an hour and filtered. One part of this alkaline meat infusion agar is mixed with three parts of ordinary 3 per cent. agar, and plates are poured from the mixture. The plates are dried and used in the regular way.

Aronson's medium has been highly recommended. Aronson combined sugars to favor the growth of the cholera vibrio, and the color reaction of Endo's medium, in an alkaline medium to prevent the growth of the ordinary intestinal bacteria. To 100 c.c. of ordinary 3.5

per cent. agar add 6 c.c. of a 10 per cent. solution of sodium carbonate, and steam for 10 to 15 minutes in the Arnold. While it is still hot, add 5 c.c. of a 20 per cent. solution of cane sugar (saccharose), 5 c.c. of a 20 per cent. solution of dextrin, 0.4 c.c. of a saturated alcoholic solution of basic fuchsin, and 2 c.c. of a 10 per cent. solution of sodium sulphite. The solutions of the sugars are sterilized before adding, and the medium is not sterilized after the sugar solutions are added. When completed, the reaction of the medium should be about —3 per cent. to phenolphthalein. In the preparation of the medium, a precipitate forms. This precipitate settles rapidly, and from the supernatant fluid plates are poured, and dried at 50° C. for half an hour before using. A large amount of suspected fecal material can be inoculated directly onto the plate, as the colon bacillus does not grow. Cholera vibrios develop in 10 to 12 hours, and begin to turn red in 15 to 20 hours. The vibrios emulsify well; and the large colonies furnish sufficient material for agglutination and microscopical examination, and for inoculation of plates.

While the colon bacillus does not grow on Aronson's medium, it remains alive and may appear in transplants from cholera vibrio colonies from the plate. For this reason, in order to get the cholera vibrio in pure culture from the Aronson plate, it is necessary to streak from the colony onto a plain agar plate. After 24 hours the colon bacillus may begin to split the sugars in Aronson's medium, and so obscure the colonies of the cholera vibrio.

Volpino found that the cholera vibrios did not always produce red colonies on Aronson's medium when incubated over night. He then examines all colonies that develop on the plate, by agglutination and microscopically. Volpino considers that ordinary agar, of the alkalinity of Aronson's medium, is almost as good as Aronson's medium for rapid diagnosis. It would seem advisable to add the sugars to the ordinary agar in order to hasten the growth of the cholera vibrios.

These selective media make it possible to detect cholera vibrios, even when they are present in small number in the stool, as it is possible to use a large amount of the fecal material for the inoculation. Cholera-like vibrios grow on these selective media; and it is very important that the organisms which develop are tested by agglutination and further culture, in order to determine the nature of the colonies.

The *cholera-red reaction* may be of value in the bacteriological diagnosis; but this reaction very frequently fails unless the culture of the cholera vibrio is pure. It may be tried on the first or second peptone culture, after about 18 hours' incubation; but it is advisable to make the test on a peptone tube inoculated from one of the characteristic colonies on an agar plate. This reaction depends on the fact that the cholera vibrio produces both indol and nitrites in peptone solution and, when a few drops of sulphuric acid are added to the peptone-solution culture, a cherry red color is produced.

Gelatin cultures of the cholera vibrio do not give any information that cannot be obtained other ways; and, since gelatin is difficult to

work with, especially in the tropics, it is not advisable to use gelatin cultures.

Complications and Sequelæ.—Since acute nephritis develops in practically all severe cases that survive to the stage of reaction, this condition can hardly be classed as a complication. But the frequency and danger of this condition must be borne in mind. Most of the complications occur during the stage of reaction, and are due to secondary infection. Lobar pneumonia, and diphtheritic inflammation of the mucous membranes of the gastro-intestinal tract are fairly common. Pregnant women usually abort, due to the action of the cholera toxin on the uterine muscle during the cramps. Suppurative parotitis, local suppurations, and gangrene, especially about the genitalia, may occur. Hematuria rarely occurs. If the patient survives the acute nephritis, there is apparently complete recovery of the kidney. Edema rarely occurs in the acute nephritis.

Clinical Varieties.—The typical case of cholera, *cholera gravis,* with the stages of evacuation, collapse and reaction, has been described above.

Cholerine.—Cholerine is a milder form of the disease, in which there is active diarrhea; but there is no collapse, and the urine is not suppressed.

Cholera Sicca.—Cholera sicca is a severe form of the disease, in which the patient dies of the intoxication before diarrhea and vomiting have set in. This form of the disease is more apt to occur in debilitated persons. In the Philippines we saw cases of cholera sicca in persons who had recently had an attack of dengue fever; and there was a case in a soldier who showed, on postmortem examination, extensive tuberculous lesions in the lungs. On postmortem examination, the intestine may be filled with liquid, from which the cholera vibrio is isolated.

At times the clinical picture of cholera is very irregular, and, especially in children, the meningeal symptoms may dominate the picture.

The cases of *cholera carriers,* persons who are not ill but are passing virulent cholera vibrios in their stools, are of great importance. These persons may pass the vibrios in the stools for as long as sixty days; and, in addition to the danger of spreading the infection to others, these carriers are in danger of developing cholera themselves if they develop any gastro-intestinal disturbance or are given a cathartic.

Treatment.—PROPHYLAXIS.—In any infectious disease there are at least three links in the chain of circumstances which makes it possible for the disease to spread: (1) a source of infection, (2) a mode of transmission, and (3) a susceptible population. A consideration of the epidemiology of a particular disease will indicate where it is best to attack this chain in order to break it.

Prophylactic methods against cholera may be divided into *public* and *personal.*

The *public measures* are generally pretty definitely laid down in the laws of different countries; and consist in control of the source of infection by the **detection and isolation of cases and carriers,** and the

control of the mode of transmission by **prevention of pollution of water** and food, and the furnishing of a suitable water supply. Attempts to control the third link in the chain, a susceptible population, consists in **vaccination** with a cholera vaccine.

When a case of suspected cholera occurs, it must be isolated at once, and a bacteriological diagnosis made as soon as possible. If the case is determined to be cholera, it is important to discover the source of infection, and to prevent the spread of the infection. All contacts must be isolated until their stools are examined for the cholera vibrio. Any contact found carrying cholera vibrios must be isolated, the same as a case of cholera, until the stools are free from vibrios. **All discharges** from cases, carriers, and suspected contacts **must be disinfected,** and all linen and bedding must be disinfected. The stools are mixed with an equal volume of 5 per cent. cresol solution, and allowed to stand for at least an hour: a 5 per cent. mixture of chlorinated lime may be used in the same way as the cresol solution. Bedding and linen can be disinfected by immersion in a 2.5 per cent. solution of **cresol.** All food containers should be boiled. As the cholera vibrio does not stand drying, terminal disinfection consists in washing the floor and walls with a 2.5 per cent. solution of cresol.

All cases and carriers must be kept in isolation until the stools are negative for cholera vibrios on three successive days.

It is not necessary to quarantine ships, or to prevent travel; but all persons traveling, by ship or otherwise, if coming from a cholera infected locality, must be detained long enough to make a bacteriological examination of the stools for cholera vibrios. This examination can be completed usually in twenty-four hours, and always in forty-eight hours. Simple detention for five days is not sufficient, as cholera carriers can be detected only by examination of the stools for cholera vibrios.

In the same way, it is not advisable to undertake any general quarantine on food supplies, as the advantages do not offset the disadvantages. It is necessary to investigate the source of the food supply, and to take proper precautions against any article of food that seems to be carrying infection. Pottevin considers that foodstuffs are not dangerous in the spread of cholera where several days elapse between the time the food leaves a cholera district and the time it arrives in a new district; but, if the time is short, the food may be a real danger. As water is the common medium by which the infection is spread, it is necessary to **guard carefully against any contamination of the water supply.** All vegetables which are eaten uncooked must be guarded against contamination; and it is best to urge the people to avoid as much as possible the use of uncooked food of any kind. An active campaign must be waged against flies.

Personal prophylaxis is very important, and consists in **drinking** only **boiled water**; in **eating no uncooked food,** especially fresh vegetables; in carefully washing the hands after going to the toilet, and before eating; avoiding all foods which lead to gastro-intestinal irritation; prompt treatment of gastro-intestinal disturbances; an active **campaign against**

flies, including the protection of all food from flies; avoiding debilitating influences of any kind; and avoiding bad ventilation and overcrowding.

Vaccination is the principal method of attack on the third link in the chain. While the healthy person has considerable resistance to infection with the cholera vibrio, due partly to the acid condition of the gastric juice and partly to the resistance of the intestinal mucosa to invasion by the cholera vibrio, it is only too evident that this resistance is not enough to protect in a great percentage of persons. Since it appears that there is at least a temporary immunity following an attack of cholera, and it is possible to demonstrate antibodies in the serum of lower animals and men after vaccination with a cholera vaccine, attempts have been made to specifically raise the resistance of persons to the cholera vibrio by **vaccination.**

1. *Living cultures* of the cholera vibrio have been used in a vaccine. Ferran was the first to try vaccination as a prophylactic against cholera, and he used living virulent cultures, recently isolated from cases. Gamaleia used living attenuated cultures. Haffkine carried out vaccination on a large scale in India. His first vaccinations were with a living attenuated culture, followed by a virulent culture: later, he used only the virulent culture. The general results of Haffkine's vaccination are that the incidence of cholera is lowered among the vaccinated; but the mortality is nearly as high in cholera cases among the vaccinated as among the unvaccinated.

2. *Killed cultures* are more convenient than living cultures to use in a vaccine. Gamaleia also used killed cultures in vaccination. Kolle used a vaccine made by growing the cholera vibrios on agar, suspending them in saline solution, heating to 58° C. for one hour, and adding 0.5 per cent. phenol to the suspension. The dose was 2 mg., moist weight, of the bacterial mass as scraped from the agar.

Murata, in Japan, tried a vaccine prepared according to the Kolle method in 1902. Using the dose of 2 mg., moist weight, of the bacterial mass, he reduced the incidence and the mortality of cholera among the vaccinated. When he increased the dose to 4 mg., moist weight, of the bacterial mass, there were no more cases of cholera among the vaccinated.

3. Various vaccines have been prepared from *filtrates* from cholera cultures, and from various *autolysates* and *extracts* of the cholera vibrio. Bartarelli prepared an autolysate by suspending agar cultures of the cholera vibrio in saline solution, heating to 60° C. for one hour, allowing it to autolyse in the incubator at 37° C. for two days, and filtering. The filtrate is the vaccine, and Bartarelli demonstrated antibody production in the serum of rabbits vaccinated with this vaccine. Strong has used such an autolysate in the vaccination of a considerable number of people, and there is considerable evidence that such an autolysate gives protection against cholera.

It appears that a strain of the cholera vibrio of low virulence is as satisfactory for a vaccine as is a strain of high virulence; but it is necessary to choose a strain that gives good antibody production. Some

strains of the cholera vibrio do not give good antibody production regardless of whether the virulence is high or low.

Cholera vaccination has been tried out rather extensively in the recent war, and the results have been fairly satisfactory. The indication is that there is good protection for three months; but that the protection has disappeared by the end of six months, and revaccination must be practiced by the end of that time. In general, the vaccine used has been heat-killed cholera vibrios suspended in saline solution. The United States Army has used experimentally heat-killed cholera vibrios suspended in oil in the form of a single dose lipovaccine.

Arnaud reports on cholera vaccination in the Greek army in the second Balkan war: 93,868 men were vaccinated, and 14,332 were not vaccinated. Of the vaccinated, 72,652 received two doses of vaccine; 21,216 received one dose of vaccine. The incidence of cholera in the unvaccinated was 5.75 per cent.; in those who had one dose of vaccine it was 3.12 per cent.; and in those who had two doses of vaccine it was 0.43 per cent. Similar results are reported by von Roemer in Batavia, and by Kersten on the vaccination of German troops in a Turkish town in 1917. In von Roemer's work, the mortality was not reduced among the vaccinated who contracted cholera.

Generally the local and general reaction following cholera vaccination is very slight. Simicek saw a case of pemphigoid eruption in a man, following the second injection of cholera vaccine, and he considered it due to hypersensitiveness.

The use of anticholera serum has not given any satisfaction in prophylaxis.

CURATIVE TREATMENT.—In treating a case of cholera, it is to be borne in mind that the patient may die in the stage of collapse, that he may die of uremia following the stage of reaction, and that there is danger of relapse as a result of errors of diet in the first few days of convalescence.

The patient is to remain strictly in **bed,** and provision is to be made at once to disinfect the stools and vomitus. Vomiting makes it impossible for the patient to take any nourishment, and it usually makes it impossible to give any medicine by mouth. **Cracked ice** will to some extent relieve the vomiting and the great thirst. **Morphin** may be given to relieve the vomiting and the muscular cramps, but it is generally agreed that morphin is to be used sparingly or not at all.

The room is to be airy and well ventilated; but the patient is to be kept warm, and external heat applied when collapse sets in.

Rogers advocates the use of **permanganates,** on account of their property of destroying toxins. The patient is given all he can drink of **calcium permanganate water** (1 to 6 grains [0.065 to 0.4 gram] to the pint); and is given a 2-grain pill (0.13 gram) of **potassium permanganate** every fifteen minutes for two hours, then every half hour until the stools become less copious and are green and more fecal in character: this occurs in twelve to twenty-four hours. Then six to eight pills are administered during twenty-four hours. The pills are made with

vaselin or kaolin, and are coated with a mixture of five parts of sandarach varnish and one part of salol; or they may be put in gelatin capsules, the junction of the halves of the capsule sealed with gelatin, and exposed to formaldehyd vapor until the gelatin is keratinized. Rogers uses atropin sulphate, in the dose of 1/100 grain, hypodermically, night and morning; and he finds that it greatly decreases the danger of collapse.

Stumpf recommended the use of **kaolin** in the treatment of cholera; and Arneth and Kuhne report excellent results from its use in the recent war. The kaolin is used as a prophylactic by putting it in the drinking water. In treatment, the patient is given the suspension to drink; and the suspension is injected into the bowel. Kuhne reports that with the kaolin treatment, the mortality from cholera was reduced from 45 per cent. to 2 or 3 per cent., in an extensive experience in Serbia. He finds it useful in prophylaxis and treatment of all forms of diarrhea. Arneth advises the usual methods of treatment, in addition to the use of kaolin.

There is general agreement that the loss of fluid and the acidosis must be combated early, as the two indications are to tide the patient over the collapse stage and to prevent his dying of uremia after the stage of reaction. These indications are met by the intravenous injection of fluid.

In the collapse stage, when the blood-pressure falls below 70 mm. of mercury, it is necessary to give an *intravenous injection*. Rogers uses the specific gravity of the blood as a guide in determining when intravenous injection is necessary. To determine the specific gravity of the blood, he uses mixtures of glycerin and water of specific gravities varying from 1.048 to 1.070. A drop of blood is placed in these glycerin-water mixtures until it is determined which mixture is the same specific gravity as the blood. If the specific gravity of the blood is over 1.062, at least a liter of fluid is injected; if the specific gravity is 1.066, at least two liters of fluid is injected. The temperature of the injected fluid is varied according to the rectal temperature: if the rectal temperature is about normal, the fluid is run in at a temperature of about 37.8° C. (100° F.); if the rectal temperature is below normal, the fluid is warmed to 38.9° to 40° C. (102° to 104° F.); if the rectal temperature is high, the fluid is run in at a temperature below the normal temperature of the body.

Normal saline solution is satisfactory for making up the loss of fluid from the body; but Rogers recommends the use of a hypertonic solution containing 120 grains (7.8 grams) of sodium chlorid, 6 grains (0.4 gram) of potassium chlorid, and 4 grains (0.26 gram) of calcium chlorid to the pint of water.

Sellards has shown that intravenous injection of a solution of **sodium bicarbonate** has great advantage over the injection of physiological or hypertonic saline solution, as it not only makes up the loss of fluid, but also meets the great requirement of overcoming the acidosis and relieving the anuria.

Sellards and Shaklee used the following solution in the stage of collapse:

Sodium chlorid	0.4	per cent.
Potassium chlorid	0.042	per cent.
Sodium bicarbonate	0.5	per cent.

They gave injections of two liters (4.22 pints) of this solution intravenously, with an interval varying from 4 to 29 hours. At times they gave four liters (8.5 pints) for the first injection; and they occupied 15 to 30 minutes in running the solution into the vein. Though they started the injections early, the urine remained acid until the stage of reaction set in—after as many as six injections; and the urinary secretion never started until after the reaction set in. The injections are repeated when the pulse becomes weak and rapid and the blood pressure falls to 50-70 mm. of mercury. The blood-pressure rises to normal or above in one to three hours after the injection.

In the stage of reaction they used a 1.5 per cent. solution of sodium bicarbonate without the addition of any other salt, giving two liters of the solution. In the stage of reaction, it is necessary to watch the reaction of the urine, as it is necessary to reduce the amount of sodium bicarbonate injected, as soon as the urine becomes alkaline.

The use of the alkaline solution may also produce muscular twitchings and cramps; possibly as a result of the precipitation of the calcium salts by the sodium carbonate.

The sodium bicarbonate solution, given early in the disease, prevented death from uremia; while, when given late in the disease, the course was modified, and the anuria was at times relieved, but the final outcome of the disease was not changed.

It is advisable to use sodium bicarbonate solution, as sodium carbonate solution is hemolytic; and Sellards found that it produced convulsions in one case. The sterilization of the sodium bicarbonate is somewhat difficult, as the salt changes to the carbonate during sterilization. In the solution used for collapse, Sellards and Shaklee added the sodium bicarbonate to the sterile solution, just before injection.

To sterilize the sodium bicarbonate solution, fill strong, narrow-mouthed bottles as full as possible with the solution, leaving only spaces for expansion of the fluid when hot; tie tightly-fitting stoppers in place. It is an advantage to sterilize the solutions in an atmosphere of carbon dioxid; this can be done by placing a dish of boiling water in the bottom of the autoclave and, just before closing the autoclave, adding a handful of sodium bicarbonate to the dish of water, then closing the door and leaving the vent open at the top until the carbon dioxid has driven the air out. The autoclave is tightly closed during the sterilization—7 pounds for 45 minutes—and is cooled down to room temperature before opening. Such solutions do not have over three per cent. of sodium bicarbonate changed to carbonate; and they keep well if tightly stoppered. The solution may be sterilized in the

ordinary way, and a current of carbon dioxid passed through it to convert the carbonate into the bicarbonate.

While there is possibility that attempt should be made to replace the calcium lost from the body, it is not advisable to include the calcium in the alkaline solution, as the carbonate formed in the sterilization precipitates it out.

Rogers now includes intravenous injections of sodium bicarbonate in his treatment of cholera; and reports the reduction of the mortality due to uremia from 11.1 per cent. without alkalis to 3.25 per cent. with alkalis.

Goff and Denney used continuous proctoclysis in the treatment of cholera; and they report that this method of treatment induced evacuation in the "sicca" cases, and encouraged kidney elimination.

Segale showed that the glycogen disappeared from the blood and there was a mere trace left in the liver in cholera. The carbohydrate metabolism does not appear to be disturbed in cholera; and it is not possible to introduce nourishment through the gastro-intestinal tract during the stage of collapse. This, with the good results from intravenous injections of glucose in other acute infectious diseases, would indicate the advisability of its use in cholera. Kausch uses a 5 per cent. solution of glucose for subcutaneous injection, and a 10 per cent. solution for intravenous injection, giving 1000 c.c. twice a day, for nutritive purposes. Strauss advises a 4.5 per cent. solution intravenously. Gaertner adds glucose to the saline solution given intravenously. All three agree that the results are good; there being increased flow of urine, with possible washing out of toxins.

The use of **anticholera serum** has not given very encouraging results. If serum is to be used at all, it must be given early, and be given intravenously in doses of 50 to 100 c.c., with an interval of eight to twelve hours.

No food can be given during the stage of collapse; but as soon as the vomiting ceases, the patient may take albumin water, broths, milk diluted with soda water and thin gruels. It is necessary to be very careful in increasing the diet, as there is danger of bringing on a relapse with all the dangers of the original attack.

Prognosis.—The average mortality is about 50 per cent., varying from 30 to 80 per cent.; about 35 per cent. of the cases dying in collapse, and about 15 per cent. of the cases dying of uremia. The mortality is usually higher at the beginning of an epidemic. Recent acute illness, or debility of any kind, kidney disease, intemperance, and youth or old age, make for a bad prognosis. If the collapse sets in early, the prognosis is bad.

Pathology.—Macroscopic.—When the patient dies in collapse, the skin is dry and wrinkled, and the fingernails are cyanotic. Rigor mortis is early and marked; so a limb may be moved, or the head may be turned from one side to the other. All of the tissues are dry, and the muscles are dark red in color. The appearance in the peritoneal cavity is striking. The omentum is shrunken and dry, and the peri-

toneum is dull, dry and sticky. The ileum is purplish-pink or rose-red in color, while the colon is normal in color; this appearance of the intestine is almost characteristic of cholera. The liver, spleen and lungs are shrunken and dry; and the heart contains dark, thick blood. The intestines are filled with rice-water material; the lymphoid follicles in the ileum are prominent; the blood-vessels about the follicles are injected, and there may be hemorrhages about the follicles. The liver is congested; the kidneys are swollen, congested, and may be ecchymotic.

The gall-bladder frequently shows a catarrhal inflammation; but the inflammation may be hemorrhagic or necrotic. It is probable that the more severe inflammation of the gall-bladder is due to mixed infection with other bacteria.

There is surprisingly small evidence of gross pathological change in cases that have died as a result of a pure infection with the cholera vibrio.

Microscopic.—The epithelium of the intestinal mucosa is necrotic, and the cholera vibrios have penetrated deeply into the mucosa or even into the submucosa. There is generally little parenchymatous change in the organs; but the liver, and especially the kidneys, show early cloudy swelling. The kidneys show necrosis of the epithelial cells, and the tubules are blocked with granular debris.

When the process continues longer, the parenchymatous changes in the kidneys are especially marked, the epithelium showing necrosis and fatty degeneration. The lungs may show lobar pneumonia as a complication.

When the patient dies in the condition of cholera typhoid, the change in the intestinal mucosa may be marked, amounting to a necrosis of the mucosa: this change is especially marked just above the ileocecal valve. This change is due to secondary invasion by other bacteria, and the cholera vibrio is not generally found in such lesions.

Greig has studied the lesions in the gall-bladder, and in different organs. In the gall-bladder, the epithelium is gone, and the wall is thickened and infiltrated with round cells, with evidence of hemorrhagic infiltration. The cholera vibrios are found in areas in the liver, near the gall-bladder; and the liver cells are necrotic in these areas. In a congested and edematous lower lobe of the lung the alveoli were filled with cellular exudate, and congestion in the alveolar walls. He found cholera vibrios in the spaces of a lymph gland near the small intestine, deep in the wall of the gall-bladder, in the liver near the gall-bladder, in the exudate in the pulmonary alveoli, and in the submucosa of the urinary bladder. Schöbl found cholera vibrios in infiltrated and necrotic areas in the liver of his experimental animals, after inoculation of a virulent culture of the vibrio into the gall-bladder.

History.—Cholera has been known in India from ancient times, and Susruta described an epidemic in the seventh century, A. D. It appears to have been endemic in the Delta of the Ganges, from where it spread as repeated epidemics over India; and there were numerous epidemics

from the fifteenth to the seventeenth century. But it does not appear that cholera was known outside India until the Indian epidemic of 1817, which spread through Eastern Asia, reached Africa in 1819 and 1820, and reached Russia in 1823.

The next epidemic started in India in 1826, and spread through Asia to Africa and all of Europe. The disease reached the United States and Canada in 1832, and extended to Mexico, Cuba and the northern part of South America in 1833 and 1834.

The next epidemic started in India in 1846, and spread through Asia, Africa and all of Europe. It reached the United States in 1848, and extended to Canada, Mexico, Central and South America and the West Indies in the following years, up to 1862.

The fourth epidemic, starting in India in 1863, spread through Asia, Africa, and Europe; and reached the West Indies and Ward's Island in 1865, spreading over North, Central and South America during the next years, up to 1873.

The fifth epidemic, starting in India in 1883, extended through Asia, Africa and Europe, and reached South America in 1885 to 1888. In 1893 it was again introduced into the United States and Brazil, extending to Argentine and Uruguay in 1894 and 1895. This epidemic continues throughout Asia and parts of Europe. The disease has been repeatedly brought to the port of New York, notably in 1911; but it has not been able to enter the United States since 1893, and it has not been able to gain a foothold since 1873.

Some parts of the world have remained free from cholera. These are usually cold regions, or islands to which the disease is less likely to be brought. The disease has not yet spread to tropical and southern Africa.

Geographical Distribution.—While the Delta of the Ganges seems to have been the home of cholera, and earlier epidemics are traceable to that origin, it appears that now the disease has become endemic in a number of other regions. The pilgrims, returning from Mecca, rather commonly carry the infection with them to their home country. The disease seems to be endemic in Persia, through India, Indo-China, Java and the Philippine Islands. It is endemic in the Balkans, and has been quite prevalent there during the recent war.

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CHAPTER XXII

LEPROSY

By George W. McCoy, M.D.

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Etiology.—Predisposing Causes.—While leprosy is, or has been in the past, a disease of all lands and of all climates, it is to-day confined chiefly to the tropics and subtropics, and to this extent *climate* may be considered a predisposing cause.

Age.—The disease by preference attacks those in youth or in early adult life; one-third of the cases occur in the second decade, and over one-half between the ages of ten and twenty-five years. It is very exceptional to have a case develop in a person beyond fifty or under six. The writer has seen one case in a child of nineteen months, but cases under five years are so rare as to be noteworthy.

Sex.—A remarkable and unexplained fact is the preponderance of cases among males. It holds true the world over that there are nearly two male lepers for each female leper. Various theories have been advanced to explain this remarkable fact, but none is convincing. Perhaps the simplest one, and one as plausible as any, is the greater opportunity for exposure to infection among men.

Race.—Various races, particularly South Sea Islanders and Orientals, have been regarded as particularly susceptible, but the writer is inclined to think that race *per se* is not a factor of much importance, and that given equal opportunities for infection, under identical conditions, there is little or no difference in susceptibility.

Heredity.—The belief in heredity as a predisposing, or, indeed, determining factor in the production of leprosy goes back to biblical times, but it has no substantial foundation. Undoubtedly, leprosy often does occur among children of lepers, but it also occurs among others who come in contact with it. In the Hawaiian experience, the disease is *apparently* acquired about as often from a brother or sister as from the father or the mother. Careful studies in the Hawaiian focus show that when children of lepers are removed from the leprous environment

at once after birth, the chances of the development of the disease are practically nil.

EXCITING CAUSE: THE ORGANISM.—We accept the acid-fast organism first described by Hansen as the cause of leprosy, but we are without absolute proof of this. The bacillus is constantly associated with the lesions of leprosy in more or less abundance, but as there is some doubt as to whether it has been cultivated, and as the evidence that the disease has been reproduced by the cultures that have been isolated is of the flimsiest sort, clear evidence of the etiological relation is lacking.

Hansen's bacillus is an acid-fast organism which bears considerable resemblance to the tubercle bacillus in size, shape and staining reactions. It is usually found in greater numbers than the latter organism and, as it appears in smear preparations from tissues, is smaller, and is often arranged in bundles. Elaborate differential staining reactions have been described, but these are not trustworthy and may lead to confusion. The organism, in some respects, bears a close relation to the non-pathogenic acid-fast organisms such as Karlinski's bacillus of nasal secretion, the margarin bacillus and the grass bacillus.

Numerous observers have, by means of special procedures, cultivated acid-fast organisms, and branching organisms having an acid-fast stage, from leprous lesions. The only ones that need be mentioned are the streptothrix, grown first by Kedrowsky and later by Bayon, and the bacillus grown first by Clegg. While these investigators thought their cultures represented Hansen's bacillus, they were unable to induce leprosy in laboratory animals by the inoculation of the cultures. The serological reactions of these organisms and of extracts made from them do not throw any significant light on their relationship to the disease.

Experimental Inoculation.—Many investigators have attempted to reproduce leprosy in laboratory animals by the inoculation of leprous tissue and, while there are to be found in the literature numerous reports of success in this direction, a careful scrutiny of the experimental data leaves one with the clear impression that the evidence is insufficient to justify the conclusion that leprosy has ever been transmitted to laboratory animals, and a very considerable experience on the part of the writer confirms this. This is true, not only for the animals ordinarily used in experimental work, guinea pigs, rabbits, rats and mice, but for monkeys and the higher apes as well. Not only has it proven impossible to infect laboratory animals, but of a large number of experiments on man, but one can be considered as possibly successful, and there is some doubt as to that one. The possible exception is the case of the convict Keanu, a Hawaiian, who was inoculated with leprous tissue by Arning. Two years after this inoculation the subject of the experiment developed leprosy and from this he eventually died. While doubt is thrown on the validity of the experiment by the fact that Keanu lived in a country in which the chances for acquiring leprosy in the natural manner, whatever that may be, were notoriously good, a careful study of the record of the case leaves one with the impression that Arning's experiment probably was successful. There is no satisfactory explana-

tion for the unsuccessful human inoculations, of which there are a considerable number of reports scattered through the literature.

Modes of Conveyance.—We do not know precisely how the causative organism enters the body, but we do know that in some manner the bacilli pass from the sick to the well and in a small proportion of cases cause the disease in a new victim.

Various theories have been advanced to account for transmission, such as infected food, respiratory infection, sexual contact, insect transmission, but proof is lacking that any of these is the method of conveyance of the disease. We may consider it a contact disease, and beyond that, in the present state of our knowledge, it is impossible to go.

It is a remarkable fact that even given the best of opportunity of transmission, for example, when the clean live with the infected, sharing the same bed and board, and when no precautions whatever are taken to avoid infection not over about five per cent. of adults are susceptible.

Symptomatology.—Period of Incubation.—This varies greatly, but it is customary to say that the average period is about two years. There are well-authenticated cases in which the time that elapsed between exposure to the infection and the development of symptoms has been as short as two months; and there are others in which ten years or more have elapsed. During this period, usually, there are no noteworthy symptoms but there may occur one or more febrile attacks, which, usually, are not regarded as of any significance until cutaneous or nerve lesions draw attention to the underlying condition. Perhaps the most striking thing about the onset and development of leprosy is the extreme slowness that ordinarily characterizes the development and evolution of the disease. The case is distinctly exceptional in which noteworthy changes occur in periods of weeks, while usually months are required to show any distinct alterations, and often during a period of years the patient will remain apparently stationary so far as signs and symptoms are concerned.

Clinical Manifestations of Types.—For convenience, it is desirable to consider the clinical manifestations of leprosy as falling under two types, depending on the prominence of, or the presence, exclusively, of cutaneous or nerve symptoms. The former is often called "tubercular leprosy," though "nodular" is a term to be preferred; and the latter is designated, usually, as the "anesthetic" type, though "nerve leprosy" is a more accurate and descriptive designation. While there are many cases that may with certainty be grouped under these headings, there are many others showing manifestations of both types and these are usually indicated by the term "mixed."

(*a*) *Nodular Leprosy.—The Skin Lesions.*—In this form of the disease the patient's or the physician's attention is usually attracted to red, reddish-brown or fawn-colored patches at one or more points. The skin is found to be slightly thickened, and it may or may not be the site of itching or of burning sensations. These spots are most often found on the exposed parts of the body, though they may also occur on any covered portion. The bronzed or fawn colored patches are of the greatest

diagnostic importance, as they are simulated by few conditions. The writer has seen a case in which the body was free from lesions beyond a fawn-colored, very slightly thickened area on the cheek, not more than one cm. in diameter, and a similar patch on the forearm, yet a clinical diagnosis of leprosy was made with considerable confidence, and this was verified by microscopical examination. These spots resemble closely the chamois-colored patches of tinea versicolor, but the microscopical examination at once shows the nature of the lesion.

The early lesions may remain a few weeks, disappear, to be replaced by others, or they may be permanent. Sometimes, they assume a ringworm appearance with a clear center; indeed they are sometimes mistaken for ringworm. These early lesions are often associated with some general systemic disturbance, but just as frequently the general health remains unaffected. These early spots are not anesthetic.

After a period that may vary from weeks to years, but one that usually is limited by months, the patches become distinctly nodular, and nodules may appear at points that have not been the site of the earlier, more superficial lesions. The nodules vary from the size of a pea to masses that can scarcely be covered by a man's hand, but, usually, they range from one cm. to five cm. in diameter. Rarely, the body may be covered with small nodules, each one about the size of a pea, and giving an appearance suggestive of a rather scanty eruption of smallpox.

The nodules may be scattered generally over the body, but the face and the backs of the hands and feet are the commonest sites. They are very commonly present on the lobes of the ears, which the experienced examiner never fails to scrutinize most carefully. The cheeks are also favorite sites, and early lesions are often found on the nose, forehead and chin. It is worth noting here that the scalp is involved rarely. In a fairly extensive experience, the writer has seen but two cases in which lesions were found on the scalp and these were near the hair margin.

The lesions, as they progress, throw the skin into creases and ridges, giving the face the "leonine" appearance which, while undeniably characteristic, is a relatively late manifestation of the disease; i. e., late in the evolution of the lesions though not necessarily late so far as the life of the patient is concerned. These extensive skin lesions may be accompanied by loss of flesh and strength, but often they have no apparent effect upon the general health of the patient. The writer has seen many lepers with typical leonine facies who were able to do a full day's work. The nodular areas are often the seat of ulcerative processes which may start spontaneously or from a slight traumatism.

Subjective Symptoms.—Febrile attacks occasionally occur during the course of nodular leprosy. These may, or may not, be associated with the development of new nodules. They are usually accompanied by sweating, loss of flesh and weakness.

The Lymphatic Glands.—These, in nodular leprosy, are often swollen but painless. The enlarged gland feels elastic and usually does not exceed the last joint of the little finger in size, but occasionally may be two or more cm. in diameter.

Mucous Membranes.—In any marked case of nodular leprosy there is very likely to be involvement of the mucous membranes. Indeed, Morrow and some other writers regard certain of these structures as the site of the earliest manifestations of the disease in many cases. Rhinitis is a usual and annoying symptom that may be associated with epistaxis. Occasionally, nodular infiltration of the nasal mucosa occurs. There is a marked tendency to ulceration of the mucous membranes. This is especially true of lesions of the mouth, throat and larynx. When it occurs in the latter situation, it gives rise to the well-known leprous voice, and in severe cases articulation becomes difficult or impossible.

Eye Symptoms.—Among the most common and distressing manifestations of leprosy are those of the eye. There is often a pronounced conjunctivitis, and this may be associated with infiltration at the sclero-corneal junction which finally is likely to involve the whole cornea leading to more or less complete blindness. At a later date the deeper structures of the eye are involved, and, in many cases, softening of sclera and cornea leads to pronounced staphyloma.

(*b*) *Nerve Leprosy.*—Pure nerve leprosy presents few features which, at first sight, would lead us to consider it as closely related to the form that has just been described. Usually, it has a much longer incubation period and is in every respect a milder disease. As the name indicates, the symptoms are chiefly referable to the nervous system and it is often called anesthetic leprosy on account of the outstanding symptoms. Many cases are so mild as not to pass beyond a paralysis of a part of a hand or of a few facial muscles. On the other hand, in many cases, there is most extensive mutilation, such as the loss of a hand or foot, manifestations which justify the term "mutilating leprosy" sometimes applied to these cases. Other cases present few or numerous spots of varying size and appearance, which accounts for the term "macular leprosy."

The *skin manifestations* of nerve leprosy may begin by the appearance of reddish patches or of patches showing a deepening of the natural skin color. In other cases, there is a loss of pigment, leading to the formation of vitiligo-like spots, frequently called leukodermic areas. In this form of the disease, the early skin lesions are more likely to be permanent than in the nodular forms. Sensory changes may be demonstrated as soon as the lesions are observed. They are chiefly itching, and impairment or loss of pain perception and of thermic sense.

The eruption, like the early manifestations in nodular leprosy, often appears on the face first, though it may be confined to the covered parts of the body. The patches vary in size from those one cm. in diameter to large plaques which can scarcely be covered by the two hands; these latter usually are found over the buttocks and on the back. In many cases, the eruption clears in the center, leaving an appearance strikingly like certain forms of ringworm, with which it may readily be confused.

There may be severe *neuralgic pains*, especially in the hands, forearms, and the face. Aside from these neuralgic conditions, nerve leprosy is not ordinarily accompanied by painful manifestations.

Nerve Conditions.—In a considerable number of cases, a definite

thickening of certain nerve trunks, particularly the ulnar, may be detected by palpation. The writer feels that he should here emphasize a warning against considering any nerve enlarged, unless the swelling can be distinctly felt as a spindle-shaped enlargement, or a definite beading. Hansen called attention to the importance of this, and, if noted, many mistakes will be avoided. Such expressions as "slight thickening" or "moderate enlargement" of a nerve trunk mean little or nothing. Patients often complain of a sense of numbness, or describe a member as dead, when there is involvement of important nerve trunks.

Affection of the Muscles.—Atrophy of certain groups of muscles, with contracture of others, leads to the characteristic deformities of the hands and of the feet. The "leper claw," so commonly seen, is a hand showing atrophy of all muscles of the member, extension of the first joint, and flexion of the last two joints of the fingers. The shrinking of the muscles is most readily observed in the thenar and hypothenar prominences. It is sometimes surprising to observe the good functional utility of a hand that is seriously deformed. Paralysis of the muscles of the lower extremities is less common than that of the upper, but, when it does occur, it leads to abnormalities of the gait, deformity of the foot, and sometimes to the inability to walk. Various degrees of facial paralysis may occur, ranging from inability to close the eye, to loss of function of all of the muscles of half or even of the whole face.

Ulceration and Mutilation.—Loss of parts of the hands or of the feet are common. This results from atrophy and from ulceration, which may bring about a melting away of the extremities by ulceration and sloughing, or spontaneous amputation may occur. The latter may involve a single joint of a finger or may destroy successively parts of the hand or of the foot and may finally result in the loss of the entire member. Carious processes play a conspicuous part in these mutilations, which may be painful and accompanied by swelling and suppuration, requiring surgical measures for relief. The description of nerve leprosy would be incomplete without mention of the trophic ulcers, usually called "perforating" on account of the tendency to deep tissue destruction. They occur chiefly on the sole of the foot, giving rise to the plantar necrosis so common among lepers, though similar ulcers on the palm are not rare. Occasionally, these ulcers are painful but, usually, they are insensitive and it is no uncommon thing to find a patient walking about in relative comfort on a plantar ulcer as large as a silver dollar and leading to extensively disorganized bony structure.

Seat of Bacilli.—In this form of leprosy, the bacilli are usually difficult to detect microscopically, and in many cases are not to be found in skin or mucous membrane lesions but are confined to the nerve trunks.

Course and Termination.—While a fatal termination is almost always the result in nodular leprosy, in the nerve type the disease may be arrested at any stage; in fact, as the disease usually lasts many years, it is very likely that the victim may die of an intercurrent affection.

(*c*) *Mixed Leprosy.*—Many cases of leprosy exhibit manifestations of both of the types that have been described. Lesions or symptoms of

each type may be present from the outset, or the case may begin as a clean-cut nodular or as a simple nerve case and gradually take on manifestations of the other type.

Generally, *the hair* over a nodular lesion falls out. This is especially noticeable when the superorbital regions are involved and the eyebrows fall out. The hair, at the site of anesthetic lesions, loses its color and finally disappears. As is true of nodular leprosy, the scalp escapes and the hair on it remains unaffected.

LEPROUS FEVER.—The febrile manifestations of leprosy are by no means constant; indeed many cases run for long periods without any fever. Fever may occur as a part of the general disturbance that marks the beginning of the disease, but its nature is not usually recognized. The later manifestations of fever fall into two groups which were differentiated to the writer by Dr. W. J. Goodhue, Medical Superintendent at the Molokai Settlement. First, there is the febrile attack, occurring coincident with and due to a generalization of the infection through the blood stream and followed by the appearance of new tubercles. This may last a few days or a few weeks but, usually, the temperature falls to normal, leaving the patient with some new lesions but otherwise not much changed. Second, there is the fever which marks the final decline of the patient. It may run steadily in the neighborhood of 39° to 40° C. (102.2° to 104° F.) for several months and is often associated with profuse sweating, and always with loss of flesh and strength. The temperature often falls to normal or to subnormal during the last days of the life of the victim.

SPECIAL TESTS.—*Microscopical Examination.*—In addition to the clinical features which have been discussed under the symptoms of the disease, we obtain much aid from *microscopical examination* of material from the skin lesions and from the nasal cavities. The specimens for microscopical examination from skin manifestations are prepared in the following manner: An area of thickening, a nodule, or even an area of discoloration, is taken between the thumb and the forefinger and compression made so as to render the area as nearly bloodless as is possible. An incision is next made to a depth of perhaps an eighth of an inch and about half an inch in length. With the blade held at an angle to the sides of the tiny wound, a gentle scraping motion is made. For this purpose a safety razor blade is very convenient, as it can be discarded after each patient. The tissue fluid and tissue elements, secured in the manner described, are smeared on a glass slide, subjected to staining for acid-fast organisms in exactly the same manner as are preparations for the tubercle bacillus, and then examined microscopically.

The acid-fast organisms usually are abundant and are readily recognized. They are found in bundles or groups, as well as scattered through the field, and are often intracellular; occasionally, very few organisms are to be seen, perhaps but one or two in a preparation. In this case it is better to make additional preparations from another part of the lesion or from other lesions.

The *examination of smears* from the nasal mucosa is frequently

resorted to and often gives valuable information. There are fallacies here, however, that need to be guarded against. Acid-fast organisms are not rare in the nasal secretions of persons other than those suffering from leprosy. In the non-leprous, the bacilli found are usually much plumper than those in leprosy. It was once thought that acid-fast organisms were to be found in the nasal mucus early in the disease. This, however, is usually not the case and as an aid to early diagnosis this examination is not of much importance. The writer has seen unfortunate errors made by placing too much dependence on the results of the examination of nasal mucus, and would warn against drawing conclusions from this alone.

Serological Tests.—There have been a number of *serological tests* proposed for the diagnosis of leprosy, but none has been found trustworthy or of practical value. In this connection, mention should be made of the fact that a goodly proportion of lepers will give a positive Wassermann reaction, even in the absence of coexistent syphilis. The reason for this is not clear but the fact seems well established.

A large percentage of lepers react to *tuberculin* given by injection or by inunction. By some, this is regarded as evidence of the nearness, from a biological point of view, of the leprosy bacillus and the tubercle bacillus. This argument is fallacious and also might be advanced to show a relationship of such dissimilar organisms as the *Treponema pallidum* and the leprosy bacillus since, as has been stated, leprosy patients often give a Wassermann reaction. Evidently another explanation must be sought.

Diagnosis.—In considering the diagnosis of leprosy we must remember that, generally, a correct diagnosis is of infinitely more importance than in most other diseases, since it may involve the whole future of the patient. With other infectious diseases an error may not do any serious harm, as at most it will merely mean a short period of detention for the patient, but in leprosy, if we err by failing to diagnose a case, we may permit the exposure of many persons, while if a case is diagnosed leprosy erroneously, the greatest injury and injustice is done the patient. He becomes an outcast, and, indeed, in many places loses his civil rights. The importance of these facts is recognized by those who are charged with the administrative control of leprosy, and boards of experts are provided to pass upon cases. That there are very real difficulties of diagnosis encountered, is shown by the fact that boards of examiners are often compelled to defer a final decision until certain obscure lesions have had an opportunity to develop or to disappear.

In countries where leprosy is rarely seen, the chief obstacle to arriving at a correct diagnosis is simply that the disease does not occur to the mind of the examiner, since in marked cases there is no difficulty in reaching a correct decision once suspicion is aroused. Very early cases may defy even the most skillful, while late ones have the diagnosis stamped so plainly upon the features as to require but a glance to reveal the nature of the trouble. As in other fields, experience in the clinical aspects of the disease is of great importance and, in this connection, it is noteworthy that certain laymen become expert in recog-

nizing cases. There is in Hawaii a police officer who frequently brings before boards of medical examiners cases so early that the most careful scrutiny on the part of experts is necessary to arrive at a diagnosis, yet this man rarely brings forward a case that proves negative when submitted to careful examination.

DIFFERENTIAL DIAGNOSIS.—Leprosy must be differentiated from two groups of diseases:

Cutaneous Diseases.—The skilled leprologist will usually be able to distinguish on clinical grounds the lesions of leprosy from those of diseases that simulate it, but often a microscopical examination is required to settle the point. The lesions of syphilis, of parasitic skin diseases, and the non-infectious dermic eruptions can be differentiated by careful attention to the history of the case and to the appearance of the skin manifestations.

Organic Nerve Diseases.—We need mention here only syringomyelia, and, since there has been some discussion as to whether this is not in reality a manifestation of leprosy, it will be readily understood that there may be great difficulty at times in distinguishing the two conditions. It is usually stated that the diagnosis is to be made chiefly by the absence of sense of heat and cold with the retention of the tactile sensation in syringomyelia, while in leprosy the latter is lost.

Complications.—The leper may, and often does, suffer from the same diseases that affect other persons, but there are several maladies that some writers believe to have a special association with leprosy. These will be briefly discussed here.

Tuberculosis.—The impression is very general that pulmonary tuberculosis is very frequently associated with leprosy. The data on this are not very convincing. Among Hawaiian and Philippine lepers, pulmonary tuberculosis is not much more prevalent than among the general population. When it does occur, it is without special features. The writer has observed, among Hawaiian lepers, a considerable number of cases of tuberculosis of the axillary and inguinal lymph glands, a number far out of proportion to the lymphatic tuberculosis among the general population. Whether this is a special condition among Hawaiian lepers or whether it occurs elsewhere, but is not recognized, is not known.

Syphilis.—It is thought by some that syphilis bears a special relation to leprosy, but the author is convinced that the coincidence of the two infections is without special significance. There is some difficulty in making a diagnosis between the two diseases occasionally, but careful observation usually will serve to make the clinical diagnosis clear, and if this fails the microscope will settle the point. The Wassermann reaction is of little value, as many cases of uncomplicated leprosy show a positive Wassermann, as has been stated before.

Treatment.—Though there is not much prospect of recovery in leprosy, we are not justified in allowing cases to go untreated.

GENERAL MEASURES.—One of the surprising features in dealing with leprosy is the improvement which cases often show when first brought under isolation at a well-managed institution for the care of these people.

Various observers have noted that many cases, perhaps the majority, will begin to improve in general nutrition, as evidenced by a gain in weight and in spirits, and even by a marked change in dermic lesions soon after isolation. Good food, kindly care, and a life now free from the harassing fear of detection must be credited with the amelioration of symptoms that is experienced. Certain it is, that the most gratifying changes often occur and that **good surroundings** and **good food** must be considered potent auxiliaries in any scheme for the treatment of leprosy.

Certain **natural baths**, especially several found in Japan, have been held in high esteem in the treatment of leprosy. At one time, it was the rule for any well-to-do leper, discovered in Hawaii, to proceed to these baths and remarkable cures are alleged to have been effected. A large number of failures were less in evidence than the cases in which improvement apparently occurred. Some of the cases alleged to have been cured were almost certainly not examples of leprosy.

Artificial baths have also been used. Indeed, a large grove of eucalyptus trees at the Hawaiian leper settlement, Molokai, bear mute testimony to the faith certain physicians have in the use of a bath, which is made of a weak decoction of the aromatic leaves of these trees. Alkalis, notably **sodium bicarbonate**, are frequently added to the baths. While it is desirable that the patient be encouraged to take frequent warm baths, it seems improbable that any medicament applied in this manner is of any special value.

MEDICINAL TREATMENT.—Volumes might be written on the medicinal treatment of leprosy; indeed the number of agents that have been employed constitute good evidence of the lack of proven efficiency of any. **Mercury**, the **iodids**, **strychnin** and **salvarsan** may be mentioned among the many that have been employed and lauded for a brief period, but finally have proven to be without specific curative value. One drug seems, by general consent, to have proven more useful than any other, though it can scarcely be said that it is a specific. We refer to the oil expressed from the seeds of *Taraktogenos kurzii* and usually known as **chaulmoogra oil.** Once hailed as a specific remedy, we now know that, at most, it only aids the sufferer, in some unknown manner, in developing an immunity by which a cure is sometimes effected. In common with others who have had much experience with the treatment of leprosy, the author has given this drug an extensive trial. The results of personal experience have been sufficiently encouraging to justify the opinion that chaulmoogra oil should be given a trial in the treatment of any case of leprosy. It is, of course, difficult to appraise the value of any particular agent when, as usually is the case, several are being tried simultaneously or in succession, and we must remember that spontaneous improvement is very common.

The general opinion is that the less pure the oil, the better the results. The drug may be administered by the *mouth* in gelatin capsules, beginning with doses of 0.3 c.c. between meals and at bedtime, and increasing until as much as 25 c.c. are being given daily. The size of the dose,

and even a continuance of the administration of the drug, depends on the ability of the patient to take and retain it without nausea or more serious gastro-intestinal disturbance.

During recent years, the *hypodermic* use of the oil has come to the front again after a long period of disuse. This we owe chiefly to the observation of Heiser and his colleagues on Philippine lepers. Several formulæ have been employed, but the following devised by Dr. Mercado has been extensively used:

Chaulmoogra oil.....	60 c.c. (f℥ii)
Camphorated oil.....	60 c.c. (f℥ii)
Resorcin.....	4 grams (1.03 drams)

Mix and dissolve with the aid of heat and water bath, and filter.

The treatment should begin with 1 c.c. of the mixture, given *intramuscularly*, twice weekly, increased gradually to 5 c.c. at each dose.

It has not been our experience that this mode of treatment yields results markedly better than those obtained by the use of the drug administered by the mouth. There are occasionally disagreeable and, very rarely, even fatal results following the injections. The writer has seen symptoms, suspiciously like those of pulmonary embolism, but fortunately without results any more serious than the alarming of those concerned in the administration of the drug. Occasionally, large abscesses develop at the site of injection, and, while these heal promptly when evacuated, they constitute an unpleasant complication. These abscesses, apparently, are not necessarily due to any lapse in surgical cleanliness in connection with the administration of the drug.

Sir Leonard Rogers has reported encouraging results from the subcutaneous and from the intravenous administration of **gynocardate of sodium** which he believes represents the active principle of the oil combined with the sodium base. The salt is used in doses of one or two grains, subcutaneously, or in smaller quantities intravenously. The intravenous method is said by Rogers to be less painful and more efficient than the subcutaneous method.

Recently McDonald of Honolulu and others used certain relatively pure compounds made from chaulmoogra oil, known as ethyl esters. These are chiefly salts of chaulmoogric and hydnocarpic acids.

The esters are given intramuscularly, beginning with a dose of 1 c.c. and increasing rapidly to 3 c.c. or 5 c.c. These doses are given once each week. Iodine may be added to the mixed esters in the proportion of 2 per cent. The intramuscular use of these preparations may be associated with the use of the same agents by mouth.

Very remarkable results are claimed for the treatment. Several observers report a large number of cases discharged as arrested. A similar or identical patented preparation was placed on the market some years ago under the name of "Antileprol."

Biologic Agents.—Bacterial **vaccines** made from acid-fast organisms, grown from leprous tissue, have been employed, but without permanently good results. It would seem likely, considering the experience with other bacterial vaccines, that any agent of this sort should be made from the

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organism cultivated from the patient to be treated. The dose should be small to begin with: perhaps 50,000,000 organisms at an injection, and the number increased until a reaction is observed. A **serum** prepared by the immunization of the horse with cultures of acid-fast organisms has been used, but it is not considered of any value.

The **venom** of certain poisonous serpents has been used in the treatment of leprosy, but there is no reason to believe that it is of any benefit.

Under this head it should be mentioned that there are examples reported of the cure of leprosy after an attack of an infectious disease, as small-pox, and also after vaccination against small-pox.

SURGICAL MEASURES.—It is the general experience that wounds in lepers will heal as they do in other persons. Surgical treatment may be undertaken, if necessary, to relieve some threatening complication, or for purely cosmetic reasons. Under the former, may be mentioned the amputation of hopelessly necrotic feet, the removal of sequestra from bones of the hand or of the foot, and finally, and perhaps most important, the performance of tracheotomy for the relief of laryngeal stenosis. The latter is an operation demanded rather frequently and the results are so satisfactory that it should be done whenever it is indicated. The writer doubts if anywhere in the range of surgery are more gratifying results obtained than in these cases. Nor is the relief only temporary. Under the influence of the rest afforded by the tracheal tube, infiltrated and ulcerated vocal cords return to a relatively normal condition, and the tube often may be dispensed with after a few weeks or months. Other cases wear the tube for years without serious inconvenience. The writer has seen this operation performed many times by Dr. W. J. Goodhue, and always with splendid results. Indeed, surgery of leprosy, as practiced by him at the Molokai Settlement, constitutes one of the most beneficial applications of the art. Nerve stretching may be employed for the relief of the obstinate neuralgias of the arm or of the leg, but only occasionally are the results satisfactory.

Nodules may be removed for purely cosmetic purposes and, when the patient wishes such an operation performed, there is no reason why it should not be undertaken. Remarkable improvement in the appearance of the countenance may be brought about by the excision of disfiguring masses of leprous tissue.

LOCAL AGENTS.—Nodular and infiltrated areas have been treated with such **caustic agents** as trichloracetic acid, carbon dioxid snow, and chromic acid, and the results appear to justify the use of these drugs.

The *dressing of ulcers* constitutes the largest part of the work at the dispensary of a leper colony. Ordinary surgical principles should be followed. **Balsam of Peru** is much used for lesions that require a mild stimulant; **silver nitrate** when there are extensive granulations, and **phenolated zinc oxid ointment** where a soothing application is required.

RESULTS.—We may sum up the results of the treatment of leprosy by saying that, while we cannot expect to cure many patients, a judicious, persistent application of general medicinal and surgical measures will go far toward ameliorating the distressing manifestations of many cases, and this is a goal well worth the best effort of the physician. Experience and observation have taught the writer that lepers almost in-

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variably do everything within their power to help the physician carry out any plan of treatment he may propose. The patience of these unfortunates and their confidence in the ability of the physician to aid them, are outstanding features at all properly conducted institutions for the care of lepers.

Prognosis.—The prognosis of leprosy, as regards life, is of course unfavorable, though the course of the disease is often so slow that there are ample opportunities for intercurrent diseases to cut short the life of the victim. A few cases die within three or four years of the onset, many survive ten or twelve years and a not inconsiderable number live much longer than this.

In a small number of cases, perhaps two per cent., active lesions disappear under treatment, or indeed without treatment, and for practical purposes the individual may be regarded as having recovered. Occasionally, all signs of the disease may disappear, or there may remain a slight deformity of the hand or other evidence of nerve involvement. These cases also may be regarded as recovered. Such cases may be discharged on condition that they report to the health authorities every three or four months in order that a recurrence may be detected promptly. The leper examining boards convened by the Hawaiian Board of Health, discharge on parole a number of recovered or arrested cases annually, and experience has shown that very rarely is it necessary to recommit the paroled persons.

Pathology.—Leprosy stands in a unique position among bacterial diseases on account of the large number of microörganisms usually found in the specific lesions. When a section of a leprous nodule, or of an infiltration, is appropriately stained, the whole of the lesion takes the tint of the dye which has special affinities for the microörganisms, and examination with higher powers of the microscope will show that the tissue spaces and even the cells are literally full of bacilli. Certain lesions of a secondary nature do not ordinarily contain bacilli. The large trophic necroses, such as involve the bones and soft tissues of the extremities, are usually free from acid-fast organisms, a point that must be kept in mind in the microscopical diagnosis of the disease. In cases that come to autopsy bacilli are found widely distributed even where the tissues show no gross evidence of disease. Thus, smears from the spleen may show many acid-fast bacilli without the organ showing any change, possibly, beyond slight enlargement. Other organs usually show smaller numbers of bacilli.

There has been much written on the presence of the leprosy bacillus in the circulating blood and rather conflicting observations are on record. The fact seems to be that there may be present, occasionally, a small number of organisms, except during the febrile attacks commonly called leprous fever, when the circulating blood may contain large numbers.

The essential lesion, the leproma, as it is often called, is a soft, elastic, slightly grayish or slightly yellowish mass which may vary in size from a pea to a mass several centimeters in diameter. The structure is made up of round and fusiform cells, sometimes with giant cells. The leprous infiltration is similar in its general characteristics, but, as the name indicates, is less clearly circumscribed. All of the structures of the skin and the subcutaneous tissues are involved in the process.

The leprous lesion is often compared with that of tuberculosis, but as is the case with other features of the two diseases, the resemblance is rather superficial. The leprous lesion lacks the tendency to necrosis

which is so early and so characteristic of the lesions caused by the tubercle bacillus; indeed, in many respects, the leprous lesions bear a closer resemblance to a neoplasm. In nerve leprosy, bacilli are likely to be scarce and difficult to find. The lymphatic glands, in nodular leprosy, always show infiltration and enlargement with numerous bacilli.

History.—There seems to be no good ground for doubting that biblical and other ancient writings referring to leprosy do, at least in large part, deal with the same disease we call leprosy to-day, though there is equally good ground for believing that the leprosy of that day covered many diseases which we now recognize under other designations.

From the twelfth to the seventeenth centuries of the Christian era, leprosy prevailed most extensively over the whole of the civilized world. Indeed, even if we make a liberal discount for errors in diagnosis and for exaggeration in the accounts that have come down to us, there still remains no doubt that this disease was one of the most dreadful scourges that has ever afflicted the human race. During this period, the contagious nature of the disease was well recognized, as of course it was in biblical times, and a very extensive system of hospitals or lazarettos was established. The number of these institutions is said to have run far into the thousands, though most of them had but few inmates. It is claimed that traces of this mediæval leprosy still remain in southern and western Europe. Of course we cannot be certain that these small European foci do not represent reinfection such as we know brought about the outbreak in the Memel district of East Prussia in the latter half of the nineteenth century. That the traces of this mediæval widespread prevalence of leprosy are in the relatively near past is emphasized by the fact that it was only about the middle of the eighteenth century that the disease disappeared from the north of Scotland.

What has often been called the modern recrudescence of leprosy began in Europe in the early part of the nineteenth century, and it was in Norway that the disease first attracted attention. It is a remarkable fact that shortly after the disease had vanished from the United Kingdom and had practically disappeared from the other countries in western Europe, it began to occur in Scandinavian countries, particularly Norway, and for about one century constituted one of the serious medical problems of those countries. This recrudescence, however, led to the careful studies that have given us our extensive, though still incomplete, knowledge of the disease.

Distribution.—In considering the present day distribution of leprosy one must carefully differentiate between where the disease *exists* and where it *spreads*, a fact which has a most important bearing on the problem of the official handling of cases. There is no civilized country which does not have its quota of imported lepers, but with rare exceptions, the disease shows no tendency to spread. In the large cities of western Europe a considerable number of lepers, infected abroad, are domiciled and only very exceptionally is the infection transmitted. That the disease does not spread in these and in many other places is well established, though why it does not do so we do not know. Obviously, if the disease does not spread in a given locality, we need not be especially concerned about measures for its suppression there. This relative or absolute immunity of certain parts of the world is

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well exemplified in the United States. There have long been two chief foci of the disease in the United States. One is in the Northwest, chiefly in Minnesota; the other is in the Gulf States, chiefly in Louisiana. There is one great outstanding difference between these foci. In the former, the disease shows a tendency to extinguishment. From a total of perhaps one hundred imported cases there has been a very slight tendency to spread; perhaps half a dozen would cover cases of local origin. On the other hand, in the Louisiana focus, nearly all of the cases are of local origin. In other words, the disease spreads in the South but does not spread in the Northwest. We also know that there are always a number of lepers in New York City, yet there is no well-authenticated case of local origin—all are imported. This striking fact of the failure of the disease to spread in certain localities is usually accounted for by the better sanitary conditions under which people live as compared with the conditions where the disease does show a tendency to spread. It would not be profitable to discuss this point but it does not seem to be a very satisfactory explanation.

The distribution of leprosy to-day is as follows: The total number of lepers in the continental United States is variously estimated. The number registered is about 300, the large majority of whom are in the United States Hospital for Lepers near Carville, Louisiana, a few in each of the other States bordering on the Gulf of Mexico, and the remainder scattered. The opinion generally held by leprologists is that the total number in this country is at least 500 and there are some who believe that it will run up to 2,000.

The Insular possessions of the United States have large numbers of lepers and special asylums are provided for them, the most important being the Hawaiian colony at Molokai and the Philippine colony at Kulion. The countries of Central and South America are all more or less afflicted with leprosy, Colombia perhaps being the country having the largest number in proportion to the population.

In Europe the disease is disappearing from Scandinavian countries but remains prevalent in parts of Russia, and occurs, although in small numbers, in nearly all the countries bordering on the Mediterranean. In Germany, there is the famous focus in the Memel district, in which the disease is now declining but remains as a unique example of a European locality in which a very considerable spread occurred in the latter half of the nineteenth century.

Not much is known of leprosy in Africa beyond the fact that it is widespread and in some parts it is extremely prevalent. Repressive measures have been taken in Cape Colony and in certain other parts that are under European domination.

In Asia, the disease is very common. India is estimated to have a million lepers, Japan about forty thousand, and the number in China is very large, but no trustworthy estimate has been made. The Pacific Islands are practically all centers of leprosy, some of them comparatively recent. Thus leprosy in Hawaii began about the middle of the nineteenth century and within a few years had become so prevalent that at one time more than two per cent. of the native people were afflicted with the disease. The splendid fight made by the Hawaiian

people against the scourge is one which might well be emulated by larger and richer communities. The disease is at present slowly declining in Hawaii.

REFERENCES

For a detailed discussion of the various problems relating to leprosy, the reader is referred to the article by the late Prince A. Morrow in the Twentieth Century Practice of Medicine, to the files of *Lepra*, and to the publications of the U. S. Public Health Service which record the work of the U. S. Leprosy Investigation Station in Hawaii.

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CHAPTER XXIII

DENGUE

By Edward R. Stitt, M.D., LL.D.

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Definition.—Dengue is an acute febrile disease which shows marked epidemic tendencies and seems limited to the tropical and subtropical regions harboring *Ædes ægypti* (*Stegomyia calopus*), the transmitting agent. Like yellow fever, it belongs to the group of filterable virus diseases. The onset is characteristically abrupt, with fever, congested facies, and pains in back, extremities and postorbital regions. The primary accession of fever lasts three or four days and then, following a remission of one or two days, we have a second febrile wave lasting two or three days and accompanied by the eruption which confirms the diagnosis. The mortality is almost negligible. The incubation period is usually from four and one-half to seven days, and probably never longer than ten days.

Etiology.—At first the investigations as to the nature of the virus of dengue had in view the discovery of a bacterial cause. McLaughlin claimed to have demonstrated a micrococcus in the blood, but the details of his technic, and the failure of subsequent investigation to confirm his findings, relegate his work to the domain of history. Duval and Harris cultivated globoid bodies from the blood, by Noguchi's method for yellow fever, but they are in doubt as to the significance of the bodies.

Exciting Cause.—In 1903, Graham reported finding a piroplasm-like organism in red cells of dengue patients and, for a time, it was believed that he had discovered the cause. He was never able to demonstrate the organism in stained preparations, and other workers have failed to confirm his findings. In order to determine whether the virus is present in the blood, Ashburn and Craig inoculated eleven volunteers, intravenously, with about 20 minims of blood taken from dengue cases in the third or fourth days of the disease, and succeeded in infecting seven of these men. Later on they injected filtrates of dengue blood, intravenously, into two volunteers, using a tested diatomaceous earth filter, and succeeded in bringing about infection. As a result of these experiments it is generally accepted that the *cause* of *dengue* is a *filterable virus*.

Cleland and Bradley have succeeded in infecting a man with a blood filtrate, which was injected subcutaneously. They met with failure in four similar experiments. The experiments of these investigators demonstrated the presence of the virus in the blood on the second and third days of the disease, and possibly up to the eighth day of the disease. In 1918, Japanese physicians reported that the virus was in the blood, from the second to the sixth day of the disease, but not for a longer period.

Epidemiology.—The fulminating spread of dengue is only exceeded by that of influenza, and in its morbidity in a community it exceeds the latter, which usually fails to affect more than thirty per cent. of the population. Many dengue epidemics have shown as high a percentage as seventy-five per cent. of the population attacked. Such rapid and extensive spread may, in part, depend on the so-called "waves of life" among insect vectors. Naturalists have often noted sudden and unusual increase in many forms of animal life. They have also noted great epidemics among and extensive migrations of insects, which may be important factors in decreasing or increasing insect-borne diseases in a locality. In 1922 a scourge of yellow fever mosquitoes, *Ædes ægypti*, was noted in the epidemic of dengue, in Texas, when from 500,000 to 600,000 persons contracted dengue, as reported by Chandler and Rice. They state that volunteers, coming from a distance, were bitten by infected *Ædes* mosquitoes and that four of the six volunteers contracted dengue. The period of continuation of the epidemic in a community is as a rule longer than that in the case of influenza. Of course the matter of importation of susceptible human material tends to prolong an epidemic in busy seaports.

Dengue, like yellow fever, tends to confine itself to tropical and subtropical seaports, and to habitations in the low-level valleys of rivers, avoiding places of high altitude. The explanation of the epidemics of yellow fever and dengue in Philadelphia in the latter part of the 18th century must have lain in the importation of mosquitoes by the ships coming from tropical ports. Even before the mosquito transmission of dengue was proven by experiment, it was recognized that such an hypothesis would explain the peculiarities displayed in the spread of the disease. For instance, it has frequently been noted that those who remained aboard ship failed to contract the disease even when they were in the midst of an epidemic and in contact with cases on board ship, which had been infected while on shore leave. Upon exposing themselves on shore they were attacked, as were the others.

The author kept numerous dengue patients in carefully screened compartments, inside large wards full of susceptible individuals, within arm's length of such other patients, without a single instance of cross infection. This shows that none of the methods of infection holding for the common exanthemata explain the transmission of dengue.

It is to Graham, in 1903, that we owe proof of the possibility of transmitting dengue by the bites of infected mosquitoes. He conducted some experiments in Beyrout which may be open to criticism, inasmuch

as an epidemic was then prevailing there. As regards his collecting mosquitoes which had fed on dengue cases, and transporting them to a village in the mountains where there were no cases, and there having these mosquitoes feed on two inhabitants of the village, with positive results as to infection, there can be no question as to his demonstrating this mode of transmission.

It was Graham's opinion that the mosquitoes which carried the infection were *Culex quinquefasciatus*, but he admits that *Stegomyia* mosquitoes were also in the collection used by him in his experiments.

Ashburn and Craig conducted nine experiments on the transmission of dengue by *Culex quinquefasciatus*, and were of the opinion that one single successful infection demonstrated this species as an efficient host.

More recently Cleland and Bradley failed to transmit dengue by means of *Culex quinquefasciatus* when two individuals were bitten, but of seven persons, bitten by infected *Ædes*, four developed the disease. The experimental mosquitoes had fed on a dengue case from three to seven days before, but as these mosquitoes were collected from places where the dengue was present, these experiments failed to demonstrate how long a period must elapse after an infecting feeding before mosquitoes can transmit the disease.

Japanese investigators have recently reported success in transmitting dengue with *Stegomyia scutellaris*, but not with *Culex quinquefasciatus*.

One of the most convincing epidemiological proofs of the mosquito-transmission of this disease is in connection with the disappearance of dengue from Port Said during 1906 and 1907, notwithstanding the existence of epidemics in adjacent parts of Egypt. This freedom was attributed to a campaign against malaria which included a general clearing up of mosquito-breeding places.

Siler, Hall and Hitchens, in 1925, in a series of carefully controlled experiments, using forty-two American soldiers as volunteers, were able to transmit dengue fever in twenty-five instances (60 per cent.) by *Ædes ægypti* mosquitoes, bred from ova. Patients were able to infect mosquitoes during the first three days of the disease. The developmental period, in the mosquitoes, was found to be eleven days, and they remained capable of transmitting the disease for sixty-six days. *Culex quinquefasciatus* seemed unable to transmit the disease, in five volunteers who were later infected by being bitten by infected *Ædes ægypti*. Twelve were reinfected by injections of blood and fifty-eight per cent. were found to be immune. Those developing the disease recovered more quickly than in the previous attack. They compare dengue to yellow fever. Both are caused by filterable viruses; both may be produced by injection of blood; both are transmitted, naturally, solely by *Ædes ægypti;* in both the patient is infective to the mosquito during the first three days of the disease; the mosquito becomes infective only after the virus has remained in its body for approximately eleven days.

Symptomatology.—There is probably no disease which shows so abrupt an onset as dengue, the interval between apparent health and the setting in of marked prostration and bodily pains being frequently

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described as a matter of minutes rather than of hours. It is not infrequent for a patient to give the exact hour of his attack. The manifestations of this sudden onset are chilly sensations, dizziness, fever, marked prostration, headache and pains in the back and extremities. Malaise and indifference to surroundings are common clinical features. Dengue presents the typical saddle-back fever course, and in the description of the disease one can most conveniently separate the manifestations into those of the primary fever, of the remission, and of the terminal febrile access.

The Primary Fever.—Temperature rises rapidly, reaching 102°–105° F. (38.9°–40.6° C.) in a few hours. Along with this we note marked redness and swelling of the face, frequently with injected conjunctivæ, giving a facies somewhat resembling that of measles, but failing to show a macular eruption, or evidences of coryza. Some authorities have designated this facial congestion as the primary rash of dengue. The complaints of the patient are chiefly centered in the widely distributed pains. Headache and backache are as constant as is true of small-pox and yellow fever. Along with the more or less generalized headache we have the almost pathognomonic postorbital pains, or rather great soreness at the back of the eyes. Indeed, one of the points always insisted upon by the writer in the examination of a suspected case was to have the patient follow the writer's finger up and down, or from right to left. Almost invariably there would be complaint of inability to comply by reason of the severe pain caused by any motion of the eyeballs.

While the headache and backache are almost constant features, the pains in the extremities are more variable. While we do occasionally meet with cases suggesting "breakbone" pains, many of these exhibit general soreness rather than aching pains. There is often a complaint of pain on movement of the joints which has caused many writers to describe at length the joint-involvements of the disease. In the writer's opinion there is no involvement of the joints. The pain is probably in the muscle tendons, and is referred to the joints, which latter fail to show either swelling, redness or tenderness.

Along with this primary fever there is a distaste for food, which is not infrequently accompanied by nausea and, rarely, by vomiting. Mental depression and irritability accompany a bodily state of intense weariness. There is leukopenia and a reduction in the polymorphonuclear percentage.

About the third or fourth day the temperature in a typical case falls by crisis, and not infrequently is accompanied by various critical manifestations, such as profuse sweating, diarrhea, polyuria or even epistaxis, which usher in the period of remission.

The Period of Remission.—Following the fall in temperature, which may reach normal or merely be a remission, there is a marked amelioration of the pains and discomforts of the primary febrile stage. The patient feels that he is about to be restored to health, and views his condition with satisfaction, except that he experiences weakness and dizziness on getting up.

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It is this remission or intermission in the fever course, separating the primary from the terminal febrile wave, that gives the "saddle-back" characteristic to the temperature chart. The duration of the period of remission may be a few hours, so that it may be missed when temperature observations are taken only in the morning and evening, or it may last for two or three days, following which we have another elevation of temperature, ushering in the terminal stage.

THE TERMINAL FEVER.—This secondary rise in temperature may reach higher levels than the primary one, but it is usually less elevated and of shorter duration.

At this time there is a return of the malaise and prostration of the primary fever, usually moderate in degree, but with more marked manifestations of nervous depression. The mental state is typically pessimistic. The pulse rate is distinctly retarded.

It is at the commencement of this stage, or shortly afterwards, that we note the *most important sign* in the diagnosis of dengue, the characteristic, or *terminal rash* of the disease. In the absence of such a rash we are in doubt as to the correctness of our diagnosis, as there are various dengue-like fevers with which this disease might be confused.

This rash may be very ephemeral, or it may last for four or five days. Usually it is quite distinct for two or three days. In my opinion it most often first shows itself about the bases of the thumbs, extending thence to the wrists. It is more marked on the dorsal surfaces. Another favorite location is over the base of the great toe, extending to the dorsum of the foot, and in particular to the internal malleolar region of the ankle. It is often noted about the elbow- and knee-joints, and such preference for joint regions, together with the fact that the pains are referred to the joints, accounts for the insistence upon the articular manifestations by many writers.

The rash is much like that of measles but lacks the dusky red appearance of the measles eruption. It may, however, be punctiform in character, and thus resemble the rash of scarlatina.

As a rule the eruption rapidly involves the trunk, and may cover the entire body. In such case it more nearly resembles the fully developed eruption of rötheln than any other exanthem.

There is often a carmine flush involving the palms of the hands and the soles of the feet.

Following the disappearance of the rash we may have more or less furfuraceous desquamation, attended by itching or pricking sensations.

CONVALESCENCE.—A peculiarity of dengue is that a disease of such short duration and lack of serious illness should be attended by such physical weakness and nervous depression during the period of convalescence.

Those who try to force themselves to resume their former duties apparently suffer more than do those who yield to their lack of energy and apathetic state. A month or more may elapse before a patient is restored to his former activity.

Diagnosis.—In the laboratory diagnosis, our most important finding is in connection with the *leukopenia.* The average is about 4,000 white cells, and there is a reduction in the percentage of polymorphonuclears, which drops to an average of 40 to 50 per cent.

In the clinical diagnosis, the sudden onset, the peculiar ocular pains, the saddle-back temperature chart, and the terminal rash are of importance. Of the diseases which may be mistaken for dengue, the following are most important:

YELLOW FEVER.—It is almost impossible to differentiate this disease from dengue during the first two days, as they both have abrupt onsets and rather similar pains. The postorbital soreness of dengue is of value in differentiation. Leukopenia is not a feature of yellow fever, and albuminuria is exceedingly rare in dengue. The jaundice of yellow fever is a late feature, and this occurs in dengue only exceptionally. The differentiating value of the slow pulse is questionable, as this may be present in both diseases.

INFLUENZA.—There is a remarkable similarity in onset and pains between this disease and dengue. As a rule the catarrhal manifestations of influenza guide us to a diagnosis, but such manifestations may not appear early in influenza. The pulse-rate in influenza is more in accord with the temperature. In some influenza epidemics, rashes have been noted rather frequently, usually of a scarlatinal type. In the recent pandemic of influenza, leukopenia has been rather frequent.

PHLEBOTOMUS FEVER.—Clinically this disease is identical with a case of dengue which runs its course in three days and fails to show a terminal rash. There is a similarity in the onset, pains and slow pulse, as well as in the presence of leukopenia. The virus of this disease disappears from the peripheral blood by the second day of the disease. Transmission is by a moth midge, *Phlebotomus papatasii,* in which the virus undergoes some developmental cycle, as the insect is incapable of transferring the infection until a period of at least eight days elapses after the time of feeding on a case which is in the first day of the fever.

TRENCH FEVER.—It is interesting to note that when this disease first assumed great prevalence in the military forces of the Allies it was usually diagnosed as influenza, or as one of the dengue-like fevers. It is proven that this disease is transmitted by the body louse, the virus being introduced by the contaminative method of rubbing the feces or crushed lice into abrasions in the skin. It is not introduced by the bite of the louse. This virus is as yet an unknown one, but it has been proven to be non-filterable. The onset of trench fever is quite abrupt, with rapid rise of fever, general malaise, pains, and even marked soreness behind the eyeballs. The fever usually falls rather abruptly to normal about the fourth day, and one or more relapses are frequent. Clinically it differs from dengue in as much as there is an enlargement of the spleen in about three-fourths of the cases. In more than one-half of the cases erythematous spots may appear on abdomen, chest and back. As a rule there is a leukocytosis, thus differentiating the disease from dengue.

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Variations in Type.—While the description given under symptomatology is applicable to the average outbreak of dengue, there are certain points which have been accentuated in the description of particular epidemics:

1. Many textbooks note the importance of the correlation existing between pulse rate and temperature in dengue, as differentiating it from yellow fever, in which Faget's law of lack of such correlation is striking.

Reports of epidemics from Australia and elsewhere have emphasized the *slow pulse* of the dengue occurring at such times. Careful and prolonged observation of this point has led the author to regard a slow pulse as an important clinical feature of the cases noted in the Philippines, this slow pulse-rate having been most marked about the fourth or fifth day, being at times as low as fifty or sixty, notwithstanding a fever of 103° or 104° F. (39.4° or 40° C.).

2. In the clinical description of certain epidemics it has been noted that *adenitis* was fairly constant. Lane noted this feature in more than one-half of his cases, the glands involved being those of the inguinal, axillary and cervical regions. This general lymphadenitis was quite marked in certain cases, and showed itself about the same time as that of the appearance of the eruption. In the Philippines the writer was unable to note any glandular involvement which could be considered as associated with dengue. (*See* Fig. 1.)

3. In certain epidemics the *fever course* seems to *lack* the "*saddleback*" *feature* above noted. The cases may run the full period of primary and terminal fevers, lacking the remission, or they may show fever for a period of three days only. Such cases are not infrequently observed in an epidemic when typical courses predominate. Such febrile courses have given rise to such designations as "seven day" fever, or "three day" fever.

4. Some epidemics seem to be characterized by an *insignificance of the* usually diagnostic terminal or *true rash.* Such an outbreak may have been one of phlebotomus fever. Where care is not taken to look carefully for the rash this may fail to be noted in probably one-half of the cases of a typical epidemic.

5. Lane has noted a very unusual feature in quite a percentage of his cases, in the occurrence of *cyanosis* of the extremities. This cold and clammy, dusky condition set in about the onset of convalescence and continued for three or four days. A neurasthenic state occasionally ensued.

6. Hematemesis or melena has been reported in some cases.

Apparently those who force themselves to work during an attack experience a more protracted convalescence than those who go to bed and take care of themselves. In one of the Australian epidemics there was a mortality of about one per thousand, but such fatalities occurred almost exclusively in the case of debilitated children, or of old people.

Treatment.—PROPHYLAXIS.—In his discussion of the epidemiology of the epidemic of dengue at St. Thomas, Lane states that *Ædes ægypti* was the only mosquito that could be considered as a transmitting agent. This, in connection with the positive experiments of the Australian and Japanese workers, would indicate the *destruction of this genus of mosquito*

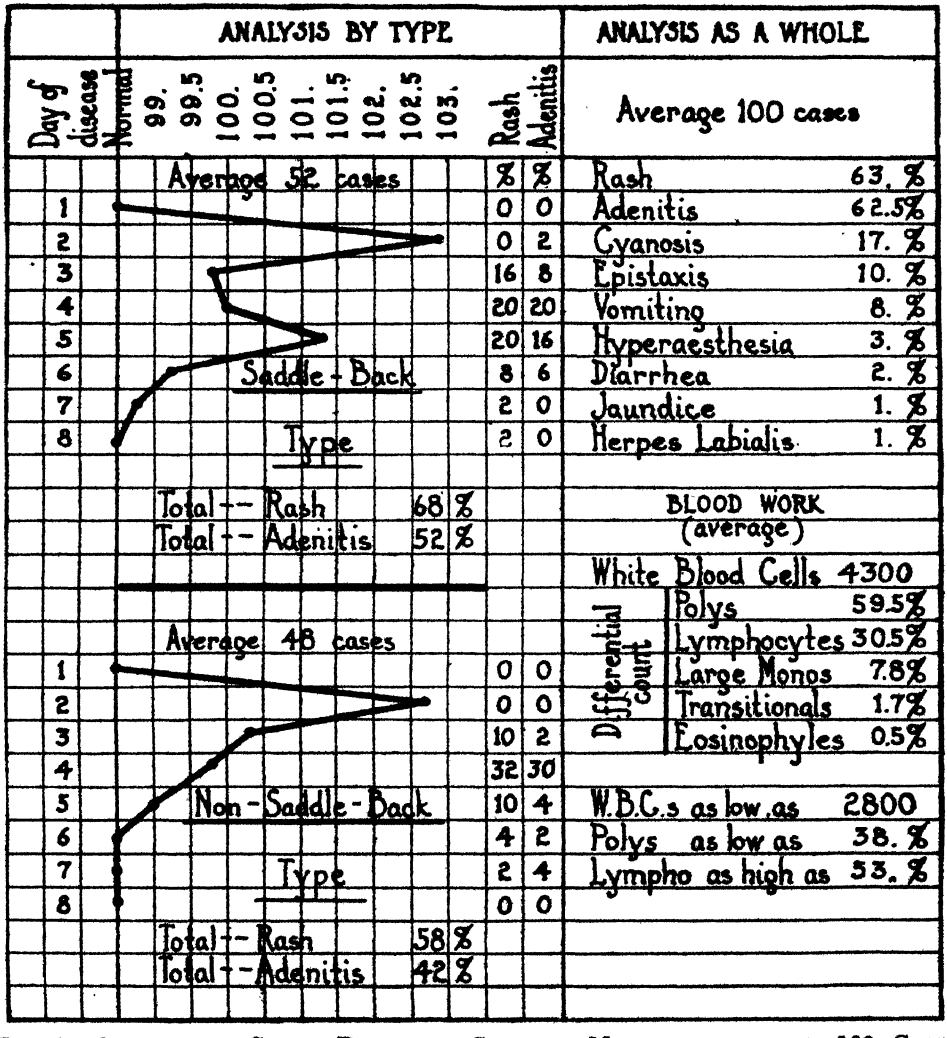


FIG. 1.—STATISTICAL CHART BASED ON CLINICAL MANIFESTATIONS OF 100 CASES OF DENGUE IN EPIDEMIC AT ST. THOMAS, V. I. (U. S. Naval Medical Bulletin.)

as our method of prophylaxis in dengue. The main points to be kept in mind in connection with this transmitting agent are its habits of biting during the day in a peculiarly stealthy manner, and the tendency of these mosquitoes to breed in the immediate environment of human

habitations. At the same time, *screening of houses,* and thus preventing the admission of the *Ædes,* is of value, because such mosquitoes tend to remain in the rooms of houses, and when infected transmit the disease to others occupying such rooms.

Outline of Habits of Ædes ægypti.—These mosquitoes are often termed the domesticated ones, in that they prefer to breed and live in the immediate environment of man. They are distinctly urban, rather than rural. In examining for breeding places we particularly *search* small *collections of water* within the house or in the yard surrounding the house. They are particularly apt to choose the water in tree-holes, old tin cans, or broken glass bottles, to deposit their eggs. It is rather interesting that the males of the *Ædes* may light on man to feed on his perspiration, but like other male mosquitoes they do not suck blood, and hence play no part in the transmission of the disease. The female prefers to feed on those of the white race, and seems to show repugnance for the black race. This mosquito makes no sound on approaching a victim, and tends to attack from the rear, and to secure a concealed place for feeding as, for example, by getting under the cover of a sleeve or stocking. This mosquito tends to bite in the daytime, but will also bite at night, if in a room where a light is burning.

MEDICAL TREATMENT.—This is almost exclusively symptomatic. Such drugs as **aspirin** and **phenacetin** are of value in relieving the pains. The insomnia which is a feature of many cases may require treatment, but as a rule this is unnecessary. The anorexia is such that the patient will rarely take other diet than a liquid one. **Fruit juices,** especially orange juice, are often palatable to the patient. It is important to keep the patient quiet during the period of remission, a time in which there is a relief from symptoms and a desire to resume work.

Prognosis.—The disease, from a practical standpoint, is unattended by fatal results. Many cases, however, show a protracted convalescence.

Pathology.—As there is practically no mortality in dengue, there has been little opportunity for pathological study, and the few autopsies that have been made in persons dying in the course of a dengue infection have failed to reveal pathological changes. It is well recognized that in the course of the disease there is a marked leukopenia, with a reduction in the polymorphonuclears.

Historical Summary.—It is a remarkable fact that a disease so striking in its clinical manifestations, and so calculated by its epidemic tendencies to impress the inhabitants of an invaded region, should have escaped the notice of medical writers until the latter part of the eighteenth century. Almost simultaneously (1779–1780) there were recorded descriptions of outbreaks of dengue from Cairo, Batavia and Philadelphia. The description which Benjamin Rush gives of the Philadelphia epidemic of 1780, under the designation of "breakbone fever," is fairly accurate, and remarkably interesting. It may be remembered that Rush also described an outbreak of yellow fever which devastated Philadelphia, and in his writings on dengue he is at pains to bring out the points differentiating bilious remitting yellow fever, as he designated yellow

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fever, from dengue. There are indications that dengue, like influenza, tends to assume pandemic proportions at intervals of fifteen or twenty years, subsiding during subsequent years to endemic invasion or localized epidemics. In 1889 there was an extensive outbreak of dengue in Asia Minor and in Greece, and with this epidemic fresh in their minds there were many who asserted that the great influenza pandemic of 1889 was but an extension in modified form of this dengue epidemic.

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CHAPTER XXIV

MALTA FEVER

(*Undulant Fever*)

By Edward R. Stitt, M.D., LL.D.

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Definition.—Undulant or Malta fever is an infectious disease caused by a coccobacillus, *Brucella melitensis*, which may be isolated from the spleen, blood or urine. It is transmitted almost exclusively through the milk of goats, in which the organism is excreted. It has been obtained from human, bovine, caprine, porcine and equine sources. It can be differentiated from the organism causing contagious abortion in cattle only by absorption of agglutinin tests, so that it seems logical to consider the organisms as belonging to the same species. We may speak of them as *Brucella melitensis*, variety *melitensis* or *abortus*.

Cases have been reported in places where goat's milk was not a factor and the organisms were found to be of the *abortus* variety, so that it seems that cases may arise from drinking milk from cows, infected with *abortus* organisms, although such a source has not been definitely proven. Other cases may arise from handling infected animals or carcasses, as in slaughter houses. Occasional cases have been reported which were thought to depend on infection, through domestic animals, as the handling of puppies from a dog which had aborted.

Although some cases may run an acute course and show a high percentage of mortality, yet the typical case is markedly protracted and of chronic or subacute character. The tendency of the febrile accessions to recur after an apyrexial interval has made the designation of *undulant fever* a favorite one. The typical case runs a course of three or four months, or longer, and the mortality rarely exceeds two per cent. Joint pains and neuralgic manifestations are fairly characteristic. The sweating and anemia, so often noted, have suggested the designation *Mediterranean phthisis*.

Etiology.—Exciting Cause.—*Bacteriology: the Organism.*—The causative organism, *Brucella melitensis*, was first isolated by Bruce from spleen cultures of two cases during life and from twelve Malta fever autopsies. By inoculating such cultures into monkeys, the disease was reproduced and the organism subsequently recovered from the spleen of

these animals, thus confirming Koch's postulates. Quite a number of laboratory workers have developed Malta fever, having become infected with pure cultures while studying the organism.

Morphology.—Morphologically, the *Brucella melitensis* is a very small organism, as studied in smears made from the spleen, averaging about 0.33 μ. In cultures it is rather coccobacillary in form and may be seen as distinct bacilli, which may form short chains in broth cultures.

Staining.—*Brucella melitensis* is non-motile and Gram-negative. When first isolated from the blood or spleen, the organism fails to show growth on plates until after seventy-two hours. Minute, dewdrop-like colonies are first seen, which later on become opaque. Original cultures are best made on glycerin agar, serum agar or blood-agar plates, but subcultures grow readily on plain agar. There is no fermentation of glucose, maltose, mannite, lactose or saccharose, and in litmus milk there is a progressive tendency to alkalinity. The optimum temperature is 37° C., but scanty growth takes place from 22° to 30° C. The growth from an agar slant emulsifies with extreme readiness in salt solution, thus facilitating suspension for agglutinating emulsions. In old laboratory cultures a brownish coloration tends to occur. This dark color is also noted in the growth on potato. Gelatin is not liquefied.

Differentiation from Other Organisms.—There have been cases of Malta fever reported in which the causative organism was similar culturally to the *Micrococcus melitensis* not responding to agglutination with the serum of that organism, but only to its own serum. Such organisms have been named *Micrococcus paramelitensis.*

While monkeys are very susceptible to infection, either by feeding or subcutaneous inoculation, it is with the goat that we are primarily concerned, as such animals suffer from natural infection and serve as the chief means of dissemination of the disease. Dogs and horses are also susceptible, but small laboratory animals, as rabbits and guinea pigs, are rather refractory. It is interesting to note that Evans inoculated one series of pregnant guinea pigs with *Brucella*, variety *abortus* and another series with *Brucella*, variety *melitensis*. The majority of the animals in each group aborted within a few days. In 1914, Kennedy found that the milk and serum of certain cows agglutinated *Brucella melitensis*, but was unable to plate out the organism from such milk. This suggested cows' milk as a possible source of infection. Bassett-Smith explained this as a natural tendency for certain specimens of cows' milk to agglutinate the Malta fever organism. In view of the marked cross-agglutination between *Brucella*, variety *abortus* and *Brucella*, variety *melitensis*, Evans considers it probable that the explanation of these investigations was that the milk came from cows infected with *Brucella*, variety *abortus*.

Resistance.—*Brucella melitensis* resists desiccation for a month or more, but is readily killed upon exposure to the sun.

Epidemiology.—In man the most important mode of excretion of the organism is by way of the urine. Kennedy found *Brucella*, variety *melitensis* in about 10 per cent. of the urines of patients examined. It

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is possible that excretion takes place through the feces, but this is rather conjectural. Lactation is rare in women with Malta fever, but in a few cases, in which the milk of such patients has been examined, the organism has, as a rule, been recovered. In addition, the organism is frequently present in the blood, blood-cultures having been positive in 65 per cent. of Eyre's cases. All evidence, however, of transmission of the disease by means of blood-sucking insects or arachnoids is practically negative.

Notwithstanding the frequent elimination of the organisms by the urine, it would seem necessary to dismiss such a means of transmission as other than extremely rare, because infections of the attendants of the hundreds of cases treated in the military hospitals of England were practically never observed. Of course the greatest care in disinfection of the urine was exercised in the hospitals where Malta fever cases were treated. This fact is surprising when we consider that the organisms retain their vitality for long periods in urine-contaminated dust. *There does not seem to be a human carrier problem in this disease.* All evidence, since the publication of the reports of the Malta Fever Commission (1905–1907), goes to sustain the view that the conclusions of this commission are valid, namely, that the *drinking of raw goats' milk is the paramount source of infection.*

In the investigations of the Commission it was found that Maltese goats could be infected by food contaminated with *Brucella melitensis*, such goats showing agglutinins in their serum in about a month, but not manifesting anything clinically. It was found that many goats showed a natural infection, one of a series of 46 animals giving cultures from the spleen and 7 others yielding agglutinating sera. Later it was found that 10 per cent. of the goats excreted the specific organism in their milk. By feeding monkeys with infected milk, 26 of the 28 animals used developed Malta fever.

About the same time (1905) a ship, the *Joshua Nicholson*, carried 65 goats destined for the United States from Malta to Antwerp. Of 10 of the crew who drank the milk, 8 became infected with the disease. Two German engineers, who boiled the milk, escaped infection. In 1905, there were 798 cases reported in the civilian population and 245 from the naval forces at Malta. In 1907, there were 457 cases among the civilians and only 12 from naval sources. The boiling of the milk by the latter, and lack of such precautions among the former, was the explanation of the small incidence in the Navy and the continued prevalence of the disease among the civil population.

The months of June, July and August give the greatest incidence of the disease and this is explained not only by the greater use of milk during the summer months, but also by the fact that, following the birth of the kid in the spring, the contamination of the milk is more marked.

Gentry and Ferenbaugh, in Texas, noted that cases of Malta fever were most common in the spring and early summer months, when the goats were in full milk and the ranchmen were caring for the kids and

teaching them to suckle. These investigators found that the Mexican goat herders attributed "goat fever" to drinking raw milk, and escaped the disease by boiling the milk. In all cases observed by them there was a history either of drinking raw goats' milk or of close contact with the bedding ground of goats. The disease in the infected areas of Texas is also known as "dust fever," this designation coming from the idea of infection taking place in the dust-filled goat pens. In 1922, thirty-five cases were reported from Phoenix, Arizona, from the sale of infected goats' milk. Lake calls attention to the difficulty in diagnosis, as the milk was chiefly consumed by patients having tuberculosis or by children.

It must be remembered that many experiments with dust contaminated with urine, which contained living organisms, failed to show the infectiousness of such material, but it is difficult to understand why such should have been the case, as such material, when applied to the conjunctival or respiratory mucous membranes, brought about infection.

Garrow calls attention to the possibility of infection through *handling the urine-soaked fleece of infected goats* or through *slaughtering* such animals or making *postmortem* examinations on them.

As the souring of milk does not seem to kill the organism, Malta fever may be transmitted by the *eating of butter or cheese made from goats' milk.*

Symptomatology.—Clinical History.—Given the history of a case covering a period of three or four months, with a wave-like temperature chart resembling that of a relapsing typhoid fever, together with notes as to varied manifestations of arthritis and, in particular, of neuritis, one would almost certainly suspect Malta fever and make inquiries as to the use of goats' milk by such a patient and make an agglutination test of the serum, or, if the patient showed marked fever, a blood-culture.

In the winter of 1894–1895, while in the Mediterranean, there were a considerable number of cases of Malta fever on a ship to which the writer was attached. Had it been possible to associate these cases with exposure at Gibraltar or Malta, where such a fever was known to prevail, it is the writer's opinion that the nature of the disease would have been readily recognized. As it was, there was great perplexity as to the proper diagnosis, and in many of the cases, had it not been for the presence of occasional fever, malingering would have been considered, as the men did not have the appearance of being sick, but complained of vague joint and nerve pains and seemed neurasthenic. Other cases, however, with high fever and sweating, led to a diagnosis of remittent fever as the port in which the outbreak occurred was a malarial one. Even the cases running a more or less continuous fever of enteric type did not resemble typhoid fever as they failed to show the early prostration, apathy and toxemia of this disease.

So varying is the type of fever, not only in different patients, but in the same patient, that in insisting upon the well-known undulatory fever curve in making a diagnosis we tend to overlook cases of Malta fever which do not exhibit this symptom.

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Incubation Period.—The incubation period usually lasts about two weeks, but cases have been reported when the first opportunity for infection preceded the onset of the disease by only five or six days. Then again there have been cases where the incubation period was apparently longer than a month.

Mode of Onset: Typical or Undulatory Case.—Following a rather insidious onset characterized by general malaise, headache, pains in the back of the neck, or general muscular pains and anorexia, a fever sets in which reaches its highest point in the evening, with rather marked remissions in the morning. As with typhoid fever, there is a progressive rise in the temperature curve for the first ten or twelve days until an elevation of 104°–105° F. (40°–40.6° C.) is reached, after which there is a gradual decline in the fever course until the normal is approximated, this wave of fever lasting for about three weeks. After a few days of slight fever or normal temperature there is a recurrence of the initial febrile attack, and it is to successions of such relapses, covering on the average a period of three or four months, but at times extending beyond the limit of a year, that we recognize the appropriateness of the designation *undulatory fever.* In most of the cases there is a rather obstinate constipation and the tongue shows a thick, white, dorsal coat with clean sides and tip. Even when the temperature is high, the apathetic, toxemic state which we associate with typhoid fever is absent. Dejection of spirits, irritability, insomnia and weakness are features usually presented by the patient. Sweating toward morning and, in some cases, a bronchial catarrh may cause a suspicion of tuberculosis, particularly as there is a rather marked tendency to anemia in Malta fever.

Of particular value in the diagnosis is the occurrence—at times during the febrile period and again not until that of defervescence or convalescence—of neuritis, especially involving the peripheral nerves. Such attacks occur in probably three-fourths of the cases, and a sudden and acute attack of sciatica may be our first clew to the real nature of the illness. The circumflex and peroneal nerves are less frequently affected than the sciatic. The acute attack tends to disappear in two or three days, but is usually followed by a long-continued tendency to neuritis, especially sciatica. Quite frequent, too, are joint pains of rather sudden onset, with tenderness and swelling, especially of the hip, shoulder, ankle and knee joints. The acute manifestations disappear in a day or so and may skip from joint to joint. Undoubtedly many of these rheumatic symptoms are really those of neuritis. In young children meningeal symptoms may be apparent.

Probably from direct toxic effect on the heart muscle, irregular action and palpitation of the heart is apt to occur. The spleen is somewhat enlarged and tender on palpation. In addition to the anemia, which eventually shows quite a reduction in the red cells, with an even more marked fall in hemoglobin percentage, there is a moderate leukopenia, in which the polymorphonuclears show a greater diminution than the lymphocytes. Some cases show a marked tendency to bleeding, espe-

cially epistaxis. Orchitis and epididymitis have been noted as occurring infrequently, and in women various menstrual disturbances have been observed. The course of pregnancy seems unaffected.

Diagnosis.—So striking have been the results of prophylactic measures in the eradication of this disease—that is, avoiding the use of, or making safe, goat's milk or milk products—that one of the first points in diagnosis now is the question, Was the infection due to the use of contaminated goat milk products?

Differential Diagnosis.—Of the diseases which resemble Malta fever it is usual first to mention *typhoid and the paratyphoid fevers.* Even if we did not have the neuritis and joint pains to guide us, we should be suspicious that a case was not typhoid fever when the patient showed few manifestations of toxemia. There is not the decided anorexia, apathy and prostration.

The sweating and marked remissions in the daily fever course suggest *malaria,* especially the malignant tertian type. Blood-examinations, even if they fail to show malarial parasites, may aid in the diagnosis by giving information as to a lymphocyte or large mononuclear increase, the former belonging to the blood-picture of Malta fever, the latter to that of malaria.

In some ways the protracted course and alternating periods of fever of *kala-azar* suggest Malta fever, but the more marked splenic enlargement and decided leukopenia of kala-azar should differentiate these two

Some cases of Malta fever show much that suggests *amebic abscess of the liver* or *pulmonary tuberculosis.* As a matter of fact, once there is a suspicion of Malta fever, one should try to confirm it by the more accurate methods of agglutination tests or through blood-cultures, rather than by clinical observations.

Laboratory Findings.—The agglutination test is carried out either macroscopically or microscopically, as for typhoid agglutination. The *Brucella melitensis* lends itself well to the microscopical technic, as clumping is marked in the field. Although Nicolle and Conor deem it important to heat the serum to be tested to 56° C. for thirty minutes, in order to destroy non-specific agglutinins, other workers prefer to use unheated serum.

It will be remembered that it was formerly customary to use low dilutions, such as a 1 to 20 or even 1 to 10, in typhoid agglutinations, whereas now we rarely attach diagnostic importance to dilutions below 1 to 80.

With Malta fever serum the textbooks still continue to note the use of dilutions of 1 to 10 or 1 to 20, thus indicating the lack of agglutinating power where very high dilutions are employed. Not only may we expect as high titers as are obtained in typhoid fever, but again, there is always the question of a pro-agglutinoid zone for specific sera where we obtain agglutination in dilutions of 1 to 50, or higher, whereas such low dilutions as 1 to 10 may fail to show clumping.

The methods of blood-culturing adopted by Eyre were very suc-

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cessful and can be recommended. He took 5 c.c. of blood from a vein, using a few drops of 10 per cent. sodium citrate in the syringe to prevent alteration of the blood. The citrated blood was then put into a flask containing 45 c.c. of nutrient bouillon. From the third to the tenth day transfers to agar-slants were made from the bouillon culture and the agar-slants examined from three to seven days following the transfer from the broth. The best time to take blood is at the height of the fever curve and at the time of day when the temperature is highest (late in the day). Some have had greater success by culturing the blood clot rather than using citrated blood. This clot culture has been much used in typhoid work. After taking from 3 to 5 c.c. of blood in a Wright's capsule the separated serum is centrifuged and made use of for agglutination tests, using the clotted blood for culturing.

Of course there is a greater chance of success with cultures made from material obtained by splenic puncture, but there is always some danger attending such a procedure.

It is always advisable to make cultures from the urine, especially about two weeks after the onset of the disease. The organisms appear to be eliminated periodically, so that such culturing should be repeated every few days.

The blood-smear, which shows about a normal white cell content, is of value in suggesting the diagnosis, as there is an increase in the lymphocyte percentage at the expense of that of the polymorphonuclears. This would be of value in eliminating a diagnosis of a pyogenic infection.

Complications.—As complications, we have *pneumonia*, *orchitis* and —more serious and more common—*hyperpyrexia* and heart-failure. While *epistaxis* is not uncommon, we may rarely encounter cases with extensive *hemorrhage into skin and mucous membranes* and *hematuria*, especially in elderly people.

Sequelæ.—When the case runs a course of several months, a marked degree of *anemia* may ensue with proportionate loss of strength. The long-continued joint and nerve pains, together with insomnia, tend to bring about a neurasthenic state.

In one case which was under observation for a long time, and which clinically was mild, except for repeated attacks of incapacitating sciatica, the patient died suddenly of *heart-failure*, apparently a sequel to the damage done to the heart muscle by the attack of Malta fever suffered some years previously.

Clinical Types.—INTERMITTENT TYPE OF HUGHES.—The general symptomatology of this type of the disease is similar to, but usually less severe than, the undulatory one. This is a subacute form which shows fever of an intermitting type from time to time. Such cases may fail to show evidence of serious illness and the patient continue his work, although aware of the progressive deterioriation of his health. Some very mild cases, which only rarely show slight fever of a few days' duration, have been designated as *ambulatory* cases. Such cases may be considered as forms of indigestion.

MALIGNANT TYPE.—In a certain proportion of cases, instead of having the somewhat insidious onset, we have the type of a severe acute infection in which the temperature assumes a high degree from the beginning of the disease, reaching 103° to 105° F. (39.4°–40.6° C.). Such cases may show vomiting and early diarrhea. Soon there sets in a typhoid state, with rather marked cardiac involvement, as shown by an irregular pulse. At times such malignant types may set in where the case has previously been running an ordinary course. These malignant cases not infrequently show a bronchopneumonia. The tendency to assume the typhoid state, the high temperature and the marked cardiac weakness are the chief features of the malignant type. Some cases may be hyperpyrexial in type. If the case does not end fatally, convalescence may set in following a crisis, or the case may gradually assume a subacute or chronic type.

PARAMELITENSIS FEVER.—It must not be forgotten that a case clinically resembling Malta fever, in which we fail to obtain agglutination with a true *melitensis* strain, may be due to an infection with *Micrococcus paramelitensis.*

Treatment.—PROPHYLAXIS.—The practical elimination of this disease from the naval and military hospitals of Malta, by the **boiling of the goats' milk** used in these institutions, points to the most important measure for the control of this infection.

It must be remembered, however, that not only the milk but also fresh cheese made from infected milk is dangerous, the organism not being killed by the souring of the milk. There is much evidence from Texas and South Africa that the dust from the goat pens may infect those working in such buildings and the handling of infected goats by slaughtering or otherwise may likewise cause infection.

To recognize the existence of the disease in goats, the usual practice is to try out the milk for agglutinins, following this lactoreaction with a serum agglutination. **Infected goats should be destroyed.** Goats can be protected from infection by vaccination with either variety of the organism.

In handling cases of the disease in man one should pay particular attention to the **disinfection of the urine,** cases of Malta fever at times showing great numbers of the causative organisms in their urine. The feces should likewise be disinfected. When we consider the frequency of these infections among laboratory workers, its infrequency among the nurses attending cases of Malta fever is surprising.

SYMPTOMATIC TREATMENT.—There is no drug that seems to have any influence on the course of the disease, and it is probable that the use of such cardiac depressants as the coal-tar products, in the treatment of the *pains* of Malta fever, has been distinctly prejudicial to the patient receiving such drugs. Neo-arsphenamine has been reported to be of value.

In view of the tendency to *constipation* in this disease it is well to use, in moderation, measures to counteract this condition. For the *insomnia and pains* **hydrotherapeutic measures** are indicated. The

tracted course of the disease makes it necessary to give the patient a **diet of sufficient food value.** At the same time one should not overfeed the patient and, at times, when there are present *anorexia* and a rather *heavily coated tongue,* the diet should be limited.

SPECIFIC THERAPY.—The best results in treatment have been in the use of **vaccines,** this being confined, however, to cases of a chronic type, for in acute conditions they may do harm. Some authorities recommend doses of one-quarter to one-half a billion cocci. Others, however, insist upon the importance of starting with small doses, as from 25 to 50 million, repeating the injection every four or five days. Later on one may increase the dose and the interval, but rarely going beyond 100 million cocci.

There have been reports of greater success with autogenous vaccines or again with sensitized ones than with the regular stock vaccine.

Prognosis.—While the disease shows a very low mortality rate, usually noted as about 2 per cent., yet from a standpoint of prolonged course and resulting invalidism it is a more serious disease than the death rate would indicate.

It is in the malignant type of this infection that we get a death rate corresponding to that of the more fatal infectious diseases.

The after effects of the disease are often incapacitating, especially as regards neurasthenia, neuralgias and cardiac weakness.

Some patients become victims of the morphin habit, as a result of the taking of the drug to relieve the neuralgia and joint pains, as well as to combat insomnia.

It is usually considered that a lasting immunity is conferred by an attack, but cases have been reported of second infections, one of the great authorities on this subject, Doctor Eyre, having had two attacks.

Certain prognostic indications may be obtained from the course of the agglutinin curve of a case. Where a fairly high agglutinin titer is followed by a decided decrease of the same, one may expect a protracted course, but a sustained high agglutinin titer makes for a favorable prognosis.

Pathology.—Our knowledge of the pathology of this disease is not very exact, due to several reasons. In the first place, owing to the very low mortality (2 to 4 per cent.), autopsy material for the study of the disease is limited. Then, owing to the great variation in the course of the disease, the findings vary greatly in cases due to the acute, short course (malignant type of the disease), and in cases in which death ensues after a protracted subacute or chronic course of several months. Careful autopsy studies would indicate that there is no particular tissue or organ peculiarly selected by the causative organism or its toxins and this fact probably accounts for the variation in findings. The most important fact in the pathology is that the disease is a bacteriemia, which fact may be practically demonstrated by blood-cultures made during febrile attacks.

There also seems to be a degenerative action upon the red cells and a lowering of the phagocytic activity of the leukocytes. Probably the

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most constant finding at autopsy is the more or less enlarged spleen. In acute cases the spleen is soft and dark, much congested and weighing up to 200 grams. In chronic cases it may be quite large and Bassett-Smith has recorded such a spleen weighing 1,200 grams. The liver and kidneys are congested. Many statements as to congestion and increase of lymphoid tissue in various areas of the alimentary tract have been recorded, but there is nothing constant. It is important to remember that there is no ulceration of Peyer's patches. At times we may find enlargement of the mesenteric glands, and from such glands we may get pure cultures of the causative organism as well as from the spleen.

History.—Hippocrates described cases of protracted fever with relapse tendencies, which had some of the characteristics of phthisis, but not showing a fatal course. It is probable that such cases were Malta fever.

Following the Crimean War there was quite an incidence of fevers in Malta, and in 1863 we had the first detailed description of the disease made by Marston, under the designation "Mediterranean Remittent Fever." This fever he differentiated from typhoid fever and from a simple continued fever which he refers to as "Maltese Fever." In his description he noted the protracted course, the tendency to relapse, the development of anemia and the rheumatic and neuralgic features of the disease as we now know it.

In 1886, Bruce isolated a coccoid organism from the spleen, which he called *Micrococcus melitensis*, and was able, with cultures of this organism, to transmit the disease to monkeys.

Diagnosis, by agglutination, was as marked an advance in the study of this disease, so characterized by variation in clinical type, as it was in typhoid fever. This method of diagnosis was first reported by Wright and Semple in 1897.

Geographical Distribution.—While Malta is the best known endemic focus of the disease, cases have been repeatedly reported from various localities along the Mediterranean coast and its islands. In localities in which systematic destruction of infected goats has been observed, a district which was originally a focus ceases to be one. In the goat-raising regions of Texas, South Africa and West Africa the disease is endemic. There are reports of infections occurring in China, India and the West Indies, as well as in various South American countries.

CHAPTER XXV

THE PLAGUE

By William B. Wherry, M.D.

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Definition.—The plague is a disease of certain rodents, which is transmissible to man. The germ, the *Bacillus pestis*, is usually inoculated by the bite of certain fleas which have fed upon rodents suffering from plague septicemia. At the site of the bite there may develop an acute inflammatory focus of infection looking much like an anthrax carbuncle. This primary plague pustule is rather rare. As a rule, the virus, without creating a local lesion, travels along the lymphatics and, lodging in the nearest regional glands, multiplies and produces an acute lymphadenitis, a bubo. This is the *bubonic plague.* The *Bacillus pestis* may pass through the lymphatic filters and, gaining the circulation, produce *secondary septicemic plague.* If the virus is not intercepted by a lymphatic filter it reaches the blood stream more rapidly, and *primary plague septicemia* results. The septicemia is usually accompanied by the development of secondary localizations in the lymphatic system, *secondary buboes,* or in the lungs, *secondary plague pneumonia.* At times the *Bacillus pestis* shows a marked predilection for the lungs and, without the intervention of rodents or fleas, spreads from man to man as a very fatal *primary plague pneumonia.*

Etiology.—Exciting Cause: Bacteriology of the Organism.—*Morphology.*—The *Bacillus pestis* was discovered independently by Yersin and by Kitasato in the first outbreak which occurred after the advent of the bacteriologic era (Hong-Kong, 1894). It is a sporeless, nonmotile rod, varying slightly in diameter and greatly in length. Often it shows marked polymorphism. In the tissues of susceptible animals, however, the rods are usually slightly less than one micron in diameter and from one to two or three microns in length. It stains readily with most of the basic aniline dyes, and if not overstained, it shows the bipolar staining very uniformly. This bipolar staining is perhaps best demonstrated by any of the modifications of the Romanowsky stains or by Giemsa's stain. It does not retain the stain in Gram's method. The rod, in the tissues and in recently isolated cultures, is surrounded by a mucoid capsule. While the bipolar-staining rods are most frequently en-

countered in the lesions of acute plague, there exists also the coccoid form which is not infrequently found postmortem in man, rats or squirrels. These faintly staining, rounded forms resume their usual shape on cultivation or when they are inoculated into susceptible animals. The *Bacillus pestis* grows well at the body temperature on plain nutrient agar-agar in the presence of free oxygen. Often the growth is mucilaginous, especially when this takes place in the presence of sera. Particularly coherent masses of growth in the proventriculus of permanently infected fleas have been described by Bacot and Martin. Two peculiarities, exhibited during the growth on artificial media are of great value in identifying the germ: on nutrient agar containing 3 per cent. sodium chlorid, large yeast-like and club-shaped forms develop; and in undisturbed broth covered with oil the growth forms stalactite-like masses hanging from the surface film.

In the primary lesions in acute plague the germs are present in enormous numbers. The blood of a plague-infected rat before death may contain more than 100,000,000 per cubic centimeter. In man the blood only occasionally contains as many as 1,000,000 germs per cubic centimeter.

Epidemiology.—Our complete knowledge concerning the epidemiology and transmission of plague was acquired during the last pandemic which began about 1894, invading fifty-two countries, and still recrudesces annually in many parts of the world. The epidemic of pneumonic plague in Manchuria, 1910-11, was the first outbreak of this form of the disease since the advent of bacteriology. Practically all the important contributions were made by the last Indian Commission, or have been incorporated in their reports, and the data presented here are from that source. The older experiments of Simond, and of Gauthier and Raybaud, and of Liston implicating *the flea* in the transmission of plague were taken as the basis of experimentation. These were amply confirmed and a mass of additional data obtained. The Commission republished from an obscure Russian journal the really wonderful experimental work of Verjbitsky.

Experiments conducted in specially constructed houses showed that plague would not spread as an epizoötic among guinea pigs if fleas were excluded, and that the chances of transmission were enhanced directly in proportion to the number of fleas. Feeding, grossly contaminated surroundings, direct contact with the sick, and infected air, played no part in the absence of fleas. This was true also in the case of rats, though here, as shown before by other workers, if the rats injured the buccal mucosa while feeding on their dead companions, infection might occur.

When healthy rats, guinea pigs and monkeys were exposed to infection in plague houses they often died of the disease; on the bodies of the dead animals plague-infected fleas were found. When such animals were protected, as by strips of sticky fly paper six inches wide, they escaped infestation and infection. Often fleas containing plague bacilli were found on the fly paper.

It was found that a rat flea could take in as many as 500 plague germs at a single feeding, and under suitable temperature conditions these germs multiplied and passed out in a viable state with the excreta of the insect. Such excreta was shown to be infectious when placed on a flea bite and rubbed in by scratching. Later, Bacot and Martin showed that certain fleas suffer from an obstruction of the stomach and proventriculus due to the implantation of tenacious masses of *Bacillus pestis*. Such fleas are apt to live for many days, though starved; they make repeated ineffectual attempts to feed. Their bite is very likely to transmit infection, for the blood, aspirated into the proventriculus and then regurgitated back into the wound caused by the proboscis, often carries with it the plague bacilli. The rat fleas, *Xenopsylla cheopis* and *Ceratophyllus fasciatus*, and the human flea, *Pulex cheopis*, all transmitted plague under experimental conditions. *Xenopsylla cheopis*, being the most common rat flea in India, was chiefly concerned there. In America the *Ceratophyllus fasciatus* is chiefly to blame.

By placing a guinea pig population in certain deserted native villages, it was found that plague in rats precedes that in humans. Rats, suffering from plague septicemia, may harbor from a few hundred thousand to a million or a billion plague bacilli per cubic centimeter of blood, while that of man rarely contains over a few thousand; hence, the chance of a man, ill with plague, of acting as a source of infection for fleas is relatively small. However, man may act as such a source of infection, or may carry in his clothing or baggage fleas which have already been infected, and these may start a new epizoötic.

In addition to the rat, and man, many other animals may acquire plague naturally. Among these, various species of ground squirrels are of great importance: the tarbagan (*Arctomys bobac*), widely distributed in Central Asia, and the California ground squirrel (*Citellus beecheyi*). Certain monkeys and tree squirrels in India have been found dead of plague. In America, the following rodents have been shown susceptible to inoculation: the brush rat, the rock squirrel, desert wood rat, prairie dog, weasel, chipmunk, and pocket gopher. The llama is said to be susceptible to inoculation. In Australia, marsupials may become infected. Bats are susceptible to inoculation. Cats may develop a chronic form with cervical buboes. Mice played no rôle in the spread of plague in Bombay but they are very susceptible. The extensive experiments of Bannerman and Kapadia showed that the common domestic animals—horses, asses, cattle, sheep and pigs—are not susceptible.

The Indian Commission made many interesting observations on the influence of meteorologic conditions on the spread of plague. It was known that in cold and temperate regions outbreaks occurred chiefly in summer; in hot, dry regions it died out in summer. Their observations showed that temperature influenced to some extent the number of rats, but especially the numerical prevalence of the rat fleas. Rats, which often outnumber the human population, breed throughout the year in equable climates; extremes of heat and cold retard their multiplication. When a rat-epizoötic like plague has temporarily reduced their

numbers, there is an accelerated reproduction. This adds a large number of young susceptible rats to the population. In this connection it may be noted that 59 per cent. of the rats in Bombay were found to be immune to relatively large doses of plague bacilli; that in San Francisco, 15 per cent. of small rats were found, by McCoy, to be immune long after the epidemic had passed.

Coincidently with the appearance of a large population of young, relatively susceptible rats, the lower temperature favored the multiplication of fleas; the high temperature of the "off season" not only interfered with the deposition of eggs but restrained the eggs from developing into larvæ. Furthermore a mean temperature of 85° F. (29.4° C.) and over, favored the rapid disappearance of the *Bacillus pestis* from the intestine of the flea. The period of infectivity of plague-infected fleas was six times greater during the epidemic than during the non-epidemic season. The interplay of these various factors largely regulates the seasonal prevalence of plague.

But where has the plague been during the interim between great outbreaks? Various centers where plague is said to persist have been described; the province of Yünnan in China; the Transbaikal region of Eastern Siberia and Mongolia; and in Uganda, Africa. Why plague has persisted in these regions is not known. Perhaps our experience with plague in California will throw some light on the subject, for this state in the Union may well be considered a permanently infected focus. Introduced about twenty years ago, plague has persisted up to the present day. Three outbreaks in rats and humans have occurred during this period and apparently the disease disappeared completely in the intervals. At the close of the last outbreak (1908), the writer described the occurrence of plague in the California ground squirrel. Its presence in these rodents had been suspected for years by Blue, Curry and others, but previous efforts to find infected squirrels had failed. Since that time, and to the present day, plague has been shown by Blue, McCoy, Rucker and others to persist among these rodents in widely scattered sections of the state.

In these rodents the disease may run an acute course, but there is a great tendency for the disease to become subacute and chronic. The writer noted the frequent occurrence of pulmonary lesions in naturally infected squirrels and in an unpublished series of subinoculations found that the bacilli from such lungs showed a definite tendency to localize in the lungs of a series of guinea pigs. In this connection it may be noted that the pneumonic plague in Manchuria was thought to have originated among the tarbagan hunters in eastern Mongolia and northwestern Manchuria.

Symptomatology.—Clinical History.—*Period of Incubation.*—The symptoms vary with the type of infection. About three-fourths of the cases are usually of the bubonic type. The incubation period is most frequently from four to six days; it may be as short as thirty-six hours or as long as ten days. During this time there are symptoms of illness which are common to many infectious diseases: malaise, headache, nausea,

sensations of chilliness and muscular pains. Pains referable to regional glands which are to be the seat of buboes are especially noteworthy.

Mode of Onset.—The onset is sudden with an initial rigor, or, in children with convulsions, is followed by a rise in temperature to 101°-103° F. (38.3°-39.4° C.). There is an increase in the intensity of many of the prodromal symptoms. The temperature rapidly rises to 103°-104° F. (39.4°-40° C.), or even to 107° F. (41.6° C.). This usually falls two or three degrees on the second or third day and then rises again to persist, with daily remissions, until it gradually falls with recovery, or suddenly drops to subnormal in fatal cases. The frontal and temporal headache is splitting. The eyes are injected and there is marked photophobia. The patient is dazed, or apathetic and drunken, or excited, restless and sleepless. Usually the bowels are constipated at the beginning of the attack; early diarrhea is said to be a bad sign.

Physical Findings.—The *earliest pathognomonic signs* appear with the development of the buboes. These may be detected early in the disease, but are most frequently evident on the second or third day. Their development is usually accompanied by lancinating pains, but at times these may be absent and tenderness may be elicited only by pressure. The buboes may develop to the size of a man's fist. In the order of frequency, the buboes occur in the inguinal, femoral, axillary, submaxillary and cervical regions. This is determined by the relative accessibility of corresponding areas of skin to fleas. As a rule the deepest seated glands are involved first. The primary buboes are usually single; though they may be bilateral and multiple. As the periglandular inflammatory exudate accumulates, the glands can no longer be felt nor moved beneath the skin. The overlying skin becomes hyperemic, edematous, and petechiæ may appear. In mild cases the lymphadenitis may subside, leaving hypertrophied and indurated glands behind, but in about ninety per cent. of cases the buboes suppurate during the second week. The formation of internal buboes is accompanied by deep abdominal and lumbar pains. Palpation will elicit tenderness over the swollen spleen, the hemorrhagic stomach and intestines, and over the deep buboes.

Either primary or secondary foci of infection may appear in the skin. These are vesiculopustular with a hemorrhagic base. Although, at first minute, they may increase to 6-10 millimeters in diameter, and roughly resemble an anthrax carbuncle. The necrotic area is finally covered by a black scab. The primary pustule is due to the localization of the bacilli in the skin after their introduction by a flea bite, and here the nearest regional glands are usually involved. The secondary carbuncles are more frequently multiple and are found most often over or near the buboes. They may be numerous and show a tendency to recur.

Hemorrhages into or beneath the skin may or may not be prominent. They may appear early, but most frequently at the height of the attack. Often petechial, but sometimes linear or diffuse patches, they appear bright red, leaden or blackish in hue. In some outbreaks these

have been so numerous, along with hemorrhages from the respiratory, alimentary, urinary and genital tracts, as to recall, in individual cases at least, the Black Death of the Middle Ages. The writer has shown that extensive hemorrhages are apt to occur when the *Bacillus pestis* infects a scorbutic animal. Women often miscarry. The pulse throughout is usually rapid and weak, and there is a marked tendency to cardiac dilatation.

CLINICAL VARIETIES.—*Primary Plague Septicemia.*—In primary plague septicemia the onset is sudden with high fever, rapid, weak pulse, delirium or early collapse. The superficial glands may not be enlarged, but are tender on pressure. There may be hemorrhages from the gastro-intestinal tract. The course is usually rapid and death may occur within a day after the onset.

Primary Plague Pneumonia.—In primary plague pneumonia the onset is very much like that of other pneumonias. A chill is followed by fever, headache, pains in the limbs, sense of distress in the chest, rapid respirations (40-70 per minute), cough and expectoration. The sputum is often thin at first and contains white mucopurulent flakes, but soon becomes bloody. There is a tendency to edema of the lungs. Most of the cases terminate fatally on the third or fourth day.

Secondary Plague Pneumonia.—Secondary plague pneumonia occurs quite frequently, especially in tuberculous individuals.

Diagnosis.—Typical cases of bubonic plague present no difficulties. The sudden onset, with high fever, pain in one or more sets of lymph-glands, often with the simultaneous appearance of a petechial rash, should arouse suspicion. The true nature of the disease is best determined by aspirating a small amount of fluid from a swollen gland and determining the presence of the *Bacillus pestis* either microscopically, culturally, or by animal inoculation. These tests should always be made at the beginning of an outbreak when sporadic cases are encountered, in order to establish the occurrence of plague.

In the absence of an epidemic, the primary septicemic cases are apt to be mistaken for streptococcus septicemia, meningitis, typhoid, etc., unless confirmed bacteriologically by blood culture, animal inoculation or by postmortem examination.

The sputum in pneumonic plague is usually crowded with *Bacillus pestis,* either alone or mixed with the other bacteria commonly associated with pneumonia.

Complications and Sequelæ.—Primary bubonic cases are always in danger of secondary septicemia with pneumonia, which is always fatal. The suppuration of the bubo is sometimes greatly prolonged. There may be otitis. Due to intoxication, there is usually prolonged weakness of the heart; there may be aphonia, aphasia, mental weakness and vasomotor disturbances. Jaundice may appear. The acute nephritis may become chronic with its attendant symptoms.

Treatment.—PROPHYLAXIS.—*General.*—General prophylaxis must be based on our knowledge of the origin and spread of the disease described more fully above. It comprises the wholesale **destruction of rats, mice,**

squirrels and their fleas; the **proper disinfestation** of plague houses, ships, wharves, stores and warehouses of all kinds, and of all dwellings which harbor the rodents concerned in the spread of plague. Knowledge of the distribution of rodents is best obtained by a well-organized force of rat catchers. **Strict quarantine** is justified, for not only may man travel during the incubation period and act as a reservoir of infection in a new place, but although healthy, he may transport plague-infected fleas which start a new epizoötic among rats. A normal pulse rate, a normal temperature, with absence of tenderness in the superficial glands is usually the criterion of non-infection. Every effort should likewise be made to limit the transportation of rats and mice.

Most important of all the measures directed against rats and mice, and one which greatly aids in their destruction by *trapping* and *poisoning*, is an attempt to *cut off their food supply*. This is best accomplished by the enforcement of regulations designed to protect foodstuffs from rats: the keeping of foods and waste food products in ratproof containers; the ratproofing of stores, granaries, warehouses, stables and all defectively constructed buildings which permit rats to gain entrance either along sewer, water or other conduits, or through other defects at their foundations. These defects are best remedied with concrete, galvanized iron netting or sheets.

Since *primary pneumonic plague* is unaccompanied by plague in rats, and transmission is by direct contact, **effective masking**, combined with **personal cleanliness**, are necessary. **Complete segregation and disinfection** produced an immediate fall in the incidence in the last outbreak. Since the convalescents from this form of the disease may expectorate virulent germs for weeks after the temperature is normal, they should be quarantined until their sputum is no longer infectious for guinea pigs.

Individual.—In the presence of an epidemic it is advisable for **all to be inoculated against plague**—especially physicians, nurses, sanitary inspectors, rat catchers, undertakers, morgue attendants and that portion of the population which is most likely to suffer on account of bad housing conditions.

Haffkine's vaccine is a six weeks old broth-culture of *Bacillus pestis*, killed by heating to 55° C. for fifteen minutes and preserved with 0.5 per cent. carbolic acid. The dose for a healthy adult is 5 c.c. injected subcutaneously into the upper arm. Children may be given relatively large doses. Those over fifty years of age should receive one-tenth less than the adult dose for each decade above that age. The inoculation does not interfere with pregnancy, but after the seventh month the dose should be given in two inoculations.

Analysis, by Bannerman, of several hundred thousand inoculations made in India shows that the Haffkine prophylactic not only reduces the incidence, but the case mortality, and that the immunity conferred lasts for two, and sometimes for five years.

Shiga's modification of a saline suspension of the Bacillus pestis from agar slant cultures is just as effective if prepared with due

precaution and may be made ready in a shorter time. The suspension is of such a density that 1 c.c. contains 2 milligrams of wet germs. First 0.6 c.c. is injected subcutaneously; and when the symptoms have subsided (a week or ten days later), a second dose of 1 c.c. is given.

The symptoms following the inoculations are severe: inflammation at the site of injection, with edema and pain, fever, headache and general malaise. These require no special treatment unless it be an ice-bag to the head. Catharsis will often give relief.

R. P. Strong presented evidence which seemed to show that inoculation with living avirulent cultures yielded greater immunity in guinea pigs than that obtained by killed virulent cultures. Rowland, on repeating Strong's work, found that this was the only way to immunize guinea pigs, but that in the case of rats far greater immunity was obtained by the use of his **nucleoprotein extract**. It is probable that the cruder methods of active immunization described above will be supplanted by improvements based on the work of the late Sidney Rowland.

SPECIFIC THERAPY.—*Serum Treatment.*—Choksy has reported favorably on the use of the **Yersin-Roux antiplague serum**. Very mild, severely septicemic, and moribund cases were excluded. Out of 1081 cases, treated in India during 1905-1907, the general mortality was reduced to 49.6 per cent. If treated on the first day the mortality was 30 per cent.; on the second day, 52 per cent.; on the third day, over 60 per cent. Choksy does not give the doses of serum used generally, but an adult is stated to have received 420 c.c. in six injections, and a child, seven years old, with septicemia, received 270 c.c. in six injections. Both of these patients recovered.

MEDICINAL AND GENERAL TREATMENT.—A favorable report on the administration of **carbolic acid** by mouth has been given by Thomson. He lost only 30 per cent. of 143 cases. Twelve grains (0.78 gram) was given in capsules every two hours, or 144 grains (9.36 grams) daily. In some cases there was carboluria which was controlled by omitting a couple of doses.

The reports of favorable results obtained by Salvation Army workers in India in the use of **tincture of iodin**, *internally*, two to four drops in a glass of water every four hours, have not received support from the experiments of Liston on guinea pigs. Some of the practitioners in India, however, have reported rapid recovery, following the intravenous injection of a pint of physiologic salt solution containing as much as seven drops of the tincture of iodin. There is not enough evidence, however, to really evaluate this method. In general, it is advisable to give **calomel** and **salts** early in the disease. Pain should be controlled by **ice-packs**, and the temperature by **sponge baths**. The buboes should not be incised until they show fluctuation. The heart is best supported by **digitalis** and **strophanthus**. It is best to avoid coal-tar products, which might depress the heart. During convalescence **over-exertion should be avoided** as the heart action may remain feeble for a long time.

Prognosis.—The mortality in untreated cases varies from about 55 to 98 per cent. As can be seen from the results of therapy, the prognosis is always bad.

Pathology.—The appearance of the *buboes* is characteristic. The *primary bubo* is composed of one or more intensely congested swollen lymph-glands, varying from one to two or three centimeters in diameter and surrounded by a serogelatinous, hemorrhagic exudate. The hemorrhages may extend beyond this area into the surrounding skin and muscles. Pressure on the neighboring vessels may result in edema of the leg or arm in the case of inguinal or axillary buboes. A femoral bubo is often continuous with one involving the iliac glands. In the neck the swelling is often so large as to produce pressure upon the larynx, trachea, cervical nerves and blood-vessels, producing the dyspnea so conspicuous in these cases. The *secondary buboes* show practically no periglandular exudations and may not be surrounded by hemorrhages apart from those into the cortex of the glands which are enlarged and moderately or severely congested. On section, the glandular tissue is intensely red or reddish-gray, firm, or soft and diffluent, according to the stage of the disease.

Microscopically, the divisions into cortex and medulla are largely effaced by cell destruction, leukocytic infiltration and hemorrhage. The blood-vessels are usually filled with fibrinocellular thrombi. The periglandular tissues show necrosis with much fibrinocellular exudation. The *Bacilli pestis* are present in enormous numbers everywhere, even in the walls of the blood-vessels where they are especially numerous in the adventitial coat.

The *spleen* is congested and enlarged, firm or soft. The malpighian bodies are increased in size. Microscopically, there is marked engorgement of the vessels, infiltration and edema with proliferation of the perivascular cells and those surrounding the trabeculæ. There is much fibrin. The *Bacilli pestis* are very numerous, especially in the pulp.

The *blood* is usually dark and fluid. The heart is often soft and dilated. Microscopically there is often cloudy swelling of the myocardium and sometimes fatty changes. In twenty cases Herzog found few changes in the heart muscle worthy of notice. In the parietal and visceral pericardium one usually finds numerous petechiæ. Occasionally there is an excess of pericardial fluid which may be bloodstained.

The *larynx and trachea* are usually congested. The congested and swollen bronchial tubes in many cases contain frothy fluid, and show submucous petechiæ.

The *lungs* are greatly congested and edematous in most bubonic cases. In the pneumonia cases the involvement is usually at first peribronchial, but later may become lobar in type. Sometimes the consolidated areas are surrounded by an areola of intense hemorrhage. Apart from the greater tendency to hemorrhage, the descriptions given of the microscopical findings in plague pneumonia resemble those due to the pneumococcus and streptococcus.

The parietal and visceral *pleuræ* often show extensive subserous hemorrhages; frequently there is *hydrothorax*.

In the *congested alimentary* tract the lymph follicles are usually swollen throughout. There are often numerous petechial hemorrhages in the mucosa of the stomach and large intestine.

The *liver* shows the usual changes accompanying infections. Many petechiæ may occur under its coat. Petechiæ or more extensive hemorrhages may be found under the serous coat and in the mucosa of the *gall-bladder*.

The *kidneys* show subserous hemorrhages and are intensely congested. Microscopically one often finds a fibrinous thrombosis of the malpighian capillaries accompanying destructive changes in the tubular epithelium. At times there is hemorrhage into the pelvis of the kidney.

Occasionally, numerous petechiæ are seen in the mucosa of the *bladder*.

The cerebral and spinal *meninges* are usually greatly congested.

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CHAPTER XXVI

THE MYCOSES

By Richard L. Sutton, M.D.

Actinomycosis, p. 119—Favus, p. 122—Mycetoma, p. 125—Sporotrichosis, p. 128—Myringomycosis, p. 132—Tinea versicolor, p. 132—Erythrasma, p. 136—Pinta disease, p. 138—Blastomycosis, p. 139—Protozoic dermatitis, p. 143—Tinea imbricata, p. 143—Ringworm, p. 145

ACTINOMYCOSIS

Definition.—Actinomycosis, or "lumpy jaw," is a chronic infectious disease due to the *ray fungus,* and characterized by the development of indolent, granulomatous tumors, which tend to break down and discharge a seropurulent fluid, containing the granular bodies characteristic of the affection. No structure of the body is immune from attack; and in the majority of instances, the skin is secondarily involved. The head and neck are involved in about 52 per cent. of the reported cases, the abdomen in 21 per cent., the lungs in 13 per cent., the tongue in 4 per cent., and the skin in 2.5 per cent. (Little, quoted by Pusey).

Some of the domestic animals, and particularly cattle, are attacked much more frequently than men.

Etiology and Pathology.—As previously stated, the disease is due to the *ray fungus,* or *actinomyces.* The organism is a ball-shaped fungus, consisting of a central, interwoven network, with radiating, bulbous mycelia—its general structure roughly resembling that of a sycamore ball. It stains readily by the Gram and Ziehl-Gabbett methods. Stokes, who has studied the fungus culturally, concluded that the various pathogenic forms can at present be classified in seven species, all of which produce characteristic changes in the tissues of man and the lower animals.

The disease is most common in laborers, and particularly in agriculturists. Both Zeisler and Varney have reported cases in man contracted while chewing uncooked grain. The affection may be transmitted from one individual to another, or from man to animals, and *vice versa.*

Histologically, the lesions are infectious granulomata. The fungus is imbedded in an amorphous granular mass, with an areola of plasma cells, and a halo of lymphoid elements. A few giant and mast cells, also, are to be found in the immediate neighborhood.

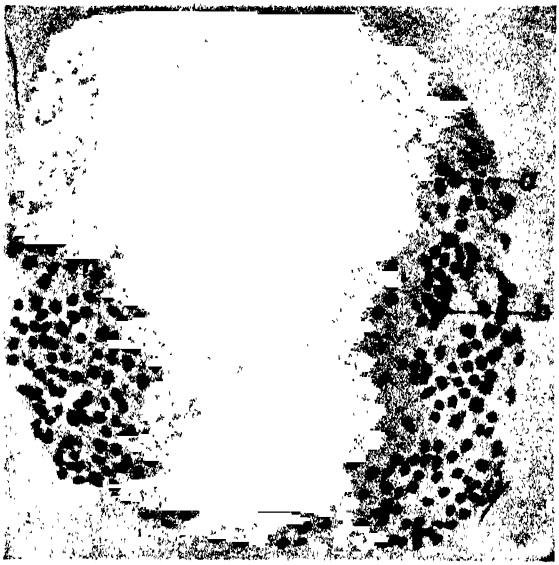


FIG. 1.—ACTINOMYCOSIS GRANULES, SHOWING RADIATING FILAMENTS.

a, granule; *b*, tips of filaments. (Courtesy Dr. Arthur E. Hertzler, from Sutton's "Diseases of the Skin," C. V. Mosby Co.)



FIG. 2.—ACTINOMYCOSIS IN MAN; EARLY

Disease contracted through decayed tooth. (Courtesy Dr. Jabez N. Jackson, from Sutton's "Diseases of the Skin," C. V. Mosby Co.)

Symptomatology.—In the mouth and throat, the fungus usually gains entrance through a decayed tooth or a diseased tonsil. The first clinical evidence of its presence often is a hard lumpy swelling in the parotid or maxillary region. The involved skin becomes elevated and



FIG. 3.—ACTINOMYCOSIS OF THE JAW; TYPICAL EXAMPLE. (Courtesy Dr. George M. MacKee.)

reddened, and pea- to walnut-sized nodules develop and sooner or later soften and break down, discharging serum and seropurulent matter which contains large numbers of minute, friable, yellowish, fish-roe-like bodies, made up of conglomerate masses of the fungus.

The *incubation period* varies, but usually extends over a period of several months; and the course of the disease ordinarily is slow and

protracted. Granulation tissue sometimes develops around the sinus openings, and the lesions may bear a striking resemblance to those of scrofuloderma. The size of the affected areas varies somewhat, but in the cervical and maxillary cases, which are by far the most common, the patches are seldom larger than the palm of the hand.

The *subjective symptoms* are remarkably slight, when the seriousness of the disorder is taken into consideration; and secondary pus infection generally gives rise to far more pain than that caused by the parent malady.

Lymph-node metastases are rare; and nodal enlargement, if present, is usually the result of secondary staphylococcic involvement. Constitutional symptoms, likewise, are largely dependent on the degree of the accompanying pus infection.

Diagnosis.—The history, localization and character of the lesions, together with the granular discharge, should serve for recognition. The presence of the fungus is, of course, pathognomonic. In doubtful cases, repeated examinations should be made in order to discover or exclude the presence of the causative organism. Syphilis, tuberculosis, sarcoma, carcinoma and mycetoma are to be excluded. The writer has seen one instance in which the affection was confused with tinea barbæ, but the resemblance was, of course, very superficial.

Treatment.—Aside from large doses of **iodin internally,** and the **x-rays locally,** the treatment is **surgical.** Any complicating pyogenic infection is to receive appropriate treatment. It is possible that **vaccine therapy** might prove helpful in severe or obstinate cases.

Prognosis.—The vast majority of the localized cases recover, but the prognosis must always be guarded, for generalized infection may occur.

FAVUS

Definition.—Favus is an infectious disease of the skin, due to a fungus (the *Achorion schoenleinii*) and characterized by the occurrence of rounded or oval, pinhead-sized, saucer-shaped, yellowish crusts, or scutula.

Etiology and Pathology.—The causative agent is a fungus, the *Achorion schoenleinii,* and it is probable, as Unna and others believe, that there are several varieties of the organism.

The disease is infectious and may be spread by the common use of combs, towels and other toilet articles, and the interchanging of headgear. The affection may also be transmitted to animals, and through them back to man. The majority of cases occur in careless or dirty individuals who live in crowded quarters. It is common in Poland, Russia and central Europe, and in some parts of France and Scotland. An occasional imported case is seen in the United States. In ten years of rather extensive clinical experience in the Middle West the author has met with but two instances, both occurring in Polish Jews, who contracted the disease abroad.

The fungus forms long, slender, branching filaments, with numerous spores, and reproduces by endoconidia, by sprouting, and by the formation of unsegmented spindles (Pusey). It is probable, as Walker has stated, that the saucer-like shape of the scutula is due, not to the anchoring down of the center of the hair, but to the fact that the fungus elements of which the scutulum is composed are more luxuriant and



FIG. 4.—FAVUS OF THE SCALP; TYPICAL EXAMPLE IN A BOY. (Courtesy Dr. George M. MacKee, *Medical Record*.)

moist at the margin, while at the center they are dry and closely packed together. Scutula develop even when the fungus is grown on nutrient agar. When an affected hair shaft is examined under the microscope (after first having been cleansed with ether, and then treated for several minutes with a 10 per cent. aqueous solution of caustic potash) it will be found to be entirely filled with long ribbon-like mycelia. The medullary canal is entirely obliterated. It is because of this complete destruction of the medullary substance that the hair shafts are so dry, lusterless and brittle. On the glabrous skin, a lanugo hair is commonly

the site of the attack. The skin is usually very superficially affected, the organisms seldom penetrating much below the stratum corneum.

Symptomatology.—The most typical lesions are to be found on the scalp; and in this region each of the crusts, which are from 2 mm. to 4 mm. in diameter, and are composed of masses of the organism, together with epithelial débris and inspissated serum, is at first discrete and penetrated by a single hair. Later, as the disease progresses, the lesions become confluent and form yellowish, or dirty yellow, scaly masses, penetrated here and there by dry, lusterless, brittle hair shafts. When a crust is removed, a small, pinkish, or reddish, variola-like pit is left.

As a result of pressure atrophy and of the accompanying slight inflammatory reaction, together with changes in the infected shaft, there is more or less destruction of the involved hair follicles, and partial or complete, but permanent, baldness commonly ensues. The crusts have a peculiar and characteristic "mousy" odor, which often proves of value as a diagnostic aid.

In long-standing and insufficiently treated cases, the saucer-shaped crusts may be few in number or entirely wanting, but the traces of pressure atrophy, the follicular changes and hair destruction, and the mouse-nest-like odor serve for recognition.

The lesions are auto-inoculable, and asymmetrically grouped. The scalp usually is first involved. No region is exempt, however, and in extensive cases, the glabrous skin may present numerous patches of the disease, and both the finger and toe-nails may contain masses of granular, yellowish detritus, consisting almost wholly of fungi. In the ungual region, the epidermis underlying the free edge of the nail is particularly subject to attack.

As in tinea trichophytina, the disease is usually contracted in early life, but unlike that disorder, there is no tendency to spontaneous recovery. In those instances in which the glabrous skin is involved, the disease may ultimately disappear from the body surface, even when untreated: but the hairy and ungual regions seldom, if ever, escape; and in these localities the disease may persist indefinitely, despite treatment. The mucous surfaces rarely are involved.

Subjective symptoms commonly are absent.

Diagnosis.—The sulphur-colored scutula, if present, are pathognomonic. In the absence of these, the history, together with the location of the areas involved, the dry, brittle, lusterless condition of the hair, the peculiar type of atrophic baldness present, and the mouse-like odor, all serve for recognition. Should these signs fail, a microscopical examination of the hairs in the affected region should be made.

Clinically, the disease differs essentially from ringworm, psoriasis and seborrheic dermatitis—affections to which it may bear a superficial resemblance.

Treatment.—The scalp should first be thoroughly cleansed by means of **oily applications,** followed by the use of soap and water. The ideal plan is **epilation** by means of the **x-ray,** as described under ring-

worm (*see* page 162), followed by the use of **mild antiseptic ointments.** Should this plan be impracticable, epilation by means of thumb forceps should be practiced. The hair should be kept clipped, and a weak alcoholic solution of **bichlorid of mercury** (1 to 2000) applied to the entire scalp once daily. In addition to this, an **ammoniated mercurial ointment** (5 per cent.) alone, or with **salicylic acid** (5 per cent.) added, should be rubbed into the affected areas each day, immediately after

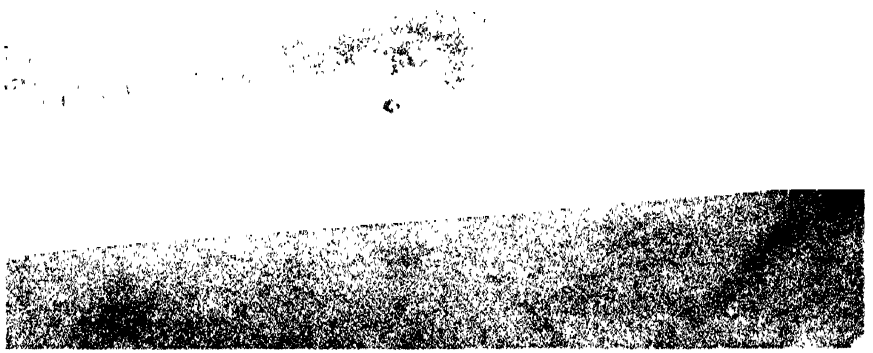


FIG. 5.—FAVUS OF THE FOREARM.

Yellowish crusts on inflamed base; a few typical scutula. Scalp also involved. (Courtesy Dr. George M. MacKee.)

epilation. Recently, Strickler, Kolmer and Lavinder have successfully employed a **vaccine** in the treatment of favus of the scalp.

Favus of the body responds promptly and favorably to frequent applications of a **mild mercurial ointment.**

Prognosis.—Untreated, the disease persists indefinitely, if the hairy regions are involved. Even with persistent treatment, the outlook in long-standing cases is discouraging. In the early cases, however, intensive and conscientious treatment is generally followed by a cure. The hair loss is usually permanent.

MYCETOMA

Definition.—Mycetoma, fungus foot, or Madura-foot, is a chronic infectious disorder of the extremities, due to a species of *streptothrix*, and characterized by swelling of the affected part, with subsequent disintegration of the subcutaneous structures, and the formation of sinuses, which open on the surface of the skin.

The malady was accurately described by Kaempfer as far back as 1712, but occurs only sporadically in temperate climates. The vast majority of reported cases have come from India, and particularly from Madura.

Etiology and Pathology.—Bacteriologically, several different fungi have been isolated. It is generally conceded that the yellow and black, at least, are due to different organisms.

Musgrave and Clegg have recently made a careful laboratory study of an organism found in a case of the ochroid type, with a fungus which they recovered, and to which they gave the name *Streptothrix freeri*,



FIG. 6.—MYCETOMA, SHOWING CHARACTERISTIC SINUS OPENINGS.

and with which they successfully inoculated a number of monkeys and domestic animals. In these instances, they succeeded in securing typical examples of Madura-foot in monkeys.

It is possible that the tissues (synovial membranes, etc.) of this part of the body are particularly susceptible to this organism.

Musgrave and Clegg found variations in the color of the granules, even when the same infecting agent was used. They conclude that all types of mycetoma are due to some form of streptothrix infection; and that the disorder differs both bacteriologically and clinically from actinomycosis—a fact the truth of which has been denied by Kanthack and others.

Histologically, the earlier changes are those characteristic of infectious granulomata. Later, as the disease progresses, all of the tissues

of the foot are involved; and the numerous abscesses and sinuses connect the part into a swollen, sponge-like mass, filled with cysts, seropurulent matter, and broken-down connective tissue.

Symptomatology.—The foot is usually the part attacked, although the hand, or even the knee, or elbow, is occasionally involved.

The organism generally gains access to the subcutaneous tissue through some slight wound or break in the skin, such as a thorn prick. In the course of a few days or weeks, the part becomes inflamed and swollen, and a firm, rounded nodule develops. This is followed by

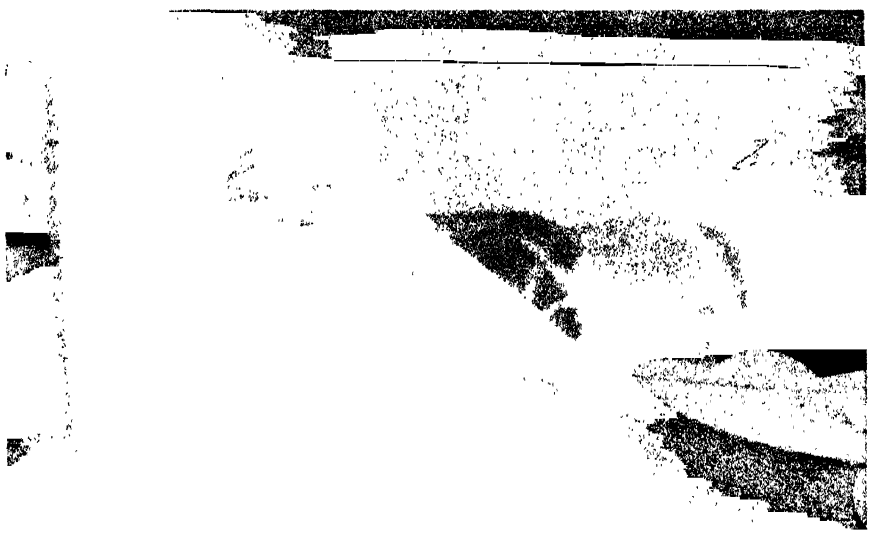


FIG. 7.—MYCETOMA, SHOWING PROGRESS OF THE DISEASE, NECESSITATING AMPUTATION OF FOUR TOES. (Courtesy Dr. John W. Perkins.)

others until the affected area soon presents a reddened or purplish, knobby appearance, not unlike that seen in actinomycosis. Many of the nodules are perforated by narrow, tortuous canals, which pass far downward into the interior of the part, and discharge an oily, seropurulent fluid containing numbers of yellowish, reddish or brownish

The progress of the malady is slow, weeks and months often being required before it is fully developed.

Clinically, the disease is commonly divided into three varieties—the yellow, black and red, according to the color of the fish-roe-like granules thrown off. The yellow, or ochroid, is the commonest type. When once the nodules have broken down, they do not tend to heal, but con-

tinue to discharge. The number of fistulous openings varies from eight or ten to a half hundred or more. As the disease progresses, the part becomes enlarged, swollen and misshapen, until finally it may almost entirely lose its original outline.

The *subjective symptoms* are remarkably trivial. Lymph-node involvement occurs only as a result of secondary pyogenic infection.

Diagnosis.—The history of the case, the location of the disease, and the presence of the sinuses, with the oily, grain-laden character of the discharge, should serve for easy recognition.

Treatment.—Internally, **iodin** is the most reliable remedy. It is possible that **vaccine therapy** might prove helpful. Locally, **curettage, the x-rays** and **caustics** may be tried. **Excision** of the affected part, however, usually offers the only hope of permanent relief.

Prognosis.—The malady is a chronic one, extending over a period of years, or even decades. As a result of disuse, the affected limb may become shrunken and wasted. While the disease does not impair the internal organs, and seldom, if ever, directly causes death, it is very resistant to treatment. It never disappears spontaneously.

SPOROTRICHOSIS

Definition.—Sporotrichosis is a chronic infectious disease due to the *sporothrix,* and characterized by the development of numerous abscesses in the skin and other organs. The malady was first described by Schenck, in 1898, and has been exhaustively studied, both clinically and bacteriologically, in this country and in Europe, and particularly in France.

Etiology and Pathology.—The causative organism is an aërobic fungus, a sporothrix, which can seldom be found in the affected tissue by direct examination, but can readily be cultivated from the diseased material on almost all of the common media. Sabouraud's peptone-glucose-agar probably is best, but the writer has repeatedly grown the organism on agar and in bouillon. In cultures it occurs as slender mycelial threads, with minute, rounded or oval spores.

The fungus is pathogenic to animals as well as to man; and several different species are recognized. French observers, especially, have done much work along this line. It is very probable, however, as Meyer and Aird have suggested, that the *Sporothrix schenckii* and the *Sporothrix beurmanii* are identical. If this be the case, confusion will be avoided by restricting the descriptive adjective to the original discoverer, Schenck.

The ages of the patients in the reported cases vary from five to seventy-eight years. The majority were from the agricultural districts. In many instances, the port of entry of the fungus into the body remains undiscovered.

Histologically, the changes are not well defined, and may bear con-

siderable resemblance to those of syphilis, tuberculosis and staphylococcic infections.

Symptomatology.—Up to this time fully one hundred cases of the affection have been reported from the United States, principally from the Middle West and the Mississippi Valley region. Hamburger, of Chicago, and Meyer, of California, have made valuable and exhaustive statistical studies of the disorder. De Beurmann and Gougerot separate the cases into several clinical types, chief among which are the "syphi-

FIG. 8.—SPOROTHRIX, FROM CULTURE. (Medium magnification.)

loid" and "tuberculoid" forms, and the "giant abscess" type of Dor. In the majority of instances, as seen in this country, the skin only is involved. The organism commonly gains entrance through some break in the skin, as a small punctured or incised wound; and at this point a small ulcer may develop, which is often spoken of as "the initial lesion." In the course of a few days or weeks, a chain of pea- to nut-sized, subcutaneous nodules appear along the course of the lymphatics, draining the part, and ultimately these break down and form sharply defined, fluctuating, subcutaneous abscesses. The overlying skin seldom ruptures spontaneously, and the abscesses may persist for weeks, giving rise to very little pain or discomfort. The *subjective symptoms* are slight,

and in the cutaneous cases, the constitutional disturbance usually is absent. Occasionally two or more of the cavities may become joined by sinuses.

The large gummatous types are rare in this country, but comparatively common in France.

The mucous membranes (buccopharyngeal) may be involved, and the lungs sometimes are attacked.

Diagnosis.—The lesions are to be differentiated from those of syphilis,

FIG. 9.—SPOROTHRIX, FROM CULTURE, SHOWING MYCELIA AND SPORES. (High magnification.)

tuberculosis and cellulitis. In doubtful cases, recourse should be had to a cultural study. In syphilis, the history, distribution and character of the lesions, together with the fact that subcutaneous abscesses are extremely rare, should serve for recognition. The same facts hold true in tuberculosis. In cellulitis, both the subjective and constitutional symptoms are well and sharply defined. The characteristic cutaneous manifestations of cellulitis are always accompanied by malaise, chills, fever and more or less prostration, and while the hyperemia and other signs of inflammation along the course of the involved lymphatics are well defined, suppuration is rare.



FIG. 10.—SPOROTRICHOSIS OF THE HAND AND FOREARM.

Infection followed injury of the hand. Note characteristic chain of abscesses. No elevation of temperature and very little pain. (From Sutton's "Diseases of the Skin," C. V. Mosby Co.)

Prognosis and Treatment.—In the uncomplicated cases, as encountered in this country, under proper treatment recovery is generally prompt and uneventful. In the rare systemic cases, the outlook is less hopeful.

Iodin, internally, in the form of the sodium or potassium salt, and locally, in the form of the tincture, can usually be depended upon to



FIG. 11.—SPOROTRICHOSIS, SHOWING CONDITION OF ARM FOLLOWING INCISION AND DRAINAGE OF ABSCESSES.

Prompt recovery under iodin treatment.

bring about a cure. If the patient is too susceptible to the drug to take it by the mouth, it should be administered in solution hypodermatically.

MYRINGOMYCOSIS

Definition.—Myringomycosis is a chronic superficial inflammatory disorder of the external auditory meatus, canal and drum, due to certain fungi, probably the *Aspergillus niger* and the *Aspergillus glaucus*.

Symptomatology.—As a result of the inflammatory process, a scaly, moist, pultaceous, greenish or brownish crust is produced, which, when forcibly removed, exposes a reddened, moist, weeping surface. The whole canal, including the drum, may be involved, or the disease may be confined entirely to the meatus. In severe and more extensive cases, the drum may become perforated, or even destroyed. Barclay, who has exhaustively studied the condition, believes that the drum is primarily attacked, the disease subsequently extending to the canal. The first symptoms are itchiness and pain of varying degree, with more or less impairment of hearing. The surface of the skin early becomes scaly and moist. There is no tendency to spontaneous disappearance.

Diagnosis.—The disease is to be differentiated from eczema and from seborrheic dermatitis.

Treatment.—Fatty applications appear to stimulate rather than retard the growth; consequently, resort must be had to various antiseptics in aqueous or in alcoholic solution. Burnett found a 1 per cent. solution of **sodium hyposulphite** valuable. Löwenberg recommends frequent washing with dilute or pure **alcohol**. The author has employed weak solutions of **silver nitrate** (1 to 5 per cent.) with very satisfactory results. In those cases presenting deep or extensive involvement, recourse should be had to the services of an aurist.

TINEA VERSICOLOR

Definition.—Tinea versicolor is a vegetable parasitic disease of the skin, due to infection with the *Microsporon furfur,* and characterized by the occurrence of yellowish, or brownish, furfuraceous, macular patches irregularly distributed over the chest and back.

Etiology and Pathology.—The disease is due to a vegetable fungus, the *Microsporon furfur,* discovered by Eichstadt in 1846, and is mildly infectious in character. At one time, it was thought that tuberculous individuals were especially susceptible to attack, but, aside from the fact that persons with excessively moist skins possibly are more liable to infection than normal individuals, it is doubtful if this is true. According to Pusey, Hublé found the disease in 68 per cent. of healthy young French soldiers, and Hazen says that it constitutes .8 per cent. of all dermatoses. Consequently, it can readily be seen that the malady is far more common in Europe than in this country.

Histologically, only the upper layers of the stratum corneum are involved, and on disappearing the disease leaves no trace.

Symptomatology.—The disease is a common one, especially in otherwise healthy individuals, and the majority of patients are adult males. The earliest perceptible lesions are minute, yellowish, macular points covered with minute scales, and usually located on the anterior surface of the chest. These gradually increase in size and number, and finally coalesce to form large, irregular plaques, which ultimately may cover



FIG. 12.—MICROSPORON FURFUR. (Moderate magnification.)

the entire upper portion of the trunk. The scaling is most readily appreciable in dry, harsh-skinned individuals, and can easily be demonstrated by gently stroking the affected surface with the sharp edge of a curette. The palms and soles are seldom affected. In rare instances the neck, and even the face and scalp, may be involved. On the face, the lesions may be mistaken for those of chloasma.

The eruption is wholly macular, although occasionally, as in a case seen by McEwen, follicular involvement may be sufficiently marked to give rise to a nutmeg-like appearance.

The course of the disease is essentially slow and tedious, and owing to the lack of subjective symptoms, the discovery of its presence often

is a matter of accident. The author has repeatedly encountered such cases during the routine examination of recruits. While the eruption may give rise to slight itching or other feeling of discomfort, as a rule *subjective symptoms* are entirely wanting. After progressing up to a



FIG. 13.—TINEA VERSICOLOR, SHOWING CHARACTERISTIC DISTRIBUTION. (Courtesy Dr. George M. MacKee.)

certain point, the eruption is apt to remain more or less stationary for months or even years.

Diagnosis.—The color, character, distribution and history of the lesions should serve readily for their recognition, and the presence of mycelia and spores can readily be demonstrated in the scrapings

after they have been treated for a few minutes in a 10 per cent. aqueous solution of liquor potassæ. In pityriasis rosea, the disease runs an acute course, and the lesions, instead of being brownish in color and irregular in outline, possess a pinkish or yellowish tinge, and are oval





FIG. 14.—TINEA VERSICOLOR, USUAL DISTRIBUTION.
Fungus recovered.

or rounded in outline. In seborrheic dermatitis, the sternal and axillary regions are favored points of attack, and the lesions, in addition to being greasy in character, and frequently circinate in outline, are definitely inflammatory. The microsporon also is of course absent. Other

affections which at times may prove confusing are, chloasma, and the hyperpigmented borders occurring in vitiligo.

Treatment.—The daily application of an **ointment** containing **ammoniated mercury** (5 per cent.) and **salicylic acid** (5 per cent.) often is followed by the disappearance of the eruption, and **sulphur** and **resorcin** also prove effective remedies at times. Walker recommends a 10 per cent. **alcoholic solution of tar.** In the writer's experience, a much more satisfactory plan of treatment is the **sodium hyposulphite** and **tartaric acid** method recommended by Crocker. The patient first scrubs thoroughly with soap and warm water, using a nail brush, and then dons clean underclothing. A 5 per cent. aqueous solution of sodium hyposulphite is then thoroughly applied to the affected surface by means of a flannel cloth, and this is followed by a 3 per cent. aqueous solution of tartaric acid, also vigorously applied with a flannel cloth. By the action of the acid on the sodium salt, nascent sulphur and sulphurous acid are produced *in situ,* and as a rule only a few applications are required to bring about a cure. The remedies should be employed nightly for one week, care being taken to sterilize the underclothing; and after this, treatment can be discontinued unless new patches develop.

Prognosis.—The disease is readily and promptly eradicated by appropriate local treatment, and even if neglected, is harmless.

ERYTHRASMA

Definition.—Erythrasma is a vegetable parasitic disease of the skin, due to infection with the *Microsporon minutissimum,* and characterized by the occurrence of brownish or reddish-brown patches in the genitocrural and axillary regions, and on other moist opposing surfaces.

Etiology and Pathology.—The affection is due to a small hyphomycetic fungus, the *Microsporon minutissimum,* which was originally discovered by Burchardt in 1859. The designation, "erythrasma," was suggested by von Bärensprung in 1862. It is a disease of adult life, and is rare in America, but comparatively common on the Continent. The organism can readily be recovered from the scrapings, and is a delicate fungus presenting both hyphæ and granules. The threads vary in length from 0.04 to 0.06 of a millimeter, and are piled in irregular shapes.

Only the more superficial layers of the stratum corneum are involved, and the hair follicles entirely escape.

Symptomatology.—The disease usually begins in the genitocrural folds, as small, rounded or irregular, well-defined, reddish-brown scaly patches. The scales are minute and furfuraceous, and can readily be removed with a sharp curet, or even the edge of a finger-nail. As the patches enlarge, they tend to coalesce, the confluent plaques retaining the clinical characteristics of the smaller lesions. In cases invading the axillæ, the disease may spread to the other flexor surface, but this course is unusual.

After becoming fully established and progressing up to a certain point, the disease generally remains stationary for months or years. There is no tendency to spontaneous disappearance. Usually the *subjective symptoms* are slight or entirely lacking; and not uncommonly the presence of the disease is discovered only by accident.



FIG. 15.—ERYTHRASMA OF THE CRURAL REGION.

Diagnosis.—The disease must be differentiated from tinea trichophytina cruris, pityriasis rosea, tinea versicolor and seborrheic dermatitis.

Tinea cruris develops more rapidly, and is accompanied by well-marked signs of inflammation. Itching and burning are frequent accompanying symptoms. The lesions are reddened, inflamed and elevated, particularly at the borders of the patches.

In pityriasis rosea, the eruption is scattered over the entire trunk

and there is usually a history of a primary "mother patch." The course of the disease is acute, and an attack seldom extends over a period of five or six weeks. The lesions are yellowish, or pinkish, in color, and rounded or circinate in outline.

Tinea versicolor is seldom, if ever, limited to the genitocrural and axillary regions, and the lesions are yellowish or light brown in color. In doubtful cases, resort should always be had to a microscopic examination of the scales.

Prognosis and Treatment.—The disease is a mild and trivial one, but is more resistant to treatment than tinea versicolor. The same methods of treatment are applicable to both disorders.

PINTA DISEASE

Definition.—Pinta disease is a vegetable parasitic disorder of the skin and mucous membranes, due to the conjoint action of several different fungi, and characterized by the occurrence of variously sized, shaped and colored scaly patches.

Etiology and Pathology.—The disease is endemic in certain tropical portions of South America, and its development is favored by careless and uncleanly habits of living. Both the white and black races are susceptible. The results of the investigations of Florez and others indicate that the affection is due to the action of several fungi, notably the aspergillus, penicillium, monilia, and, possibly, a trichophyton (Blanchard and Bodin).

Histologically, the disease at first is confined to the outer layers of the epidermis, but later the prickle layer, and even the stratum germinativum and the corium sometimes are involved.

Symptomatology.—The spots first appear on the exposed surfaces, particularly the face, neck and hands, and they may develop on some previous eruption. Occasionally, an attack is preceded by gastro-intestinal disturbance, but this is the exception and not the rule. The lesions are wholly due to the growth of fungi and may be superficial or deep. The color varies from grayish to bluish or black. As a result of the inflammatory reaction, there may be more or less sloughing, with the consequent formation of smooth, whitish, atrophic cicatrices. The patches are irregular in outline and distribution, sharply defined, and more or less itchy from the beginning. No part of the body is exempt, but the palms and soles are seldom attacked. In their general character, the lesions at first closely resemble those of tinea versicolor (Hazen), but later the deeper layers of the skin become involved, and ultimately the rete may become fairly riddled with fungi. The scaliness is at first furfuraceous, but later lamellar, and a hyperkeratinization of variable degree frequently develops. The mucous membranes are involved only in extreme cases. In many instances the hair in the involved areas become thinned, dry and harsh, and may fall out, probably as a result of fibrosis with ensuing atrophy. The course of the disease is chronic, and

may extend over a period of many years, and there is no tendency to spontaneous disappearance. There is intense itching at times, but aside from the discomfort of the cutaneous changes arising from frequent and violent scratching, the general health is not affected.

Treatment.—In the earlier stages of the disease, mild **parasiticidal ointments,** as **ammoniated mercury** (5 per cent.), **sulphur** and **salicylic acid** (10 per cent.), **tincture of iodin,** and similar agents, may prove effectual. As the deeper layers of the skin become involved, however, recourse must be had to **chrysarobin** and similar vigorous medicaments.

Prognosis.—The disease is obstinate and resistant to treatment and exhibits no tendency to spontaneous cure. Many of the cases persist through life.

BLASTOMYCOSIS

Definition.—Blastomycosis is a chronic infectious disorder due to a yeast fungus, the *blastomycete,* which attacks the skin and various internal organs, giving rise to numerous minute, chronic abscesses. The disorder was first described by Gilchrist in 1894, and has been extensively studied by Hyde, F. H. Montgomery, Hektoen, Ricketts, Pusey, Ormsby and Miller, Varney, Bowen, Kessler and others, in this country, and Buschke and Büsse in Germany.

Etiology and Pathology.—The disease is due to a vegetable fungus, the *blastomycete,* a peculiar budding organism which superficially resembles an ordinary yeast cell. The organism can usually be readily recovered from the miliary abscesses, and is easily cultured, best on maltose agar. Guinea pigs and other laboratory animals are susceptible to infection. The organisms are rounded or oval in outline, occur singly or in pairs, and average about 10 or 12 microns in diameter. They possess a distinct capsule, and the central portion is made up of finely granular protoplasm. In the body they reproduce by gemmation without spore formation.

Histologically, there is marked acanthosis, many of the interpapular projections extending far below the ordinary level. As Hazen says, when shaved off, the prolongations may resemble carcinoma of the skin, except that the normal relationship of prickle and basal cells is undisturbed. The small abscesses lie between these epidermal downgrowths, and contain numerous polynuclear cells, as well as serum and fungi.

In man, there is often a history of trauma preceding the development of the first lesion. The majority of cases occur in persons who lead an outdoor life. For some unknown reason, the disorder is quite prevalent in and around Chicago, a considerable percentage of the recorded cases having been reported from that region. It is also a fairly common affection in other parts of the Middle West. It is very rare in England, and comparatively so on the Continent.

Symptomatology.—In the skin, the lesions consist of collections of elevated, warty, suppurating, pea-sized, papules or papulopustules, with

sharply sloping, purplish-red borders, and numerous subdermal miliary abscesses, filled with pus and seropurulent matter. The surface of the lesions is moist and crusted; and when the masses of dried pus and débris are removed, the oozing, granular points are exposed. The patches increase in size, either by peripheral extension or through the development of satellite lesions. When healing does occur, the surface is left rough and verrucose. The ulceration is comparatively superficial, and in many respects the many lesions resemble those of tuberculosis verrucosa cutis, a disease with which blastomycosis was formerly very frequently confounded.

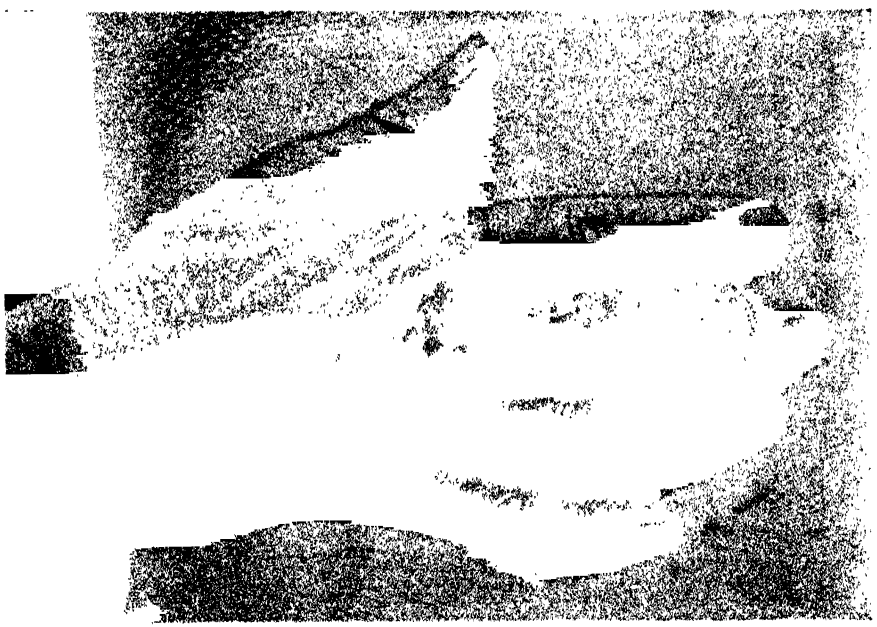


FIG. 16.—BLASTOMYCOSIS OF THE HAND, FOLLOWING INJURY OF FINGER. (Courtesy Dr. Otto Leslie Castle, from Sutton's "Diseases of the Skin," C. V. Mosby Co.)

The general health, except in the somewhat rare systemic cases, is unaffected. The commonest sites for the lesions are the uncovered areas —the hands and face—although no portion of the body is exempt. Several instances have been recorded in which the eyelid was involved. The mucous membranes occasionally are attacked.

The initial lesion is an indolent reddish papule or papulopustule, which bleeds easily, and at the border of which the characteristic minute abscesses containing the organism can always be found.

The course of the disease is essentially chronic, although spontaneous healing may occur.

Diagnosis.—The disease is to be distinguished from tuberculosis verrucosa cutis, sporotrichosis, syphilis and lupus vulgaris.

In tuberculosis verrucosa cutis, the lesions develop more slowly, the

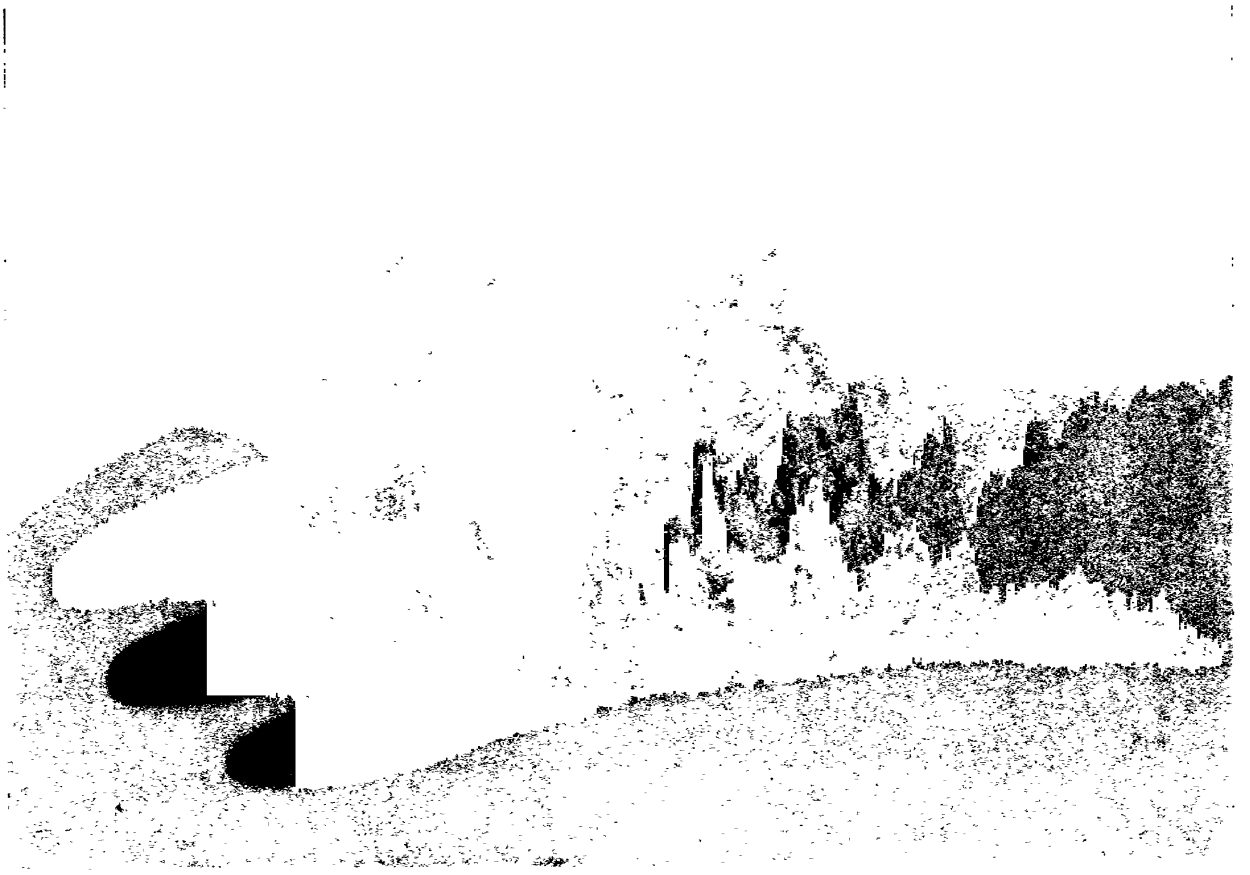


FIG. 17.—BLASTOMYCOSIS OF THE HAND IN A FARMER.
Duration three months. Presence of fungus demonstrated. (Courtesy Dr.George M. MacKee.)

margins of the patches do not slope so abruptly, and the miliary abscesses characteristic of blastomycosis are absent. In sporotrichosis the lesions usually develop along the course of the lymphatics; giving rise to hard, subcutaneous nodules which finally break down, but never give rise to the granular, suppurating patches seen in blastomycosis. The vegetating syphiloderm is at first tubercular and characteristic in outline (segmentary or circinate), finally breaking down and becom-



FIG. 18.—BLASTOMYCOSIS OF THE EYELID, A NOT UNUSUAL LOCATION. (Courtesy Doctors J. B. and J. C. Kessler.)

ing covered by a foul, greenish crust. The Wassermann test is positive.

In lupus vulgaris, the progress of the lesions is very slow, marked ulceration may occur; and the miliary abscesses pathognomonic of blastomycosis are absent.

Treatment.—Internally, **iodin** to the limit of toleration is the most reliable remedy. Gilchrist has reported improvement following the injection of a sterilized autogenous filtrate from living organisms. Stober has used **vaccines** with encouraging results.

Locally, dependence is to be placed in the **x-ray, curettage, superficial cauterization** or **excision.** The careful and thorough use of

Roentgen therapy has in the writer's hands proved the most valuable of all agents. Of the various antiseptics, **iodin** is one of the most effectual.

Prognosis.—The systemic cases generally prove fatal (90 per cent., Stober). The cutaneous cases are obstinate and resistent, but perseverance in treatment is usually followed by a cure. Recurrences are not uncommon. Occasionally, the lesions disappear spontaneously.

PROTOZOIC DERMATITIS

Definition.—Protozoic dermatitis, dermatitis coccidioides or coccidioidal granuloma is a chronic inflammatory disease of the skin, which occurs almost exclusively on the Pacific coast and is closely allied to, if not identical with, blastomycosis. The affection was first described by Wernicke, of South America, in 1890, and has been carefully studied by Rixford, Gilchrist, Howard Morrow, D. W. Montgomery, Chipman and others in this country. Pusey has reported one characteristic case occurring in a foreign-born woman in Chicago.

Etiology.—Ophüls believes that the causative organism is larger than the blastomycete, that it multiplies by endogenous sporulation and that there is no budding. Hektoen has found that the nodules are tuberculous rather than blastomycetic in character.

Symptomatology.—The lymph nodes are early and extensively involved, and the disease is prone to become systemic and generalized.

Treatment.—The treatment is the same as for blastomycosis.

Prognosis.—The prognosis, in so far as life is concerned, is always serious.

TINEA IMBRICATA

Definition.—Tinea imbricata is a vegetable parasitic disease of the tropics, characterized by imbricated, scaly patches, which usually take the form of concentric rings. Manson states that its distribution corresponds closely with that of the cocoanut tree (Burma, Southern China and the Malay archipelago).

Etiology and Pathology.—As previously stated, the occurrence of the affection is practically confined to certain tropical countries. Children are attacked oftener than adults.

The causative fungus resembles in many of its characteristics the trichophyton, but grows in the horny epidermis in much greater abundance than the ordinary types of that organism. Castellani, who has recently made an exhaustive study of the fungus, believes it to be an endodermophyton. Under suitable conditions, the lesions develop very rapidly following inoculation.

Symptomatology.—The lesions are at first rounded or oval in outline, slightly elevated, and brownish in color. Ultimately, the epidermis in the center of the ring becomes broken and splits up and loosens, as the patches enlarge, forming imbricated, paper-like scales.

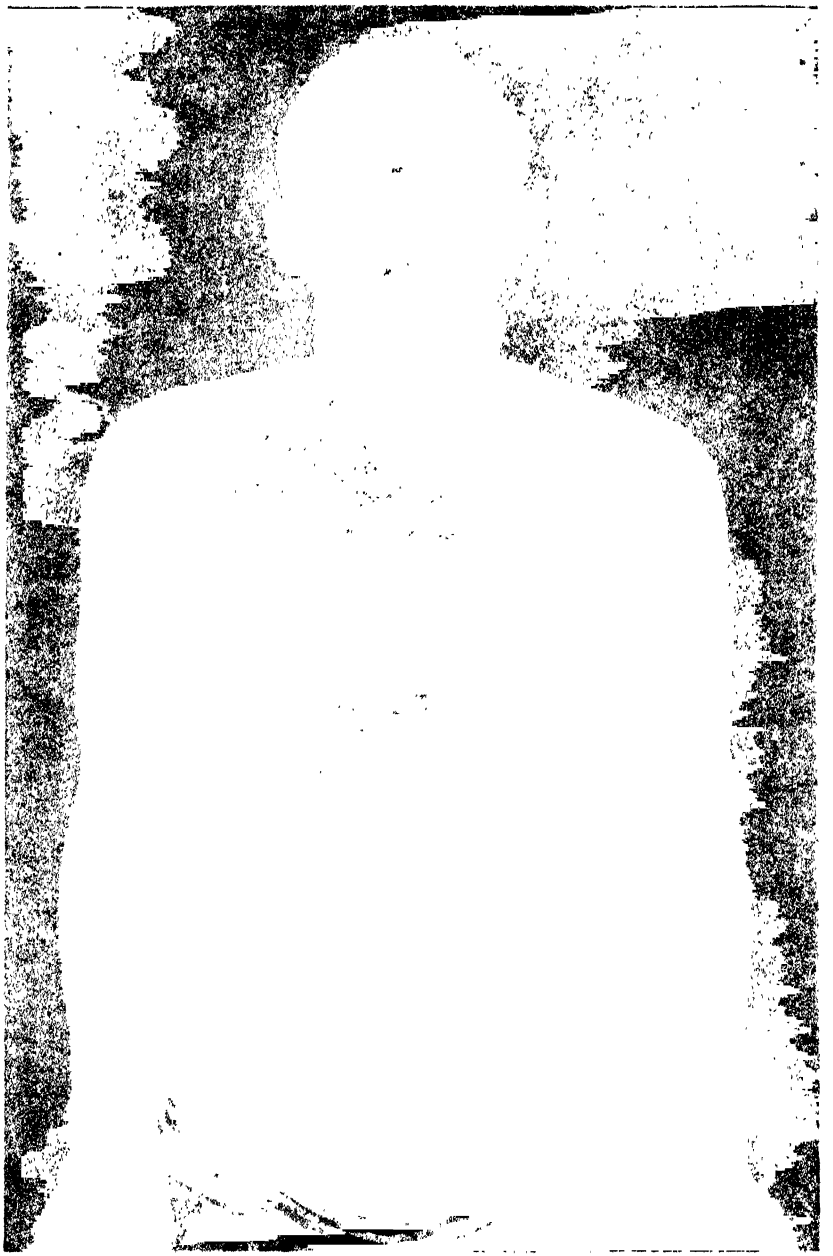


FIG. 19.—TINEA IMBRICATA. SHOWING CHARACTERISTIC "WATERED-SILK" APPEARANCE. (After Hengeller.)

As the rings increase in diameter, new lesions develop in the central portion. These undergo the same involution changes as the earlier ones, until ultimately a series of three or more may be present at one time. Owing to the frequent intersection of two or more patches, gyrate or serpiginous figures may be formed. As a rule, the extending margin of the ring is narrow—from 1 to 5 cm. in width—and if the inflammatory process is very acute, vesiculation and even suppuration may be present. In the majority of instances, only the superficial layers of the skin are involved, although Königer and others have observed cases in which both the hair follicles and shafts apparently were attacked. In the older lesions, the scales are thin and quite large, from 1 to 2 cm. in diameter. According to Castellani, the nails occasionally are affected. In very dark-skinned individuals, the patches appear lighter than the normal skin: in light-skinned individuals, darker.

The lesions are extremely itchy, especially when the patient becomes warm or perspires. The malady is a chronic one, and in the majority of instances involves large areas on the trunk and limbs. The scalp and face generally escape.

Diagnosis.—The peculiar, shingle-like character of the affected areas (Manson has compared the ringed appearance of the body to that of a piece of watered silk), the extensive involvement, and the history, should serve to exclude ringworm and tinea versicolor—the only two disorders with which it is likely to be confused.

Treatment.—The patient's clothing should be sterilized or destroyed. Of the various remedies suggested, **iodin liniment,** as recommended by Manson, probably is the most reliable. The parasiticides commonly employed in the treatment of ringworm often give good results here, and **ammoniated mercurial ointment, sulphur,** in ointment, or better in vapor form (Bonnafy and Mialaret), **resorcin** or **chrysarobin** may be tried.

Prognosis.—The lesions respond readily and favorably to treatment: but owing to the extent of the areas involved, and the tendency to relapses and recurrences, it is not always easy to bring about a permanent cure.

RINGWORM

Definition.—Ringworm is a disease of the skin due to a vegetable parasite, the *Tinea tonsurans*. The cause of the disorder was discovered by Gruby in 1843, and independently by Malmsten in 1844, but despite the confirmatory evidence presented by Bazin in 1853, it was not until the epochal researches of Sabouraud in 1892, that the medical world fully realized the wide and diverse character of the etiologic fungi found in the various clinical types of the disease.

Sabouraud at first separated the causative organisms into two main classes: the small-spored fungus, or *microsporon,* and the large-spored fungus, or *megalosporon.* The latter was further divided into two varieties: the *Megalosporon ectothrix,* in which the fungus grew and

multiplied on the outer surface of the affected hair shaft, and the *Megalosporon endothrix*, in which the fungus invaded and practically confined itself to the interior of the involved shaft. In those cases presenting both topical and internal involvement, the term "endo-ectothrix" was applied.

For purposes of finer differentiation Sabouraud separated the organisms according to their resistance to standardized solutions of potassium hydroxid. Later, finding this plan impracticable, he studied the organisms culturally and found that there exists a great number of different varieties of tinea—eleven of the microsporon and a score or more of the large-spored forms. Of the latter, a half dozen types are common, and, singly or combined, give rise to the majority of cases of ringworm, as ordinarily encountered.

Of the various microsporons, the *Microsporon audouini* is most common in this country and in England, and usually is of human origin. The *Microsporon tardium*, likewise of human origin, is the cause of a small percentage of British and Continental cases. Of the microsporons of animal origin, the *Microsporon felineum* and the *Microsporon lanosum* are the more important.

According to Sabouraud, the *Trichophyton crateriforme*, the *Trichophyton cerebriforme*, the *Trichophyton acuminatum*, and the *Trichophyton violaceum*, all endothrices, are the more important of the large-spored fungi, and all may, at one time or another, involve either the glabrous or hairy surfaces, although the so-called cerebriforme type appears to have a particular affinity for the bearded region.

The *Epidermophyton inguinale*, which is generally the causative factor in "eczema marginatum," and in so-called "crotch ringworm," never attacks the hair shafts; and for this reason, Castellani and others hold that it is not a true trichophyton, but an epidermophyton. This organism also, as Whitfield and Sabouraud have shown, exhibits a special predilection for the interdigital spaces and similar moist areas.

Basing his statistics on Parisian cases of the disease, Sabouraud found the various types of infection caused by the different organisms to be, as follows:

Organism	Scalp	Beard	Glabrous Skin	Nails	Total
Microsporon audouini	132	0	0	0	132
Microsporon lanosum	12	1	2	0	15
Trichophyton crateriforme	112	0	3	0	115
Trichophyton acuminatum	47	1	4	0	52
Trichophyton violaceum	33	2	1	1	37
Trichophyton cerebriforme	5	7	1	0	13
Trichophyton asteroides	5	0	10	0	15
Trichophyton rosaceum	0	5	0	0	5
Trichophyton ochraceum	1	1	5	0	7

The fungi grow by preference in the corneous layer of the epidermis, and the more deeply-seated lesions are usually a result of hair shaft

involvement. The connective tissue occasionally is involved, however, particularly in megalosporic ringworm; and marked inflammatory reaction may ensue. The lesions differ clinically according to the character and number of organisms present, the anatomic location, and the extent of the involvement, and, to a certain degree, the individual susceptibility of the patient.

For purposes of description, five different varieties of ringworm are recognized:

I. Ringworm of the glabrous skin, including the palms and soles.
II. Ringworm of the genitocrural region.
III. Ringworm of the scalp.
IV. Ringworm of the beard.
V. Ringworm of the nails.

Etiology and Pathology.—As previously stated, ringworm is due to a vegetable fungus, of which several different varieties are recognized. Many of the domestic animals (the cat, dog, horse and cow), and even wild animals (hedgehog), and birds may become infected with the organism and serve as sources of contagion to man. In children, the disease is most often contracted through the interchange of headgear, and the common use of combs, brushes and other toilet articles. In adults, bathing establishments frequently serve as disseminators of the disease. Ringworm of the glabrous skin occurs more often in children than in adults; while the scalp cases are practically all confined to individuals below the age of puberty.

No race is exempt. Hazen has reported numerous examples of all types in the negro.

The scalp cases are particularly common in orphanages and similar institutions, where children live in crowded quarters.

The comparative frequency with which the various types of fungi occur has already been discussed.

As a rule, the cutaneous involvement is comparatively superficial, only the outermost, keratinized, layers of the skin being attacked. Occasionally, the deeper layers are implicated, however, as in kerion; and fungi may be found deep in the follicles, and even in the perifollicular tissues (Robinson).

In the hairy regions, the fungus often pervades the entire shaft, clear to the bottom of the follicle. It is for this reason that the disease is so difficult to eradicate. Local applications, no matter how readily absorbed, pass downward only to the appended sebaceous gland, exerting no influence on the organism in the basal portion of the follicle.

The fungi can readily be found in the affected tissues by treating the affected scales and hair shafts with a 10 per cent. aqueous solution of potassium hydroxid, with or without the addition of gentle heat, and examining with a medium or high-power lens.

If more detailed study is desirable (for the recognition of special types of organisms), recourse should be had to various cultural methods.

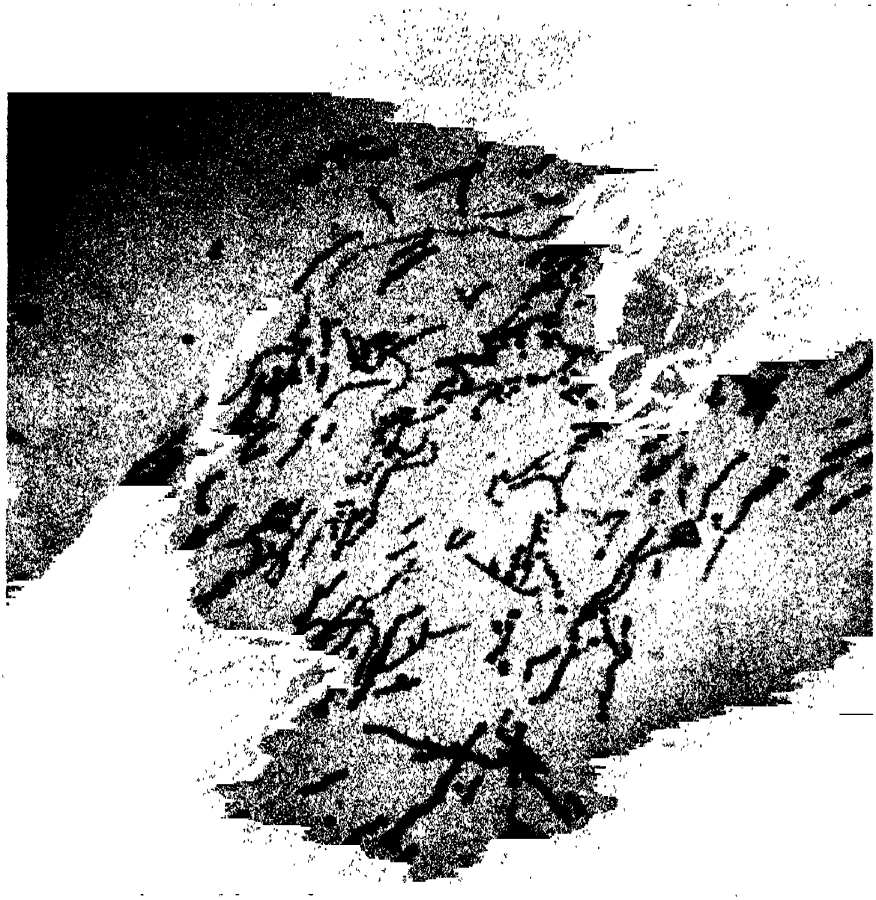


FIG. 20.—LARGE-SPORED RINGWORM RECOVERED FROM AN INFECTED HAIR. (High magnification.) (Courtesy Dr. George M. MacKee, from Sutton's "Diseases of the Skin," C. V. Mosby Co.)

The maltose or glucose mixtures suggested by Sabouraud are the best. He recommends the following:

Water	1000.0	parts
Crude maltose	40.0	"
Granulated peptone	10.0	"
Gelose	18.0	"

Water	1000.0	parts
Glucose	40.0	"
Granulated peptone	10.0	"
Gelose	18.0	"

The growths become perceptible in from seven to ten days, but it requires from a fortnight to six weeks for them to become sufficiently characteristic for gross recognition.

Types of Ringworm.—I. RINGWORM OF THE GLABROUS SKIN.—Ringworm of the non-hairy surfaces usually begins as a flattened pinkish papule. The lesion tends to spread peripherally, and may or



FIG. 21—RINGWORM OF THE CHEST; CHARACTERISTIC CIRCINATE LESION. (Courtesy Dr. George M. MacKee.)

may not clear up in the center. Hazen, who has had a wide experience with the disease, divides ringworm of the glabrous skin into five general clinical groups.

(1) Small, scaly, rounded areas, not clearing in the center, almost non-inflammatory, confined chiefly to the neck, face and shoulders, and frequently associated with tinea tonsurans, usually due to a microsporon.

(2) Widely disseminated, superficial, inflammatory, non-ringed lesions, due to an endothrix, or to the *Trichophyton ochraceum*.

(3) Completely ringed lesions, clearing in the center, and sometimes composed of rings within rings, slightly or markedly inflammatory, with vesicles at the margins. An endothrix occasionally is responsible, but more often it is due to the *Microsporon lanosum*, or an ectothrix.

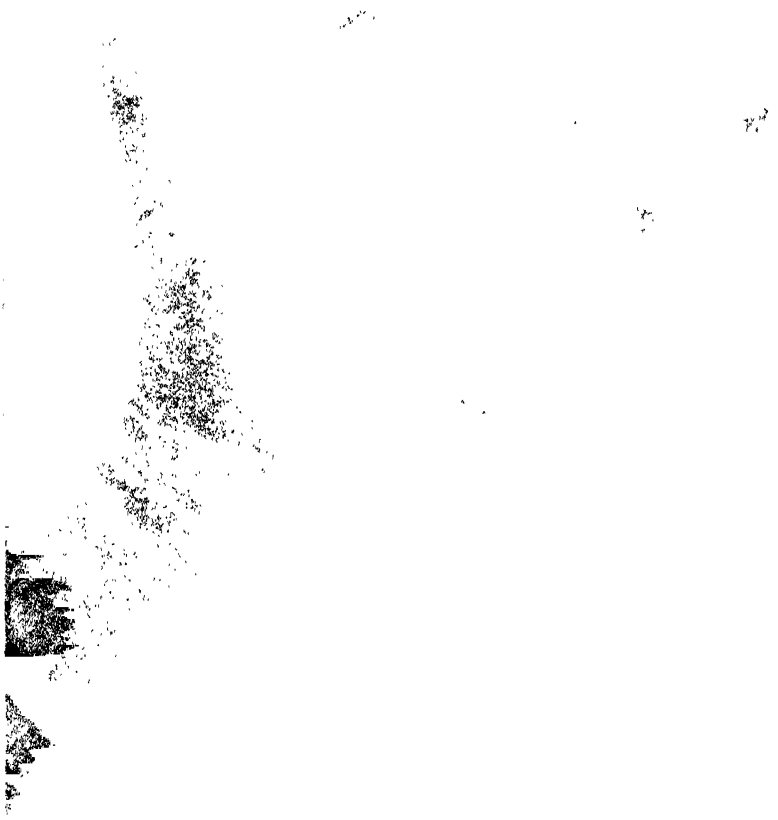


FIG. 22.—RINGWORM OF THE PALM; LESION SUGGESTIVE OF CHRONIC ECZEMA.

(4) Rounded, elevated lesions, not clearing in the center, often of considerable depth, and nearly always caused by an ectothrix, usually the *Trichophyton asteroides* or *cerebriforme*.

(5) Deep, kerion-like lesions, usually located on the hands or fore-

arms, and always due to an ectothrix—usually the asteroides or cerebriforme, not uncommon in hostlers.

Group 3 of Hazen's classification is very frequently encountered, and may be taken as characteristic of the corporeal type of the disease. Here the initial plaque is sharply defined, and actively inflamed. The lesions clear in the center and gradually increase in size until a diameter of 8.0 or 10.0 cm. is reached. They then remain stationary



FIG. 23.—RINGWORM OF THE PALM AND THUMB.

for a week or more, and may ultimately disappear without treatment, leaving no trace.

By the coalescence of two or more lesions, gyrate figures may be produced. In some instances, only the uncovered surfaces are attacked. As a rule, the involvement is not extensive. Itching and burning may be present, but the *subjective symptoms* are neither marked nor severe.

Recently, Ormsby and Mitchell, in an exhaustive and classical contribution, have added much to our knowledge concerning ringworm of the palms and soles. As these investigators have proved, many palmar and plantar eruptions formerly diagnosed as instances of ringworm,

pompholyx, etc., undoubtedly have been due to infection with some variety of trichophyton or epidermidophyton.

In these localities, the lesions may be suggestive of a mild psoriasis or seborrheic dermatitis, and from these mild chronic or subacute inflammatory manifestations, the symptomatology may vary to that of a vesicular or moist eczema, or a severe and extensive pompholyx. Ormsby and Mitchell, Sabouraud, Whitfield and others found that the fungi could readily be recovered from the cutaneous lesion, and isolated by cultivation on appropriate media.

II. Ringworm of the Genitocrural Region.—Ringworm of the genitocrural region, or tinea cruris, or, better, epidermophytis inguinale, may begin as a flattened, pinkish or reddish papule, as on the trunk, or

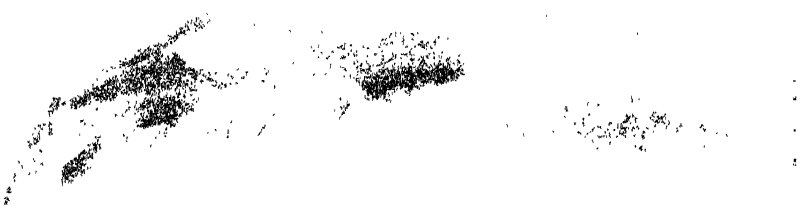


Fig. 24.—Ringworm of the Hand.

The lesion developed on the palm, and extended laterally. (Courtesy Dr. George M. MacKee.)

it may first become apparent as a superficial, sharply circumscribed, intertriginous eczema. Where the scrotum comes in contact with the thighs, the affected areas may retain their moist, weeping characteristics for a long time, but as the disease extends laterally, and involves more extensive areas on the thighs, perineum, and even upward over the pubes, the patches are less inflammatory in type, except near the advancing margins where more or less vesiculation generally is present. To those cases which are markedly inflammatory in type, the term "eczema marginatum" often is incorrectly applied.

Occasionally, the infection may be interdigital, and involve either the toes or fingers. It is extremely probable, as Sabouraud says, that the *Epidermidophyton inguinale* is the usual, if not invariable, cause of these intertriginous eruptions.

Dhobie itch (washerman's itch) is an allied affection occurring in tropical countries and often complicated by furunculosis and infectious eczematoid dermatitis. Owing to the excessive heat and moisture, and consequent scratching, the parts soon become raw and inflamed. Stitt, who made an exhaustive bacteriological study of the disorder, concluded

that the condition was greatly aggravated by a symbiosis between the infecting fungus and a coccus, probably a staphylococcus.

The affection is always worse during the heated season; and partially



FIG. 25.—RINGWORM OF THE TRUNK.

Note circinate lesions, with tendency to the formation of gyrate figures. (Courtesy Dr. George M. MacKee.)

or completely disappears, even without treatment, during the winter.

Diagnosis of the Glabrous Skin and Genitocrural Region.—Ringworm of the *glabrous skin* is to be differentiated from psoriasis, pityriasis rosea and seborrheic dermatitis. In psoriasis, the lesions exhibit a marked preference for the extensor surfaces of the elbows and knees, develop

slowly, seldom become circinate, and when the superficial scales are forcibly removed, invariably show the characteristic "bleeding points."

Pityriasis rosea usually begins as a "mother spot" on one of the

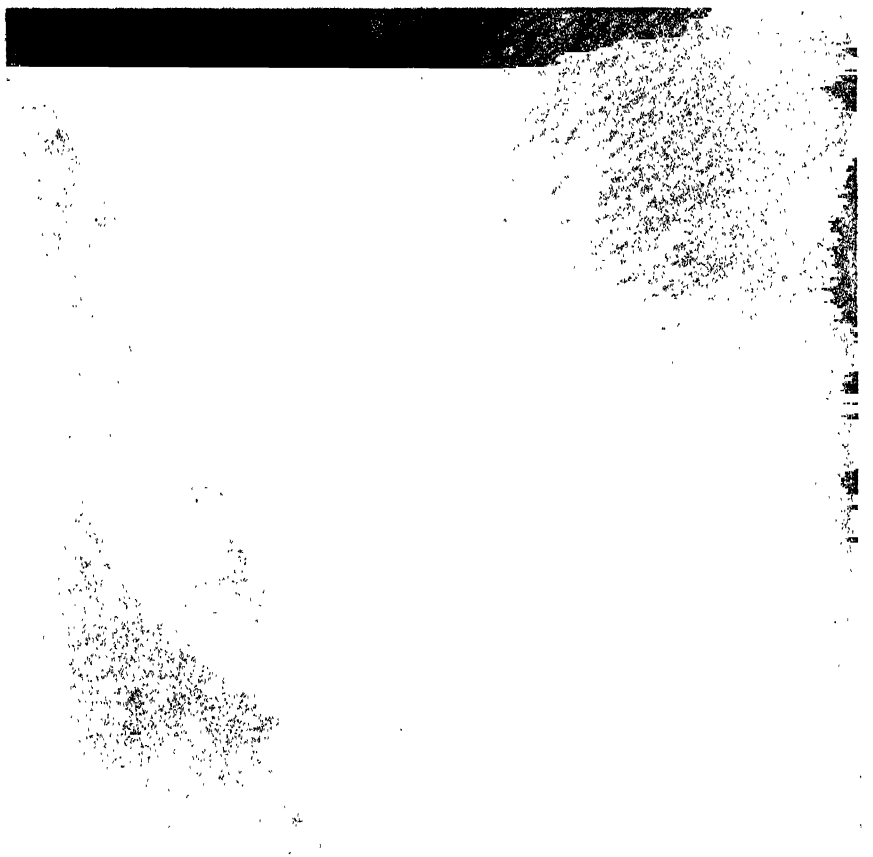


FIG. 26.—TINEA CRURIS (RINGWORM OF THE CROTCH). (Courtesy Dr. George M.

lower abdominal quadrants, and the general eruption, which ordinarily is confined to the trunk, develops rapidly. The lesions are oval in outline and very superficial. They develop quickly; and the scales are free from fungi.

In seborrheic dermatitis, the lesions commonly appear first on the scalp. From this point, they extend downward, to the nose, and then



FIG. 27.—RINGWORM OF THE AXILLA, GIVING RISE TO A TYPICAL PATCH OF "ECZEMATOID RINGWORM," OR "PARASITIC ECZEMA." (Courtesy Dr. George M. MacKee.)

the sternum, following the median line of the body. The lesions may be gyrate, but seldom possess the regular circinate outlines which are characteristic of many cases of tinea corporis. The scales are

unctuous and greasy; and vesiculation never occurs. In the *axillary and inguinal regions,* the resemblance may be much closer, however, and sometimes it is necessary to resort to a microscopical examination in order to reach a positive conclusion.

The *crural* cases must be differentiated from eczema, seborrheic dermatitis and erythrasma.

Ringworm of the palms and soles may bear a striking resemblance to eczema and to pompholyx.

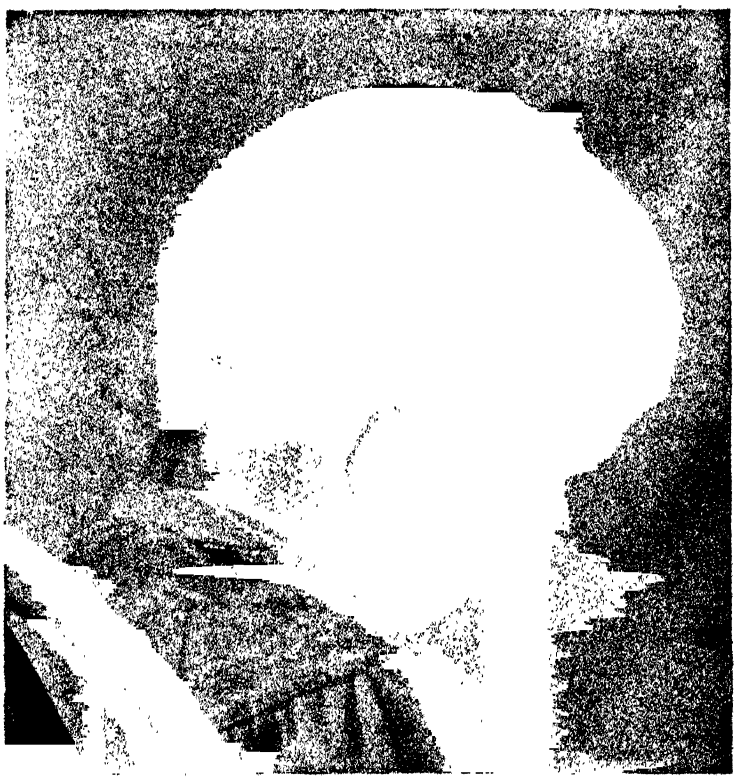


FIG. 28.—RINGWORM OF THE SCALP, SHOWING KERION. (Courtesy Dr. George M. MacKee, *Medical Record.*)

Obstinate cases of intertriginous dermatitis of the extremities should always be subjected to a laboratory examination. If the eruption has been preceded by typical epidermidophytic crural lesions, the chances in favor of a fungous infection are very great; and careful search will almost invariably reveal the presence of the offending vegetable parasite.

III. RINGWORM OF THE SCALP.—Ringworm of the scalp, or tinea tonsurans, is practically always a disease of childhood, examples in adult life being extremely rare. It usually begins as a small, reddened, scaly spot, which develops insidiously, and exhibits little or no tendency

to central involution. The loss of hair is more or less patchy; and the shafts are dry, lusterless, and easily broken. The bald areas are somewhat scaly, and marked here and there by blackened, broken stumps. Owing to the subacute inflammation present, with consequent edema, the area may be slightly elevated above the level of the surrounding healthy skin. Itching is variable, but usually slight in degree. In the



29.—Disseminated Ringworm of the Scalp in a Little Girl. (Courtesy Dr. George M. MacKee, *Medical Record.*)

more acute cases, vesiculation and pustulation may be present. On the perfectly bald areas, the follicles may be distended or slightly elevated, giving rise to a "goose skin" appearance. The individual lesions are oval or rounded in outline and seldom attain a diameter of more than 10 or 15 cm., when they remain stationary. New ones are constantly developing, however; and when the hair is closely clipped from an infected scalp, a score or more of infected areas may frequently be discovered. The character of the scales varies with the degree of

inflammation present. Generally, they are bran-like, and loosely adherent. As a rule, they contain numerous fungi; and the disease frequently is disseminated by the common use of combs and brushes.

Clinically, several varieties of ringworm of the scalp are recognized. Hazen, who is as concise as he is scientific, describes the various types, as follows:



FIG. 30.—LARGE-SPORED ECTOTHRIX RINGWORM OF THE SCALP, WITH KERION.

(1) Gray-patch ringworm, caused by microsporons, usually the audouini, short incubation period (from two to five days). Begins as a small, rounded, erythematous patch, upon which there may be a few superficial vesicles. The acute inflammatory manifestations quickly subside; and the patch becomes covered with scanty, furfuraceous grayish scales. The hairs fall or break off just above the skin surface. As a rule, the small-spored parasites cause large patches and the large-spored small patches. Coalescence may occur; and in rare in-

stances, almost the entire scalp may be involved. Associated lesions may develop on the adjacent glabrous skin.

(2) Disseminated ringworm, occasionally due to microsporons, but usually to the *Trichophyton crateriforme*. Numerous small bald spots appear over the entire scalp, many of which contain groups of blackened, broken hair stumps. The interlesional areas are usually covered with grayish furfuraceous scales.

(3) Black-dot ringworm, due to infection with the *Trichophyton acuminatum*, and characterized by small, widely-disseminated patches. The affected areas are smooth and free from scales, but contain numerous, small, black comedo-like dots, the tips of broken-off hair shafts.

(4) Bald ringworm, probably due to a resistant type of *Trichophyton endothrix* (Dubreuilh and Freche), and presenting numerous smooth, shiny patches resembling those due to alopecia areata.

(5) Pustular ringworm is a conglomerate folliculitis due to pus-producing ectothrices, or to complicating pus cocci. It is characterized by the presence of one or more rounded, boggy, carbuncle-like tumors (kerion, or kerion celsi) which vary from 1 to 5 cm. in diameter, and which, on disappearing, may give rise to permanent baldness. The surface of these lesions is reddish or purplish; and is marked by numerous pin-head to pea-sized pustules, and gaping follicular orifices. The subcutaneous tissues also are involved, and often are completely honeycombed with pus pockets, which discharge through the follicular openings. The tumors are exceedingly sensitive and painful; and the suppuration may give rise to a considerable degree of fever. Owing to the severity of the inflammatory process, the tissue reaction may be sufficient to overcome the infection, with ensuing spontaneous cure.

Diagnosis.—As previously stated, the vast majority of cases of ringworm of the scalp occur in childhood. The disorder is to be differentiated from alopecia areata, eczema, seborrheic dermatitis and favus.

In alopecia areata, the lesions develop suddenly, the affected areas are absolutely devoid of hair; there is no associated scaliness, and no fungi are to be found.

Eczema of the scalp seldom, if ever, gives rise to baldness. The affected areas are intolerably itchy, and oozing and crusting are prominent features. Multiple lesions are the exception rather than the rule. The hair shafts are not loose or easily extracted.

It is sometimes difficult to distinguish some cases of patchy seborrheic dermatitis of the scalp from early ringworm; and recourse occasionally must be made to a microscopical examination of hairs and scales from the affected area. The material should first be treated on the glass slide with a fresh 10 per cent. aqueous solution of potassium hydroxid, for several minutes, when the ringworm fungi, if present, can readily be found.

Favus in this country is rare. The sulphur-yellow crusts, the mouse-nest-like smell, the associated scalp atrophy, and the history will usually prove sufficient for recognition. In doubtful cases, recourse should be had to laboratory aids.

IV. RINGWORM OF THE BEARD.—Ringworm of the beard, or *Tinea trichophytina barbæ*, may be divided into two clinical varieties, superficial and deep, according to the character of involvement.

In the superficial variety, the lesions are usually circinate, and may resemble those occurring on glabrous skin, or on the scalp of very young children. The deep type may begin as a superficial infection, or the deeper structures may be involved almost from the first. In both forms, the hairs become dry, lusterless and friable, and can readily be extracted, bringing the root sheaths away with them. Vesiculation and pustulation are uncommon, but in severe examples of the deep type, one or more areas of conglomerate folliculitis (kerion) may develop. These reddish, boggy, tumor masses, studded with numerous dead or broken hairs, or by gaping, follicular orifices, are very sore and tender, and ultimately break down and become fluctuant. The disease develops slowly and is very sluggish in its course. The sites of predilection are the under surfaces of the jaws and the cervicomaxillary folds.

Diagnosis.—The disorder is to be differentiated from sycosis, seborrheic dermatitis and eczema. True sycosis (staphylococcic perifolliculitis) often develops on the upper lip, and follows a pustular infection of the nares. Single hairs are involved, and the characteristic lesion is a superficial, hair-pierced papule, or pustule. In doubtful cases, recourse should be had to a microscopic examination. In both seborrheic dermatitis and eczema, the inflammatory process is superficial, and the hairs never become loose or fall out. Fungi are of course absent.

V. RINGWORM OF THE NAILS.—Tinea unguium, onychomycosis, or ringworm of the nails, is a fairly common clinical condition. The parasite gives rise to degenerative changes in the nail itself, as well as in the nail bed. One, or rarely, two or more finger-nails or toe-nails may be attacked. The appendages become dry, lusterless, brittle and frequently misshapen. They may be ridged, either transversely or longitudinally. The free margin is usually lifted out of place by subungual masses of horny cellular detritus. This corneous material contains numerous fungi.

Pathology.—The causative organism in ringworm of the nails is usually an endothrix, or an endo-ectothrix (neo-endothrix), not uncommonly the *Trichophyton cerebriforme*, although Sabouraud believes that the *Trichophyton acuminatum*, and the *Trichophyton violaceum* are not infrequent offenders. The fungus can, as a rule, be readily recovered from the hypercornified masses beneath the distal margin of the affected nail.

Diagnosis.—The condition must be differentiated from psoriasis, eczema and favus. In ringworm, as in favus, the disease is usually confined to one or two nails; while in psoriasis and eczema, as well as in various trophic disorders which might give rise to similar nail-bed deformities, several digits generally are involved.

Ringworm of the nails is usually secondary to ringworm infection on other parts of the body. These facts, together with the invariable

presence of the fungus in tinea unguium, should render the condition easy of recognition.

Treatment.—In treating ringworm of the non-hairy surfaces, almost any of the milder **antiseptics** may be employed with success. An **ointment** containing **ammoniated mercury** (5 per cent.), **salicylic acid** and **sulphur** (10 per cent.), or **chrysarobin** (1 to 10 per cent.) may be employed; or, recourse may be had to frequent applications of the **tincture of iodin.** On the palms and soles, **Whitfield's ointment,** which consists of salicylic acid (3 per cent.) and benzoic acid (5 per cent.), in lard

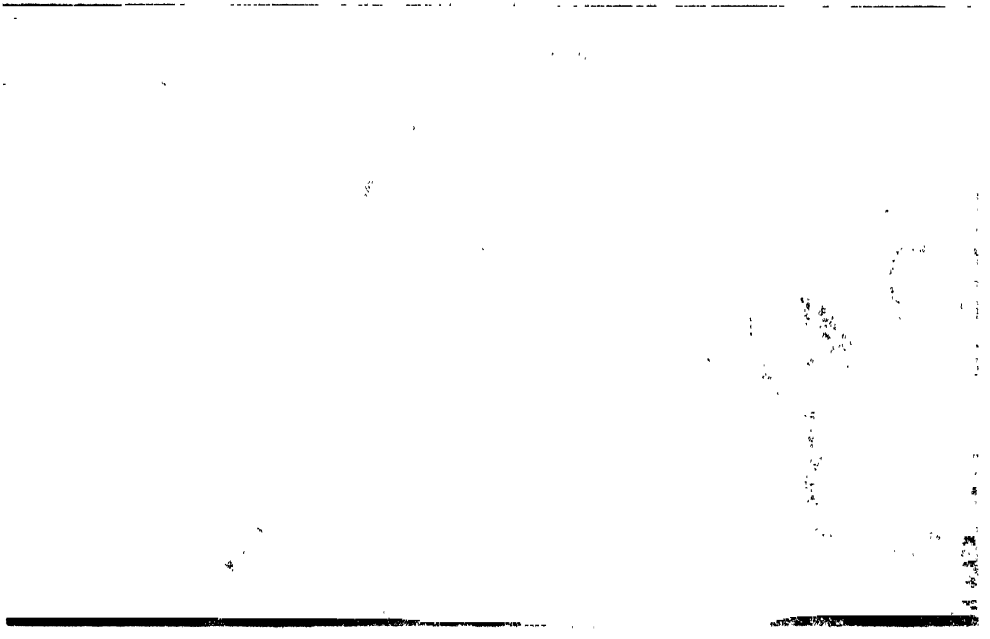


FIG. 31.—RINGWORM OF THE

Numerous mycelia and spores recovered from scrapings. Great improvement following the use of *x*-ray. (Courtesy Dr. George M. MacKee.)

or vaselin, is one of the most reliable of all applications. If the inflammatory process is very acute, the tri-weekly use of an **aqueous solution of silver nitrate** (10 per cent.) often proves beneficial.

In tinea cruris and in dhobie itch, recourse may be had to **Whitfield's ointment** or to **iodin preparations,** interspersed with the use of **calamin lotion** and similar soothing applications for the relief of itching. In advanced cases, recourse must be had to more powerful remedies, such as **chrysarobin**—in ointment or in collodion or **traumaticin**—or even pure **formalin.** The latter may be painted on well once weekly and allowed to remain for five minutes. It is then washed off and **calamin lotion** or a **dusting powder** is applied.

Ringworm of the nails is an extremely obstinate and persistent

disorder. Hazen recommends that as much of the **nail** as possible be **removed** and the matrix treated with a strong **salicylic acid ointment.** After the horny tissue is curetted away, **iodin** is to be frequently applied. In severe cases, it may be necessary to remove the entire nail.

In the milder cases of ringworm of the beard, frequent **epilation,** or the constant use of a mild **ammoniated mercury** (5 per cent.) or **yellow oxid of mercury** (10 per cent.) **ointment** will bring about a cure. The beard should be kept clipped, and as fast as the lesions become apparent, the diseased hairs should be extracted. Frequent washing with **soap and soft water** should be practiced; and the entire bearded area should be sponged with **alcohol** once daily. In severe and long-standing cases of tinea barbæ, the treatment is that of ringworm of the scalp. Recently, Strickler, Lavinder and others have employed **vaccines** with benefit in ringworm and favus of the scalp and beard.

Ringworm of the scalp is one of the most resistant of all cutaneous disorders to treatment. The successful treatment of the condition is dependent upon the prevention of the development of new foci, and upon the eradication of the lesions already existing.

In babies and in very young children, a weak **ammoniated mercury or sulphur ointment** should be applied two or three times daily; and the scalp cleansed three times weekly with **dilute alcohol.** In the older cases and in those instances where the disease has involved the deeper structures, the hairs must be removed before the antiseptics can reach the bottoms of the affected follicles. This may be done mechanically by means of epilating forceps, or with **Unna's "rosin stick,"** or better, by means of an epilating exposure to the **x-ray.** The marginal hairs, as well as those in the center of the patch, should be removed. The entire scalp should be kept in as aseptic a condition as possible. The hair should be closely clipped, and frequent washing with soap and soft water, followed by the daily application of a 1 to 2000 aqueous solution of **mercuric chlorid** should be practiced.

Of the various parasiticides, **ammoniated mercury** is one of the best. **Iodin** (in lard, or goose grease), **chrysarobin, tar, resorcin, sulphur** and **betanaphthol** all have their advocates. As previously stated, in order to be effectual, the diseased hairs should first be removed; and for this purpose, nothing is so satisfactory, when properly employed, as the **x-ray.** It is very essential that the dosage be accurately gauged—if insufficient in amount, depilation will not result: if too long an exposure be made, permanent baldness will ensue. For this reason the scalp should be carefully mapped out (so as not to doubly expose any single area), and the agent applied in a systematic manner. One of the best of all methods is that employed by MacKee and Remer (*Medical Record,* New York, 1915, lxxxviii, p. 217):

"The first step, for convenience, is to cut the hair close to the scalp. The next step is to divide the scalp into four equal-sized, triangular-shaped areas in the following manner: A mark is made (with a skin pencil) about 2 inches inside the hair line above the forehead in the

median line (Figs. 32 and 34). This we will designate point A. A steel tape measure is then placed with zero on point A and stretched along the median line over the vertex to the neck. At 10 inches another mark is made (point B, Fig. 34). This will usually be about 2 inches inside of the hair line of the neck, but will vary somewhat in accordance with the size of the head. Points A and B should be adjusted so that they are about the same distances inside of the anterior and posterior hair lines. As a matter of fact, A and B, in some instances,

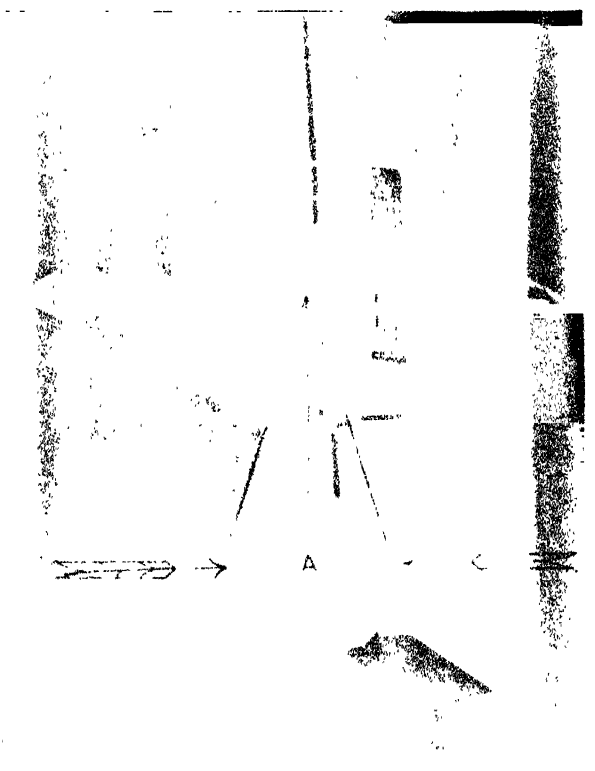


FIG. 32.—X-RAY TREATMENT OF RINGWORM OF THE SCALP. (Courtesy Dr. George M. MacKee, *Medical Record.*)

may fall exactly at the hair line: but this makes no difference so long as the distance between them is exactly 10 inches. Point C is then indicated by a mark in the middle line exactly halfway between points A and B (Figs. 33 and 34). On every skull there is a flat surface just anterior to the occiput and point C will fall from 1 to 1½ inches in front of the center of this area. As a matter of fact, it is a good idea to insist upon point C being exactly at this location and adjust A and B so that they will be just 5 inches anterior and posterior to C. Point D is then located just above and in front of the right external auditory meatus (Fig. 34). The exact position of this spot is found by measuring

5 inches from A, B and C. Point E represents the same location on the left side. It is essential that each point be exactly 5 inches from every other point, with the exception, obviously, of the distance between points A and B, which should be 10 inches.

"The next step is to draw lines between the various points (Figs. 32, 33 and 34). This will divide the scalp into four triangular-shaped equal areas. The reason for this will be made clear later.

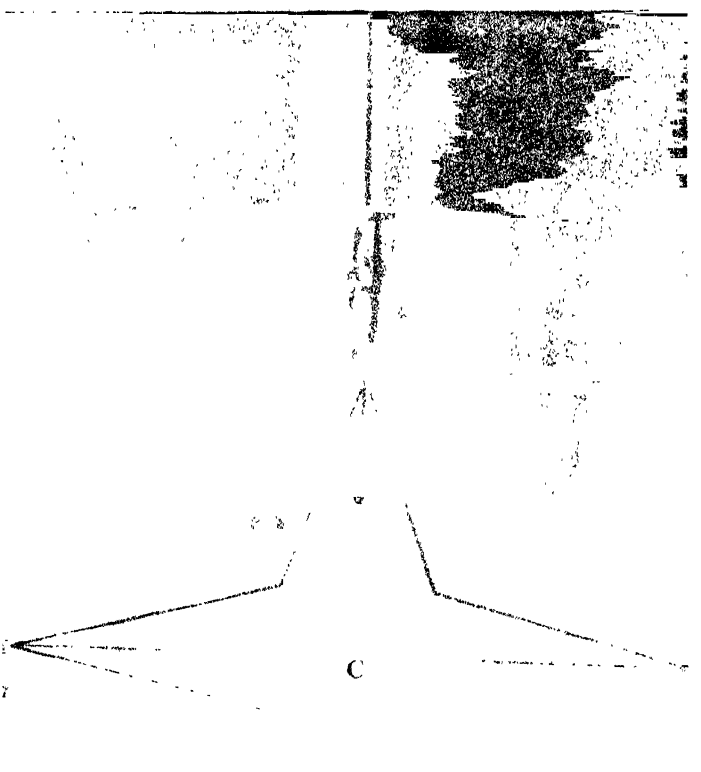


FIG. 33.—X-RAY TREATMENT OF RINGWORM. (Courtesy Dr. George M. MacKee, *Medical Record.*)

"Next, each point—A, B, C, D, and E—receives an epilating dose of *x*-ray in the following manner:

"For point A the child lies on its back on a table. The entire face below the hair line is protected by a lead mask. The tube is placed with the anode exactly over and 6½ inches from point A (Fig. 32). It will be seen that the vertical rays will strike point A, while half of the oblique rays will fall upon the anterior portion of the scalp, and the remaining half will strike the protecting shield on the face and be wasted (Fig. 34). The measuring pastille is now placed on point A, and the epilating dose administered.

"Points B, C, D and E are now to receive the epilating dose in

the same manner with the following exceptions: For point C the patient may recline on a table or sit upright on a chair. No protection is required. Here the oblique rays spread over the anterior, posterior and lateral portions of the scalp (Figs. 32 and 34). For point B, the child may lie on his side on the table or sit in a chair with his forehead resting on the table. It is necessary to protect the neck, shoulders and back. Here half of the oblique rays will reach the posterior portion of the scalp, while the other half will spread over the shoulders and

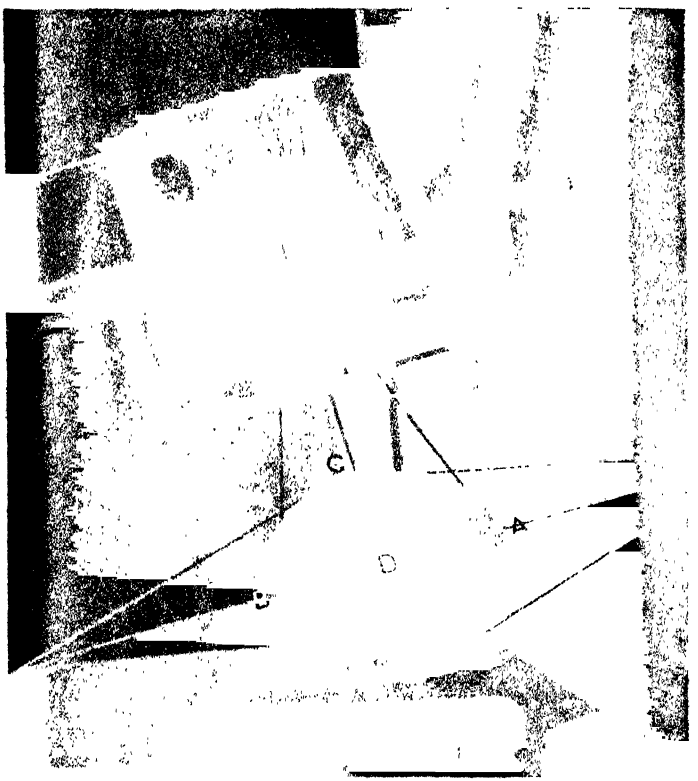


FIG. 34.—X-RAY TREATMENT OF RINGWORM. (Courtesy Dr. George M. MacKee, *Medical Record.*)

back (Figs. 32 and 33). For points D and E, the patient lies on his side on a table; and the ears, face and neck are protected (Figs. 33 and 34). Here, as in points A and B, half of the oblique rays are lost.

"It is of the utmost importance that each treatment be at right angles to every other treatment. For instance, an imaginary line drawn from the anode to point A will be at right angles to lines extending from the anode to points C, D, and E. Figs. 32, 33 and 34 will explain these angles better than words; and also, they will demonstrate that the lines drawn upon the scalp between the five points aid one in quickly determining the correct angle.

"A study of these illustrations will show also how the vertical rays strike the five points, while the oblique rays from one treatment overlap and reinforce similar rays from other treatments. For instance, if a full epilating dose be administered to point E and to no other portion of the scalp, the hair will fall out over only a very small area. But when similar doses are applied to points A, B and C, the oblique rays overlap and complete alopecia is the result (Fig. 37). In explanation, it may be stated that point E, being in the field of vertical rays, receives the full epilating dose; while a point halfway between E and B receives one-half an epilating dose. But this point also receives one-half an epilating dose, when point B is treated. In this way, the entire scalp, when the five points have been treated, receives a full epilating dose. Scientifically, the well-known laws of intensity being in inverse proportion to the square of the distance and directly with the size of the angle of incidence, account for the equal distribution of the dose. This method of treating the entire scalp by five exposures was originated by Kienbock and is exceedingly accurate, as shown by Adamson, Pirie, Sequeira and others.

"For the purpose of determining the epilation dose, both the equality and quantity of ray must be estimated. There are numerous radiometers designed for the purpose of measuring the quantity, but we rely entirely upon either the Holzknecht or the Corbett radiometer. They both are modifications of the original Sabouraud-Noiré method of utilizing the change in color produced in platinocyanid of barium when under the influence of the *x-ray*. The Corbett radiometer, the most recent and most scientific quantity instrument, consists of a series of colored glass tablets, each piece of glass representing the color assumed by the double-cyanid of barium after it has received varying amounts of exposure—in other words, they represent doses of *x*-ray measured in Holzknecht units. The Sabouraud (barium) pastille is placed on the scalp and the *x*-ray is applied until the pastille matches in color the particular glass tablet that corresponds to the epilating dose (5 H). The pastille and the tablet are compared in a black chamber under the influence of reflected artificial light. The colored glass tablets are standardized by the tintometer; and are both accurate and permanent. The Holzknecht instrument has a piece of celluloid, which, colorless at one end, gradually assumes color which becomes deeper as the other extremity is approached. One-half of a Sabouraud pastille is placed under the celluloid strip, the other half is placed on the scalp and exposed to the *x*-ray. It is then compared with the half pastille under the celluloid and moved along the colored strip until the colors register. A scale of figures on the instrument allows a reading to be made in Holzknecht units. There are many technical details connected with the work that we cannot discuss here. Suffice it to say that in experienced hands this method of measuring the quantity is absolutely reliable.

"In such delicate technical work it is, of course, advisable to utilize, especially in the beginning, as many safeguards as possible; therefore, it is advisable to work with a constant amperage voltage, and milli-

amperage, and a fixed parallel spark gap, a fixed distance, etc. In our technic, however, we are constantly changing these factors; and therefore, disregard the indirect and depend entirely upon the direct methods of measurement of quantity.

"Since the advent of the Holzknecht radiometer, we have had no difficulty in estimating the quantity of ray employed. We have, however, had a great deal of trouble in measuring the quality; and this



FIG. 35.—X-RAY TREATMENT OF RINGWORM OF THE SCALP.

Showing tube stand and shield fitted with wooden pegs for the purpose of holding the head steady. (Courtesy Dr. George M. MacKee, *Medical Record.*)

was entirely due to the impossibility of obtaining tubes that would maintain a constant vacuum during the treatment. Water and air-cooled tubes lessened the difficulty. The air-cooled hydrogen tube, also, has given good satisfaction. But the remarkable Coolidge tube has completely overcome all difficulties in this respect. This tube will maintain a constant vacuum with light or heavy currents for long periods of time and may be used on one case after another throughout the entire day. For the direct estimation of quality, we utilize the Benoist penetrometer, aided by indirect instruments such as the Heinz-Bauer qualimeter, the milliamperemeter, etc.

"We employ a 'hard ray'; never less than No. 8 of the Benoist scale; and earnestly advise against the use of soft rays. The original epilating dose, as devised by Sabouraud and Noiré (B 1 or H 5) was based upon the use of 'hard rays,' obtained by exciting a tube with a static machine. This fact has been generally overlooked and the use of 'soft' rays has been one of the causes of bad results in the past.



FIG. 56.— OF THE SCALP IN COURSE OF TREATMENT WITH X-RAY. (Courtesy Dr. George M. MacKee, *Medical Record.*)

"We place the pastille on the scalp as advised by Hampson and others, instead of halfway between the anode and the scalp. There is no doubt in our mind that both accuracy and safety are enhanced by placing the pastille on the scalp. At half distance, the slightest movement of the child will alter the relative positions of the head, pastille and anode; and this will cause a faulty estimation of the dose. With

the pastille placed on the scalp, it makes no difference if the head moves a little closer to or a little further from the tube during the exposure. Lateral motion, however, must be avoided in any case. Furthermore, the changes in color are less marked at 'skin distance' than at 'half distance'; and these light brown shades are more easily estimated than are the deeper orange tints. The original dose of 5 H was estimated with the pastille at 'half distance'; so that when the 'skin distance' is employed, the color change in the pastille will be four times

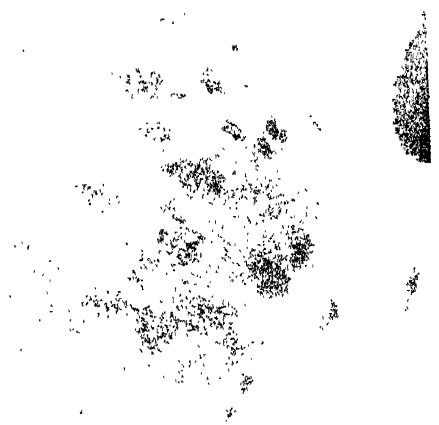


FIG. 37.—RINGWORM OF THE SCALP AFTER COMPLETE DEPILATION WITH THE X-RAYS. (Courtesy Dr. George M. MacKee, *Medical Record.*)

less than at 'half distance.' In other words, when the pastille is placed on the scalp, the dose must be multiplied by four. Therefore, the epilating dose at 'skin distance' will be 1¼ H. As a matter of fact, ¾ H to 1 H will usually suffice; and 1¼ H is the maximum. If this is exceeded, permanent alopecia is likely to result. The maximum dose will produce a complete depilation: but experience has shown that if most of the hair falls out the result will be perfectly satisfactory; so that a dose of 1 H at 'skin distance' will usually suffice for all practical purposes. When employing the 'skin distance,' the distance between the scalp and anode of the tube is a matter of little moment so long as it is not too close and the same distance is employed for each of the five ex-

posures. A working distance of 6½ inches has been found satisfactory.

"The age of the patient makes no difference, if the head of the patient can be kept quiet during the exposures. For this purpose, a shield fitted with pegs made of soft wood may be used, as shown in Fig. 35. The pegs must be made of very soft wood, so as not to act as a filter to the ray; and should be of a length that will fix the anode at the proper distance from the scalp."

Prognosis.—Ringworm of the general glabrous skin responds promptly to treatment. In the palmar and plantar regions, it is more

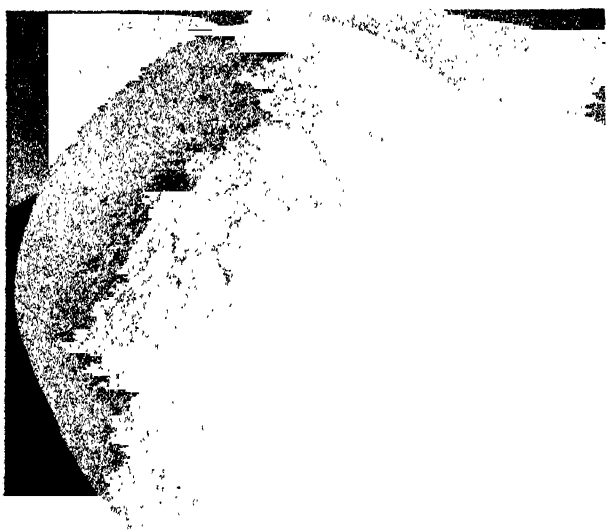


FIG. 38.—DISSEMINATED RINGWORM.

After the treatment of a single patch with the *x*-ray the hair fell out over the entire scalp. The hair has not been clipped. (Courtesy Dr. George M. MacKee, *Medical*

resistant: but with proper medication, a cure may safely be promised in a few weeks. Tinea cruris likewise is somewhat stubborn and resistant to ordinary therapeutic measures.

Ringworm of the scalp has long been considered one of the most refractory of all cutaneous disorders; particularly, when the disease is of long standing, and extensive areas are involved. Since the advent of roentgenotherapy, however, the condition is much more amenable to treatment; and in the majority of instances, a cure may safely be promised in from three to ten months. In the markedly inflammatory (kerionic) types, the outlook for early recovery is better than in the subacute forms; owing to the fact that the cutaneous reaction is so severe that it aids in the destruction of the offending organisms.

In early childhood, the process is usually superficial; and early improvement may safely be expected.

Ringworm of the beard is less obstinate than that of the scalp, largely owing to the more severe inflammatory reaction set up by the fungi in this locality, but, even in favorable instances, several weeks of treatment generally are required to bring about a cure.

CHAPTER XXVII

SPRUE

By Carl Michel, M.D.

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Definition.—Sprue is a chronic infectious mycotic disease of the gastro-intestinal tract, characterized by acute manifestations as various parts of the tract become infected. The causative organism is the *Monilia psilosis* (Ashford). Clinically, the disease is afebrile and of insidious onset. Its principal symptoms are (1) sore mouth and tongue, (2) light, foamy diarrhea at recurrent periods, (3) disturbance of liver function, (4) progressive emaciation.

The pathology consists of an acute and chronic inflammatory process of the mucous membrane of mouth, tongue and other parts of the gastro-intestinal tract, associated with a marked diminution in size of the liver, anemia, and a decrease of fatty tissue throughout the entire body. The disease prevails in tropical and subtropical countries, attacking all classes, chiefly those of the white and mixed races whose resistance has been lowered by tropical living conditions.

Synonyms for sprue are Ceylon sore mouth, *psilosis linguæ et mucosæ*, chronic tropic aphthæ, diarrhea alba, endemic diarrhea, phthisis abdominalis, white purging, white flux, aphthoides chronica. The term sprue was selected because the mouth lesions resemble aphthous stomatitis, or thrush, found in children of the temperate zones.

Etiology.—Predisposing Causes.—Sprue is primarily a disease of *tropical countries*, although cases have been reported originating in Holland, Germany and the United States. These cases are, however, very few in number. Warm climates with high temperature and high humidity are especially favorable for the prevalence of sprue. In these

regions, and in the lowlands of tropical countries, the infection is permanently endemic.

If the disease is found in dryer and cooler climates, it is milder in character, and the cases are fewer in number. Thus, during the cool months, in the tropical countries, the symptoms abate, and during the warm months they are aggravated. This was so evident to experimenters in tropical medicine that a change to a cooler climate was made an important factor in the treatment of the disease.

Sprue has been classed as a disease affecting those in the *prime of life*, i.e., from 20 to 45 years of age. These observations have been confirmed by Bahr in Ceylon and Ashford in Porto Rico. There is no doubt that the disease prevails at all ages, but up to the present time most cases brought to the attention of the physicians are of middle age.

The susceptibility to sprue depends a great deal upon the *physical condition* of the individual. The female who stays indoors and whose general systemic condition is weakened is very prone to contract the disease. The proportion of cases occurring in the female as compared with the male is about 3 to 1.

The disease has been described primarily as a "*white man's disease*," affecting those who have lived in the tropics over an extensive period. Recent observations, however, show that the disease is quite as prevalent among the mixed races, and has a high mortality in these cases. It is also well known that the brown and black races are almost insusceptible to the disease, the cases being few in number.

Little stress can be laid upon *heredity* as a factor in sprue. From observations in the endemic areas the conclusion may be drawn that the natives are the least susceptible to the disease, and it is possible that a relative immunity has developed. Sprue is a low grade infection, and extremely favorable conditions are required for the production of the disease. When the individual's resistance decreases, the susceptibility increases.

It is of interest to note that sprue and pellagra seem closely allied, and that one is often mistaken for the other. Pellagra is most prevalent among the poorer classes where there is a low nitrogenous and protein dietary, while sprue is prevalent among the middle and wealthy classes where all kinds of foods are abundant.

In Porto Rico the disease is an *urban* one, and Ashford reports most of his cases from cities and towns where there seem to be constant endemic areas. The rural districts are comparatively free. The newcomer to the tropics is especially susceptible. It is well known that the change of environment from a temperate climate to a tropical climate, and the change in diet, lower the resistance and predispose not only to sprue, but also to other tropical diseases. This is a most important predisposing factor, and accounts for the prevalence of sprue among the white and mixed races which invade the tropics.

Sprue differs from the other diseases in that *filth* and squalor are of *secondary importance* in the production of the disease. It is often

found in the cities where sanitary conditions are far better than in the rural communities, where there is little or no sanitation.

The disease seems to be due to *diet,* but absolute evidence is still lacking. Ashford has isolated the *Monilia psilosis* from loaves of baked bread, thus demonstrating the high resistance of the organism to heat.

In the institutions of Porto Rico where the *food* is properly handled and *cooked,* sprue is not prevalent, while in these same institutions cases of pellagra are often found.

Occupations do not seem to bear any definite relationship to the disease. The *occupation* in which the disease occurs most often is that of the housewives.

The white man uses more *alcohol* in the tropics than in any other locality, and this results in irritation of the gastro-intestinal membranes, which open a portal of infection for the monilia. The mixed races in the warm countries eat heavy, and highly seasoned foods and, to aid digestion, alcoholic liquors are indulged in. The result is usually some form of gastritis, and sprue supervenes. This fact cannot be emphasized too strongly as a most important factor in the causation of sprue.

After a prolonged stay in the tropics, one becomes adapted to the climate, or the highly organized nervous system breaks down, after which the general vitality is diminished. Following this a susceptibility to tropical diseases is developed.

Severe *mental strain* or over-work can readily be classed as a predisposing factor in the causation of sprue. *Exhausting diseases,* particularly those involving the gastro-intestinal tract, are likely to terminate in sprue. Among these diseases are dysentery, gastritis, hemorrhoids and fistula. In the female, frequent child-bearing, prolonged lactation, miscarriages and anemias are causative factors. Other diseases are appendicitis, syphilis and malaria.

Very often sprue is found to be associated with other diseases and in Porto Rico over 60 per cent. of the sprue cases had intestinal parasites. Tuberculosis, filariasis, diabetes and a pellagra may coexist with sprue. When pellagra is present with sprue one often masks the symptoms of the other. This renders the diagnosis extremely difficult.

Little work has been done on the *epidemiology,* using the specific infection theory as a basis for observations. Ashford, in Porto Rico, however, has observed the prevalence of the disease in 36 cases of illness among the members of families in which there is an infected individual, and he therefore classifies sprue as a communicable disease. Galloway, in Singapore, has traced more than 25 out of 104 cases to indirect infection. Further survey, using the infection theory, will bring to light a great many important facts which will be of assistance in the establishment of preventive measures.

In the eastern tropics the disease is primarily a white man's disease. The Caucasian element of the parents predominates in children born in tropical countries and makes them susceptible to the diseases of the white race. Young persons born of white parents, and reared in

the tropics, are particularly subject to degenerative disorders, and sprue is very often found among them. This same condition is noted in the Spanish and mixed races inhabiting warm countries.

EXCITING CAUSE.—Many theories have been advanced as to the causation of sprue. Among them are the following:

(1) Sprue is a food disease.
(2) Sprue is a deficiency disease.
(3) Sprue is a bacterial disease.
(4) Sprue is a climatic disease.
(5) Sprue is a fungus disease.

The hyphomycetic theory has been frequently mentioned by the French and Dutch observers. J. Cantlie, in Africa, believed that the disease and the fermentative changes were caused by a parasite or microörganism inhabiting the gastro-intestinal tract.

De Dantec succeeded in isolating a yeast fungus which he considered an important etiological factor. Bahr recently stated that he believed the *Monilia albicans* to be the etiological factor. Most of the French workers agreed with him and strongly supported the fungi theory.

In 1914 Ashford described a Monilia found in all cases of sprue. To the organism he applied the name *Monilia psilosis*. He continued his work over a period of years, and in 1917 he was able to conclusively demonstrate that *Monilia psilosis* was positively associated with sprue. The observations are being confirmed in the east by workers in China.

Morphology.—The *Monilia psilosis* (Ashford) is a large, round, clean-cut yeast. The diameter is from 4 to 7 microns, and it has few granules and a nucleus. There is also usually a pale vacuole in which a violently motile bacilli-like body darts about. The contour is always extremely sharp and well-defined, and this contour becomes a shell-like envelope in the older yeasts. Often when thickened at one pole the yeast cell becomes oval in form. This gives it a true signet-ring appearance. The common variations are those of size, multiplication of the nucleus, and increase in the number of motile bodies which are then found elsewhere than in the pale vacuole. Typically, the Monilia is not a granular yeast. With this typical form before us many involution forms are to be considered. Through reproduction by germination great numbers of smaller yeast-like cells of varying size are thrown off. These are imperfect in development and do not contain the internal structure of the typical full-grown cell. Intermingled with these yeasts are blunt ovals which become hyphæ. In evolution forms, and in degraded types, nuclei are infrequent and small. Large nuclei and a tendency to mycelial formation indicate favorable media and increased virulence of the organism.

Monilia psilosis always produces mycelium. There are many strains, which, when grown on glucose media, make these elements difficult to demonstrate. The inverted pine tree growth on gelatin stab cultures is very characteristic of the *Monilia psilosis*. The segments of the

hyphæ are clear cut and not granular. They are of all sizes, from 2 to 5 microns in width, and of all lengths. They contain pale vacuoles as do the yeasts, but these are molded to the shape of the segment and lie in a line of compartments. In addition, large and brilliant nuclei are seen arranged in a beaded formation. Budding takes place at the extremity of the article and offers no peculiarity except that there is never a sterigma. The articles are usually straight and unbranched. The extremities are rounded and bulge slightly.

Staining.—The Monilia can be readily stained by Gram's method. The most preferable stains are that of Romanowsky, and the Giemsa stain, which is best for bringing out the nuclear elements. Ashford finds Bodin's victoria-blue stain the best for demonstrating the outer shell and mycelium.

Cultures.—The Monilia grows most favorably and most typically on Sabouraud's glucose agar, containing 4 per cent. glucose and with an acidity of plus 2.

The growth on this media is of a faint greenish to a yellowish creamy color. It is soft and elevated, with clearly defined borders. When the culture-tube is held up to the light the mycelial extension can be seen beneath the surface. In young cultures the growth is shiny and glistening. In old cultures the growths develop a waxy appearance and have many different forms. The following are descriptive: (1) a dirty, creamy growth with a hard parchment covering; (2) a honeycombed muddy growth, and (3) a pitted or crater-like dirty growth.

The Monilia grows slowly and a well-defined growth appears within from three to four days. The first growths are slow, but after transplanting, the growths are more rapid.

Gelatin.—In gelatin the Monilia produces a fine, long, hair-like mycelial extension, branching out into the solid medium from the line of inoculation. The appearance is that of an inverted pine tree. This medium is never liquefied by the *Monilia psilosis.*

Litmus Milk.—The alkali reaction of the milk is heightened, and the bluish color increased. Acid or coagulation are never produced. There is, however, a slight digestion of the casein.

Fermentation Tests.—The sugars normally fermented by the *Monilia psilosis* are glucose, levulose and maltose. Saccharose is fermented at times, but this is not typical. Galactose is rarely fermented. Gas is produced within two days, and rapidly increases until the seventh day, when it terminates. The most gas is produced in glucose media; the next highest amount of gas is produced in levulose media, and the least in maltose media.

Bouillon-containing Sugars.—The inoculated medium is clear, with an abundant sediment collecting at the bottom of the tube. The medium may be clouded temporarily when freshly inoculated, or when gas bubbles disturb the sediment. A line of demarcation is produced where the surface of the liquid medium comes in contact with the sides of the glass tube. Pellicles are rarely formed.

Pathogenicity for Lower Animals.—The virulence of the *Monilia*

psilosis is mild, and to obtain the best lesions in the animal, cultures taken direct from human cases should be used. Cultures that have been passed through animals have a high virulence. After having been grown on artificial media over an extended period the virulence is diminished. The virulence can be regained by passing the cultures through animals. A virulent culture, when inoculated into the peritoneum, will kill the animals within forty-eight hours. The pathology produced will be one of a mycotic septicemia. Rabbits, white rats, guinea pigs and monkeys have been successfully inoculated, and the disease resembling sprue in the human produced. An autopsy of the animals that have been inoculated over an extended period will show (1) emaciation of the animal; (2) decrease in the fatty tissues; (3) inflammation and eroded areas in the mucous membrane of the mouth; (4) swelling, congestion and inflammation of the submaxillary and cervical glands; (5) congestion to a high degree, and bloodiness of the liver, kidney, spleen and lungs. Very often small white spots can be seen. From these spots the Monilia can be recovered.

The stomach wall is inflamed without ulceration. The mucous membrane is covered with a white, grumous coating which is filled with yeast-cells. The intestines are inflamed and also coated. They are greatly distended with gas.

Toxins.—The toxins elaborated by the *Monilia psilosis* are probably endotoxins. Experiments have demonstrated that 5 c.c. of a virulent bouillon culture, when injected into a guinea pig, will kill the animal within 48 hours. If the same culture is filtered through a Berkefeld filter, injections of bouillon in doses up to 20 c.c. will not produce symptoms. In sterilized cultures the endotoxins are not readily liberated from the cells.

Distribution of the Organism.—(*a*) *In the Body.*—The organism in the body is found in the mouth and may also be localized in any part of the gastro-intestinal canal. In the active cases of sprue the organism may be easily isolated from scrapings of the tongue, and it is also very often found in the feces. In the inactive cases the organism is difficult to isolate, and at periods it may be temporarily absent from the tongue and from the feces. In cases which are fatal the organism may be readily isolated from the stomach or any part of the gastro-intestinal canal which shows infected areas. The organism has never been found in the liver or spleen of the human.

Ashford has succeeded in isolating the Monilia in about 3 per cent. of all normal individuals. The cultures were made from scrapings of the tongue and feces.

(*b*) *Outside of the Body.*—The *Monilia psilosis* has a very high thermal death point, which is 72° C. with an exposure of ten minutes. This makes conditions very favorable for it to thrive outside of the body.

The organism has been recovered from milk. Ashford has succeeded in isolating the organism from the inside of a loaf of baked bread, and he lays stress upon this fact as an important feature in the trans-

mission of the disease. Undoubtedly, other sources of infection will be found. Researches are yet to be made to definitely trace the infection outside the body.

Modes of Conveyance.—As the disease involves the gastro-intestinal canal, the infection is undoubtedly transmitted by food. Ashford has proven this by transmitting the disease through feeding experiments to the lower animals. The disease seems to be endemic in cities and families, and undoubtedly the carrier or a person who has the disease in a mild form may infect others by the improper handling of food products. As the Monilia is extremely resistant, the ingestion of contaminated food products through the mouth is frequently the source of infection.

Types of Infection.—In about 3 per cent. of the individuals examined in the tropics the organism can be isolated from the feces. In the mild type of infection there are but few symptoms, such as gastric disturbance and a burning sensation behind the sternum. The infection changes about and the symptoms likewise. The disease may be classified as an acute, subacute and chronic form. In each instance, the infection may be moderate, severe or even intense.

The diagnosis of sprue was formerly made and recognized by physicians only when the symptoms were complete, and where there was a generalized infection of the entire gastro-intestinal canal. Manson classifies the disease as:

I. INCOMPLETE SPRUE.—(*a*) *Gastric Cases.*—The principal symptoms are an inflammatory process in the mouth, distention of the stomach, emaciation, pale, copious but solid stools.

(*b*) *Intestinal Cases.*—Cases are often found in which there are no mouth lesions, with little or no distention of the abdomen, but in which the stools are liquid, pale and frothy. Usually the patients have had some other form of the disease, which has changed to this form.

(*c*) *Sprue without Diarrhea.*—It sometimes happens that under treatment the diarrhea and mouth symptoms subside; nevertheless the stools remain copious. In these cases there is a progressive wasting, and the patient dies of inanition.

II. COMPLETE SPRUE.—In complete sprue the infection exists throughout the entire gastro-intestinal system, and the symptoms are (1) mouth symptoms, (2) gastric symptoms, (3) intestinal symptoms and (4) constitutional symptoms. There is progressive wasting, and cases terminate fatally. It is this form which is most often recognized. The symptoms are complete, and therefore the greatest number of cases which are diagnosed as sprue are of this type.

Symptomatology.—CLINICAL HISTORY.—The incubation period is unknown, and the onset insidious without any marked symptoms. The patient may only complain of weakness and lassitude. The first symptom may be that of a sore mouth, or a copious diarrhea occurring in the morning. The first complaint is usually indigestion with eructations of gas and a "heart burn" sensation in the stomach which is difficult to relieve.

PHYSICAL FINDINGS OF COMPLETE SPRUE.—Following the onset, the symptoms become more severe. The mouth and tongue become raw and tender and the use of vinegar, alcoholic drinks and spiced food causes a severe burning pain. There is a severe burning sensation along the esophagus which extends behind the sternum. There is a constant belching of gas. The patient states that the pain is relieved when the stomach is empty. The patient gradually becomes weaker. The pulse becomes slower, and the tension is lower. The temperature is subnormal or normal. In very few cases has any fever been noted.

The patient becomes progressively emaciated. The skin is pale, and of a yellowish hue, and there is a general appearance of a marked loss of fatty tissue over the entire body. The wall of the abdomen in the epigastric region is soft and relaxed, while in the region of the intestines the abdomen is very often greatly distended. There are from eight to ten bowel movements daily, the feces being white, foamy and foul-smelling.

After passing gas the patient is considerably relieved. The use of starchy foods or sugars aggravates the symptoms. If no treatment is instituted, the patient becomes progressively weaker, and is forced to remain in bed. The skin becomes wrinkled and dry. As the anemia becomes severe the mentality is diminished and the special senses may become impaired. The symptoms are those of a progressive toxemia.

The heart sounds are weakened, and the pulse becomes thready. All the symptoms are followed by a gradual failure of circulation, and unless arrested the cases terminate fatally. The course of the disease is slow and gradual, and may extend over a period of from three months to fifteen years. Very often, when under treatment, the symptoms subside for long intervals, which are again followed years after by acute attacks.

SPECIAL SYMPTOMS AND FEATURES.—(1) *Tongue.*—The mouth is full of mucus due to the inflammation of its mucous membrane. The tongue is coated and covered with fur, through which the fungiform papillæ may be seen projecting. During acute exacerbations the tongue is clearer, and the characteristic lesions are found on the point and sides. They consist of small inflammatory areas, of a cherry red color, and form small ulcers. Later on the ulcerations develop on the upper side, causing the tongue to become extremely tender. Similar patches may develop underneath and, when located on the frenum, cause a great deal of discomfort. The lesions are transitional and change location often. After the disease becomes chronic the color of the tongue is darker; the upper surface is smooth and glistening. Small furrows and cracks develop and make the tongue greatly resemble a syphilitic tongue. The tongue continues to be tender. Ulceration of the mucous membrane near the molar teeth may often be seen. This lesion is named Crombie's ulcer. The gullet and uvula may also be congested and inflamed. The reaction of the mouth is alkali, and as the disease advances the reaction becomes acid.

(2) *Diarrhea.*—The diarrhea of sprue is of two kinds, one chronic

and habitual, and the other acute. The character of the diarrhea is an important diagnostic factor. In the mild type of the disease it consists usually of one copious movement in the morning of a pale gray color, pasty, fermentating, foul-smelling and of acid reaction. The stools also contain undigested food. When the mouth lesions or the intestinal lesions become aggravated, the diarrhea is increased to five or six movements a day, and is very difficult to control.

(3) *Stomach.*—Gastralgia is most common, and burning of the epigastrium is universally complained of. The symptoms of hyperchlorhydria are marked. The pain in the stomach is usually relieved upon belching, and as a rule the symptoms of burning disappear when the stomach is empty. Observations in a series of cases, by Van der Scheer, showed three cases with a normal acidity, and hyperchlorhydria in 13 cases. Achlorhydria was noted in 2 cases. In cases of achlorhydria the pepsin is usually absent and the lab-ferments diminished. The free hydrochloric acid is diminished in all cases, and may be absent in some.

(4) *Intestines.*—The intestinal symptoms are least noticeable. The patient usually complains of a fullness and tightness of the abdomen. This is relieved upon passing gas. The abdomen walls are doughy, and the lower region distended with gas which is produced by the activity of the Monilia on carbohydrates and sugars in the gastro-intestinal canal. Ulceration of the anus rarely occurs, and the author has observed only one case.

(5) *Liver.*—One of the most important diagnostic features of sprue is the gradual diminution in size of the liver. The decrease in size can be noted as the case advances. This condition is a progressive atrophy caused by the toxemia, and does not present any gross symptoms. Icterus is never noted. The infection never seems to invade the liver, but the bile-ducts are involved.

(6) *Pancreas.*—In sprue the unabsorbed fat content of the feces is notably increased, and Cammidge's reaction is positive in many instances, which suggests active degenerative changes. The pancreatic duct often becomes involved, but rarely are there any definite clinical symptoms of pancreatitis.

(7) *Kidneys and Spleen.*—The kidneys and spleen do not seem to be involved, and present no gross symptoms.

(8) *Circulatory System.*—The veins are usually distended. The pulse is soft and compressible. The blood-pressure is less than normal, and the heart sounds are weakened and irregular. Hemic murmurs may be heard. A circulatory failure develops; the legs and ankles become edematous. Petechiæ may develop, due to the extravasation of blood from the vessels.

(9) *Nervous System.*—The mentality in severe cases may become involved and impaired. The patient becomes dissatisfied, irritable, and complains constantly. All the nerve energy is decreased and the special senses are impaired. In some cases paresthesia is noted on the

outside of the upper legs. All reflexes are impaired and sluggish. Tetanic-like attacks have been observed in some cases.

(10) *Respiratory System.*—In the later stages of the disease the respiration is impaired, and it seems an effort for the patient to breathe. Râles may be heard in the lungs.

LABORATORY FINDINGS.—(1) *Blood.*—The blood picture is one of an anemia brought about by a systematic toxemia. The hemoglobin is diminished, and may vary from 20 to 60 per cent. The number of red cells is decreased to one or three million, depending upon the condition of the patient. The decrease in hemoglobin is in proportion to the decrease in the number of red cells. Thus in severe cases where the hemoglobin is 25 per cent., the red cells number one million. The red cells show a poikilocytosis with normoblasts.

The number of leukocytes is decreased and, in a case with a white cell-count of 2,200, the differential count showed: neutrophils, 68 per cent., small lymphocytes, 29 per cent., large lymphocytes, 11 per cent., and eosinophils, 2 per cent. Myelocytes are not found. The principal findings are a lymphocytosis and an increase in the eosinophils.

Bassett Smith explains the blood-findings as being due to the cirrhotic changes in the mucous membranes of the gastro-intestinal tract which prevent the absorption of the nitrogenous products required for the formation of red blood-cells.

(2) *Feces.*—The feces are of a pale gray color, soft, foamy or fermentating, extremely foul-smelling and acid in reaction. Examination shows undigested muscle fibers. Iodin stain shows few unchanged starch cells. The fat content is increased, due to a partial failure of saponification and absorption of fats that are normally absorbed. The fatty acid crystals are also increased. This indicates that there is some impairment of pancreatic and liver activity.

Rechartz demonstrated that the bilirubin, which is the normal coloring matter in the feces, has been changed into a hydrourobilin which gives the feces the pale color, and also indicates an involvement of the bile ducts.

The *Monilia psilosis* can be isolated by making a plate culture on Sabouraud media. The dilution method or the streaking method can be used, the latter requiring the least time.

(3) *Urine.*—An analysis of the urine shows an increased amount of indican. This occurs in 85 per cent. of the cases, and demonstrates an hepatic insufficiency which allows an absorption of intestinal toxins into the general circulation, where they are converted into indican. Acetone and mono-acetic acid may be found, and show abnormal tissue waste. Albumin and sugar are not found in cases of uncomplicated sprue.

Cammidge demonstrated that his reaction was positive in 60 per cent. of all cases. This indicates degenerative changes in the pancreas or an infection of the pancreatic duct.

(4) *Mouth Cultures.*—The Monilia is most easily demonstrated in scrapings from the tongue during an acute attack. After the tongue

has become smooth and does not show any acute inflammation the Monilia is not found as often. The method consists in scraping the tongue with a glass slide or spatula and then inoculating tubes or plates of Sabouraud glucose media. The cultures are incubated from three to five days and the growths examined. The cultures are best examined on wet slides or stained with methylene blue. The Monilia can be then identified by its morphology and growths, as described by Ashford.

SPECIAL EXAMINATION: COMPLEMENT-FIXATION TEST.—The complement-fixation test is positive in sprue, and has its value as an aid in the diagnosis and index of the progress of cases under treatment. In a series of 100 cases the test was positive in 98 per cent. of the cases diagnosed clinically and mycologically as sprue by Ashford.

The complement-fixation test in sprue requires careful interpretation. In order to establish a positive standard, careful preliminary tests were made to determine the specificity of this test to the clinical cases. All of the tests made were checked up clinically and mycologically by Ashford.

Preparation of Antigens.—Cultures of Monilia are made on Sabouraud's glucose media, incubated four weeks. The growth is washed off with distilled water, using one culture to 10 c.c. The emulsion is shaken in a machine for two hours and incubated for four days to allow autolyzation. Half of one per cent. phenol is then added as a preservative and the emulsion heated to 58° C. for one hour. Cultures are made to test its sterility. It is then titrated for its hemolytic and anticomplementary action. In the tests 0.1 c.c. should be used as a standard. This emulsion can be used for six months and the standard does not change, which makes it a very stable antigen. Old cultures make the best antigens. Antigens made of young cultures lose their stability. Antigens made from the liver and heart of animals that died of acute sprue are of no value. Liver extracts from a patient dying of sprue are unsatisfactory.

Serum.—The serum used was decomplementized by heating for an hour at 56° C., 0.2 c.c. of serum being used. It is advisable to heat all serum, to destroy the thermolabile anticomplementary enzymes. If natural, only 0.1 c.c. was used. It is of interest to note that in Porto Rico the complement content of human blood is extremely high as compared with the United States, and heating at 56° C. for thirty minutes does not destroy all the complement. This may be overcome by heating the blood at 56° C. for an hour and allowing it to stand for at least twelve hours before using.

Complement.—In these tests 0.3 c.c. of a 10 per cent. solution of guinea-pig serum is used.

Amboceptor.—Antisheep amboceptor 1/1000 solution of serum titrated so that 1 unit = 0.2 c.c. In the tests 1½ units or 0.3 c c. is used.

Erythrocytes.—One c.c. of a 5 per cent. solution of sheep corpuscles is used.

Technic.—The technic employed in these tests may be that of Wassermann or of Noguchi. In the Wassermann test two series of tubes

are set up. One series contains 0.1 c.c. of normal serum. In the other 0.2 c.c. of inactivated serum is used; .07 c.c. of *Monilia psilosis* antigen is then added to each series. A control series of five tubes each is set up for each test, and the following antigens are used: 0.1 c.c. of antigen prepared from a non-virulent Monilia isolated from feces, 0.1 c.c. of a white monilia antigen, and 0.1 c.c. of a combined antigen prepared from a mixture of all the antigens used. Another series of controls is used with syphilitic antigen. To all these tubes 0.3 c.c. of a 10 per cent. guinea-pig serum is added and 1 c.c. of salt solution. The tubes are then heated in a water-bath for half an hour, after which 0.3 c.c. of 1/1000 antisheep amboceptor and 1 c.c. of 5 per cent. sheep erythrocytes are added. The tubes are again incubated for thirty minutes and the results taken.

In the Noguchi test similar technic is employed, using the same number of controls.

The Noguchi method is the more delicate, and when this test is negative the cases are also found to be negative mycologically and clinically. In all cases which give a positive result by the Wassermann reaction the *Monilia psilosis* can be isolated from the feces, and the case has clinical symptoms, with the exception of a few instances. The results of all these tests depend upon having proper antigens, and it is noted that antigens prepared from young cultures will not give a pronounced reaction.

Specificity of the Test.—Out of over 400 tests made, including various diseases, in all cases which were diagnosed clinically as sprue and from which the *Monilia psilosis* was isolated from the tongue and feces, the complement-fixation test was positive.

The other monilia antigens which may be used give faintly positive results only in severe cases of sprue. In these tests the results with other monilia antigens are about 15 per cent. positive, while the reaction within the psilosis antigen is 100 per cent. positive. It is of interest to note that this reaction varies with the condition of the patient. In cases of chronic or latent sprue, and in cases which have recovered, the reaction tends to become negative.

Pellagra having been demonstrated by Goldberger as a diet-deficiency disease, it is often confused with sprue. The complement-fixation test is negative in almost all cases.

Diagnosis.—The diagnosis of sprue can always be made on the following clinical findings (Ashford):

1. Lesions of the mouth.
2. Light, foamy, foul diarrhea.
3. Excessive intestinal fermentation.
4. Diminution in size of the liver.
5. Progressive wasting.

The laboratory findings, by isolation from the tongue and feces, are in confirmation of the clinical symptoms, and with the aid of complement-fixation tests little doubt can be left in making a positive diagnosis.

STOMATITIS.—In the tropics stomatitis is very common and may be confusing. The tropical stomatitis does not change its location as does sprue. Very often the stomatitis is found in conjunction with pyorrhea.

DIARRHEA.—Diarrhea of all kinds being very common, care must be taken in making a positive diagnosis. White flux, a diarrhea due to a temporary insufficiency of the bile secretions, may be confusing, but the condition readily responds to treatment.

GASTRIC DISORDER.—In cases of atrophy of the stomach, with a history of alcoholism, there is a degeneration of the stomach walls with symptoms simulating sprue.

ANKYLOSTOMIASIS is prevalent where in all regions sprue is endemic, and the clinical resemblance to sprue is remarkable. Laboratory findings readily clinch the diagnosis.

PERNICIOUS ANEMIA.—Progressive pernicious anemia is similar in respects to the toxemia of sprue. The blood findings vary sufficiently for a positive diagnosis to be made.

PELLAGRA.—In countries where sprue is not common, the cases are often diagnosed as pellagra. A study of the dietary of the cases following Goldberger's observations greatly assists in making a positive diagnosis. The skin lesions are absent in sprue, as are also the mental symptoms of pellagra. The isolation of the Monilia from the tongue and feces, and the complement-fixation test will decide the diagnosis.

Complications.—The complications of sprue are indefinite in character and seem to have no radical relationship to the disease. The complicating diseases are *acute diarrhea* and *dysenteries* due to pathological changes in the intestine. *Hemorrhage* rarely occurs, but in a few instances severe ulcerations of the bowels are found. *Pancreatitis* in a mild form is present in many cases. *Jaundice* and *diabetes* may occur and are usually caused by the action of the toxins on the internal secretory glands and by hepatic failure to neutralize the toxins formed in the intestines. *Myalgia* often occurs and the upper legs become affected.

Diseases Associated with Sprue.—In Porto Rico, at times, cases of pellagra may be found in cases where sprue is present. The diagnosis is complicated, cases of sprue being often diagnosed as pellagra. The differential diagnosis can be based upon the isolation of the Monilia from the tongue and feces, a complement-fixation test, and the skin lesions of pellagra.

No disease is found constantly associated with sprue, but sprue may predispose to one of the other diseases. In the tropics ankylostomiasis is the most common disease associated with sprue. Observers have found tuberculosis of the lungs, and diabetes associated with sprue. Filariasis has been observed by the author in a number of instances.

Sprue and dysentery are two distinct diseases and owe their origin to different causes, but both are common in the tropics and seen in combination. The attack may commence with an acute illness, with fever, and then becomes chronic. After the diminution of the dysentery symptoms, the history is that of sprue.

Treatment.—GENERAL TREATMENT.—In the treatment of sprue numerous remedies have been tried and abandoned. Of these, diet has remained the most reliable and successful means of treatment. Even with diet the treatment of sprue depends entirely upon the individual, and one diet may agree with one and disagree with the other case. The important feature in the treatment is the coöperation of the patient with the physician in following out the instructions minutely. The patient should **not** be allowed to **exert himself** in any way, and to obtain the quickest results the patient should be **kept in bed.** The **clothing** should be **warm** and all precautions be taken to prevent chilling of the body. As the gastro-intestinal canal is the source of the toxemia, all efforts should be made to induce **asepsis** of the **gastro-intestinal tract.**

DIETARY TREATMENT.—In the treatment with diet, no hard and fast rules can be set down, as the food which agrees with one individual will not agree with the other. The diet must therefore be selected in each case, the object being to find a diet which is easily assimilated and which will tend to inhibit gastro-intestinal fermentation, and which will decrease the activity of the Monilia in the intestines. Of all diets, the milk diet has constantly proven the most favorable.

Milk Diet.—The patient is usually kept in bed, and seven to eight pints of **milk** are given. The milk may be boiled and diluted with vichy water, which makes it pleasant to take. The milk should be sipped through a straw. As the case improves the amount of milk can be increased to eight or ten pints. After continuing the milk diet for from one month to six weeks the diet may be amplified by the addition of strawberries, bananas or apples. Broths may also be given, then meats and then toast and mild tea.

Ferris, in China, had success in the treatment of cases by **combining the milk with peptones.** In the tropics, where it is difficult to procure fresh milk, condensed milk may be used. The peptone is dissolved in diluted condensed milk, using from one-half ounce to two ounces of peptone to sixty ounces of diluted milk. In a general milk diet it is advisable to begin with sixty ounces of milk in twenty-four hours, and to gradually increase to one hundred ounces in twenty-four hours. Usually within six weeks, if conditions are favorable, the stools will become solid. In prescribing a milk diet, care should be taken that the patient procures and assimilates enough food, as in several cases starvation has been noted where the milk diet had been continued over too long a period. The use of **lactic acid bacilli cultures** is a valuable adjunct and produces very good results in the treatment.

Fruit and Milk Diet.—To the milk diet fruits may be added, such as strawberries, using from three-quarters to two and a half pounds per day. Bananas may also be taken, using from twenty-four to thirty-six per day.

Fruit Diet.—Van der Berg had good results by putting the patients on a fruit diet consisting totally of grapes and pears.

Meat Diet.—In some cases a meat diet is very beneficial and pro-

duces good results. The meat juices may also be used. Beef tea and calf's-foot jelly may be given with toast. When the patient is on a strict meat diet, from three to four pounds are prescribed to be given daily. It is noticed that as soon as a meat diet is commenced, the stools become very dark in color.

Mixed Diet.—The object of all diets being to prevent fermentation, carbohydrates and sugar should not be used in any form. In the treatment of cases, the author usually begins on a milk diet with cultures of lactic acid bacilli. As soon as the patient responds, the diet is gradually increased by the addition of fruits and meat juices. This is continued for two or three weeks and then small pieces of meat are given. The first carbohydrate given is a piece of well-toasted bread. Then vegetables are added to the diet, and finally roasted potatoes and the légumes. The success depends entirely upon the gradual adaptation to the diet. It is recommended that the high protein diet be continued for a period of at least nine months.

MEDICINAL TREATMENT.—The treatment of the disease with drugs has been very unsatisfactory, and constant results are never obtained. In comparison with the dietary treatment, drugs are of secondary importance. The treatment with drugs is largely to relieve symptoms, and most drugs usually prescribed for intestinal diseases are of no value, and are contra-indicated.

Mineral acids should **never be given** during the acute manifestations. **Bismuth** when given acts as an **irritant** and may cause violent pain and severe purging. A great deal of undigested matter is excreted in sprue and the astringents should be used with caution.

Tannic acid and preparations simulating its action should **not** be **used**, as they usually cause an arrest of absorption and assimilation. **Iron** and **arsenic** are to be used with extreme **caution**. At times, when hypodermic injections of iron or arsenic are given, small abscesses form at the site of injection, which usually contain sterile pus due to extreme lowering of resistance. When acute symptoms have abated, **organic iron preparations** are of value. The best results in the treatment of sprue could be obtained by proper **intestinal antiseptics** which would act upon the fungi without causing irritation of the gastro-intestinal tract. **Salol** and other intestinal antiseptics have been used, but are without definite value. The treatment by medication being symptomatic, drugs can be used as follows:

Purgatives.—**Castor oil** in tablespoon doses seems to be the best purgative, and can be used often. The mild **salines** are next in value. **Calomel** should be prescribed with **extreme care**, as any drug which irritates the intestines will aggravate the symptoms of sprue.

Emetics.—Cantlie first used powdered **ipecac** in doses of from twenty to thirty grains daily for two or three days, with good results. **Emetin** or **apomorphin** should **never** be given. In the treatment of gastric disorders **sulphurous acid** has produced good results in diminishing the infection in the upper part of the gastro-intestinal canal. It can be given to mild cases in doses of 5 to 15 drops, well diluted in water. The

digestive ferments are of value in cases where there is a permanent impairment of digestion. **Pepsin, pancreatin** and **diastase** have been used with good results.

Treatment of Diarrhea.—The treatment of the diarrhea in sprue does not follow the general line of treatment. The **opium group** is the most effective in controlling the diarrhea. **Tincture of opium** in doses of twenty minims, or **opium and lead acetate** in doses of ten grains are used. In some cases **lactic acid** in doses of from twenty to twenty-five drops well diluted in water can be given after meals. **Chalk mixture** in combination with opium is very useful. In most countries the natives have remedies of reputed value. **Phosphate of lime,** powdered crab's eyes, cuttle-fish bones and the **barks** and **roots** of **tropical plants** in great numbers are used for the treatment of sprue.

Relief of Pain.—Painful sore tongue is relieved by painting with a 1 per cent. **cocain solution,** or by using **glycerin** and **diluted phenol,** 2 per cent. to 4 per cent. in equal parts, which is applied to the tongue. Strong acids and hard foods are to be avoided. Pain in the esophagus is relieved by an application of **adrenalin chlorid solution** in doses of from five to ten drops. Abdominal pain is relieved by the application of **hot pads.**

Specific Treatment.—Sprue was for years thought to be caused by an entozoön, and this led to the use of specific remedies. Of all remedies, **santonin** is the one used at the present time. Santonin was first used by Colin, in 1878, and then passed into disuse until revived by Charles Begg, of Hanchow, in 1898. Begg advocated the use of chrome santonin, which is prepared by exposing the white santonin to sunlight until it becomes yellow. Begg states that by the process of exposure and chemical decomposition of the white santonin, the therapeutic value is produced. He recommends the use of a **preparatory treatment with castor oil** for two days. This is followed by the administration of **chrome santonin** in 5 grain doses **with olive oil** once or twice a day. This is continued for from one week to ten days.

Ashford, however, claims, on the basis of his observations, that the dietary treatment has more therapeutic value in the treatment of these cases than the santonin.

Vaccine Therapy.—Owing to the unsatisfactory results obtained by drug treatment and the difficulty in procuring the proper diet in the tropics, it was endeavored to find a specific vaccine for the treatment of sprue. Some authors have reported on the use of various bacterial vaccines. With the reports and evidence that the *Monilia psilosis* was the etiological factor in causing sprue, it seemed probable that a vaccine could be developed. Experiments also demonstrated that the *Monilia psilosis* elaborated endotoxins against which animals could be immunized by the injection of killed cultures of the Monilia.

Preparation and Injection of the Vaccine.—Cultures of *Monilia psilosis,* recently isolated from a sprue patient, should be used. Inoculations are made on Sabouraud's medium and incubated four days at 37° C. An emulsion is then made of the 4 day cultures, using one

culture in 10 c.c. of distilled water. This is shaken in a machine for two hours, after which it is heated to 37° C., for five days, which allows autolyzation to take place. After the addition of phenol (to make one-half per cent. of the volume) the vaccine is sterilized at 56° C. for one hour. Cultures are now made to test it for sterility, and animals are injected with from 5 to 8 c.c. If the animals show no signs of infection in two weeks and the cultures show no growth, the vaccine can be used. The difficulty in preparing the vaccine is due to the high thermal death point of the Monilia, which is 70° C. Autolyzation is used to lower the thermal death point.

Owing to the difficulty of counting the number of Monilia in the emulsion, and because of the polymorphic forms of the organism, the following method of standardization was adopted:

Ten c.c. of the emulsion is put in a Purdy graduated centrifuge tube and centrifuged at a medium speed for five minutes, after which a reading is taken. The amount of sediment composed of Monilia should be 1 per cent. in the standard of emulsion used. The primary dose of this emulsion given is about 0.05 c.c.

There is no guide to the dosage of the vaccine thus prepared except its injection into normal persons and patients having sprue. For this purpose a primary dose of 0.05 c.c. of a 1 per cent. solution of the emulsion has been used.

The dosage of the vaccine was determined by its effect on normal persons and patients having sprue. Ten normal persons were injected with doses of from 0.1 c.c. to 0.2 c.c. and the reactions observed; 0.2 c.c. produced a fairly severe local reaction which lasted about 4 days and subsided, without gastro-intestinal symptoms being produced. In normal persons or those suffering with other diseases, doses of vaccine up to 0.6 c.c. have been administered without producing any other than a local reaction.

Patients having sprue are injected with from 0.05 c.c. to 0.1 c.c. and observed. The injection of 0.05 c.c. produced a local moderate reaction and an increase of gastro-intestinal symptoms. The injection of 0.1 c.c. produces a severe reaction in some cases, the site of the injection becoming deep red and inflamed for an area of 1 cm. Around this an area of erythema extends for 7.5 cm. The tongue becomes very sore, and the diarrhea increases with a great deal of flatulence, accompanied by a rise in temperature from 2° to 4° F. (1.1° to 2.2° C.). These symptoms may be severe enough to require the patients to rest. They complain of depression and weakness.

The most marked features of the reactions to be observed are the increased soreness of the tongue and aggravation of gastro-intestinal symptoms.

The reaction is most severe on the second day after the injection, and commences to subside about the third to the fifth day. Considering the degree of local and general reaction that is produced, especially in very severe cases of sprue in which there is marked disability, it seems preferable to administer a primary dose of not more than 0.05 c.c.

The second injection is given from eight to ten days after the first injection. The time of this administration should, it is believed, vary with the condition of the patient. The dosage given is about twice the first dose, from 0.15 c.c. to 0.2 c.c. being injected The interval of the dosage depends upon the condition of the patient, the ten-day interval being the most preferable.

In most cases the second reaction is not as severe as the first. A moderate local reaction is, however, produced which lasts from four to five days, accompanied by an increased soreness of the tongue, slight flatulence, fever of from 1° to 3° F. (0.55° to 1.65° C.) and slight diarrhea. These symptoms subside rapidly, and after five days improvement is noted in the general condition of the patients. There is an increase in appetite and the patients usually gain several pounds in weight. The intestinal symptoms are notably diminished.

The third injection is given ten days after the second, from 0.5 to 0.6 c.c. being given. The reaction which follows is very mild, subsiding after about two days' duration. The intestinal symptoms are very slight.

The fourth injection is given about ten to twelve days after the third and practically no reaction results, except a slight local induration, and redness. The amount injected is from 0.5 to 0.7 c.c. The general health of the patients is by this time greatly improved and in most cases there is a gain in weight of about two pounds per week. The symptoms of sprue are diminished.

The fifth injection of 0.9 c.c. is given from twelve to fourteen days later, and there is usually a slight or no gastro-intestinal reaction. The patient complains of weakness which lasts for one day. The diet is then increased and the patients are allowed to have sugar and cereals in small amounts.

The sixth injection of 1.4 c.c., given fourteen days after the fifth, produces nothing but a localized reaction which lasts from two to three days. The sprue symptoms are absent and the patient is allowed all kinds of food, including sugars and all carbohydrates.

The injections should be gradually increased and continued over an extensive period, usually three months and a total of about ten or twelve injections.

The most notable feature is the gain in weight, which is progressive from week to week. There is also, in all cases, a great improvement in the general physical condition of the patient, and the disappearance of the Monilia from the feces. The results of this treatment are very favorable.

The best constant results are obtained by the use of autogenous vaccines and these should be prepared for all cases if possible.

Other Treatment.—Often where there is extreme anemia blood transfusion should be resorted to. Of these methods the citrate method seems to be the best in the tropics, and is most preferable unless one has had considerable experience in direct transfusions.

Treatment of Convalescence.—During the treatment in severe cases the patient should remain in bed. Even after all symptoms have

disappeared extreme care must be taken as to diet. The patient should eat sparingly, avoid exposure, overwork and fatigue. At times a change of climate has a distinct advantage.

Prognosis.—The prognosis in cases under fifty years of age is very good, and recovered cases have few complications. The mortality is about 10 per cent. Statistics have been unsatisfactory in connection with sprue, the incorrect diagnosis very often being made.

Pathology.—In sprue the pathology seems to bear little relationship to the severity of the symptoms. In attempting to describe the condition the most prominent pathology is the catarrhal inflammatory condition of the entire gastro-intestinal tract, and the presence of abnormal coloring matter in the feces. The diminution in the size of the liver is also worthy of consideration. This is probably caused by a disturbance of the glycogen function by the toxins of the Monilia, accompanied by a possible infection of the gall-ducts. The diminution in size of the liver is transitional, and in cases that have recovered from sprue the liver increases in size and recovers its functional power to a great extent.

The secretory function of the pancreas becomes disturbed. This is caused by an invasion of the pancreatic duct and occurs in about 60 per cent. of the cases.

The infection is of a mild type, and as it proceeds to invade the entire gastro-intestinal tract the virulence is increased. The production of the mycelium which penetrates the mucous membrane gives rise to the catarrhal inflammation and the destruction of the epithelial lining of the mucous membrane. In the latter stage after the destruction of the mucous epithelium the pathology is that of a gastro-intestinal intoxication. The toxins are absorbed into the circulation and produce the systemic toxic infection.

The activity of the Monilia in the gastro-intestinal tract prevents proper absorption and assimilation. Associated with this disturbance are (1) lowering of body temperature, (2) anemia, (3) loss of body fat, (4) atrophic changes in the heart, liver, spleen, kidneys, pancreas and other organs, and (5) a marked decrease in the resistance of the individual, to such a degree that secondary infections often follow.

Sprue is primarily an infection of the gastro-intestinal tract, and never is there an invasion into other parts of the body by the Monilia. Liver abscess is rarely ever seen in sprue.

Ashford's experiences with feeding experiments in sprue show that the Monilia can be traced throughout the entire gastro-intestinal canal. Bahr's observations confirm this. He found yeast-like infection throughout the entire gastro-intestinal canal in cases of sprue. The organism can also be demonstrated in the epithelial tissue of the mucous membrane. More recently Doddard Fischer, in describing the anatomical findings in sprue, traced an organism of the oïdium form throughout the entire gastro-intestinal tract.

Morbid Anatomy.—The body is thin and greatly emaciated. The skin is dry and scaly. The color is pale, with a yellowish tinge. The

lower part of the abdomen is distended, and the walls are doughy and soft.

Heart.—The heart is pale and somewhat smaller than normal. The muscles are pale in color, and soft. Fatty tissue is absent. Microscopic sections show a shrinking and an atrophy of the muscle fibers. There is an absence of fat between the fibrous tissue. Small pigmented areas may be seen. The endocardium is normal.

Mesenteric Glands.—The mesenteric glands are hyperemic and swollen. Sections show an acute inflammation of the glands.

Digestive Tract.—The digestive tract being the seat of the infection, the most characteristic changes are found here. The changes may vary in type, and parts may be acutely infected, while in other parts the infection is chronic; also the changes may be localized or may be generalized.

Tongue.—The tongue is smooth, and inflammatory patches of varying sizes are found in the mouth. There is a sclerosis of the superficial layers which often extends into the deeper layers of the tongue. The filiform papillæ are atrophic and the fungiform papillæ are swollen and infiltrated. Sections show an acute subepithelial inflammation with an infiltration of lymphocytes into the deeper layers. The epithelial layer of the mucous membrane is loose and, in parts, absent. Mycelium and Monilia are often found in the cells during an acute attack.

Esophagus.—The membrane is pale and smooth with inflammatory patches scattered throughout. The inflammation is accompanied by thickening and infiltration. The mucous layer is denuded of epithelium, and congested. Kolberg found the Monilia in the mucous membrane of the esophagus.

Stomach.—The lining is covered with a white grumous coating. Sections show a congestion and distention of the capillaries. The villi are normal. The mucous membrane is thinned in parts.

Intestines.—The duodenum is thickened from edema. The mucous membrane is smooth and presents no atrophy. The lymphoid tissue is inconspicuous.

The jejunum, ileum and colon may be covered with mucus. The membrane is pale, and throughout it are scattered areas of inflammation, which are pink and granular. The mucosa is partly atrophied. The submucosa shows greatly distended fibers, and between the spaces is an infiltration of leukocytes which may form nests. The glands of Lieberkuhn and Peyer's patches are atrophied. The fibers of the submucosa are separated.

Liver.—The surface is pale and smooth. The size is greatly diminished. Sections show a shrinking of the liver cells; some are vacuolated, and the cytoplasm is granular. No gross apparent change has taken place, nor is there an increase in fibrous tissue.

Pancreas.—The pancreas is soft and pale and diminished in size. The amount of fibrous tissue is not increased. In parts of the gland the acini are congested, and there is no periacinus fibrosis. The islands of Langerhans are normal.

Kidneys.—The capsule strips with ease, and the tissue is soft and pale. The capillaries are distended and inflamed. The malpighian tufts are edematous. Serum is present in small amounts in the capsular spaces. The cells lining the glomeruli have pale, granular-staining cytoplasm with mild degeneration.

Spleen.—The spleen is pale, soft and friable. It is smaller than normal. The sinuses are dilated. The trabeculæ are prominent and the vessel walls in the malpighian bodies show a thickening. A hyaline degeneration is present. The bladder and prostate gland are normal.

In all organs there is a marked absence of fatty tissue, which indicates a starvation of the tissues.

History and Distribution.—The term Inlandse Sprouw was first applied to this disease by William Ten Rhyne in 1687. In his writings he describes the lesions of the mouth, of the esophagus and intestines, which he differentiates from the lesions of leprosy occurring in the East Indies.

Later, in 1766, Hillary of Barbadoes gave a most excellent description of this disease. His description is the most complete, and he applies the name of "aphthoides chronica" to the disease. In 1843 Schonenberg described a similar disease existing in Haiti and in Porto Rico which he called "indische spruw." Later the disease was described in the West Indies by Bostoski. The most recent and thorough work on sprue in Porto Rico is that of Ashford, who not only investigated the disease from a dietary viewpoint, but also demonstrated the relationship of the *Monilia psilosis* to sprue.

Most descriptions of sprue have originated in the east and southeastern part of Asia and later in the Malay States. In 1837 it was described as "aphthæ orientalis" by W. Bosch, the disease occurring in Sumatra and other islands of lower India. The disease was also described by Gruner (1857) and Lobell (1868).

In 1880 Van der Berg gave a most thorough description, using the term "indische spruw." His observations were made in Batavia. About the same time Manson, making observations in south China, described and clearly defined the disease, using the term "sprue." The disease is not common in northern China or in northern Japan.

Thin, in 1897, reported on cases from the coast of China, Manila, Straits Settlements and Ceylon. He paid particular attention to the tongue lesions, and named the disease *psilosis linguæ et intestinorum.*

In Cochin China, the disease had been noticed for a long time, and the term *diarrhée de Cochin-chine* was adopted by the French. In 1875 Barallier gave a description of the tongue lesions of this disease which greatly resembled a description of a sprue tongue. In Ceylon the term *Ceylon sore mouth* was applied to sprue. McLead and Gilis reported the disease in western Asia. Cases of diarrhea alba and hill diarrhea, which have been classed as sprue, are often found outside of China.

Buchanan noted cases in Bengal. These cases had mouth lesions complicated with diarrhea alba.

Previously the disease was not thought to have extended west until Begg, in 1911, described cases in Kongo and Morocco.

It is now definitely known that cases of sprue exist outside of the endemic region, and even in the temperate zones. Sporadic cases have been reported occurring in England. Rechartz has reported three cases in Germany. Talma of Utrecht describes sprue in the case of a person who had never left the country.

In 1918 Wood described cases of tropical sprue occurring in North Carolina.

The author has recently had a case under observation in which the diagnosis was clinically confirmed. The patient had never been in the tropics and resided in the southern United States. The patient had been to Europe over twenty years ago. The *Monilia psilosis* of Ashford was isolated from the feces.

Sprue exists in the southern United States, and physicians, not being familiar with this disease, have made a diagnosis of pellagra. The tongue lesions also have been mistaken for syphilis.

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CHAPTER XXVIII

LEISHMANIASIS

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Definition.—Under the name leishmaniasis are included the diseases due to protozoa belonging to the genus leishmania. There are two forms of disease due to leishmania: one a general or visceral disease which commonly progresses to a fatal termination; and one a cutaneous affection which tends to recovery. Again, each of these two forms of leishmaniasis is divided into two types, mainly according to geographical distribution, in each case the types of the disease tending to differ somewhat clinically.

Synonyms.—For the Indian visceral type: Kala-azar, Kala dukh, Dum-dum fever, Tropical splenomegaly. For the Mediterranean visceral type: Splenic anemia of infants, Infantile kala-azar, Ponos. For the Oriental cutaneous type: Oriental sore, Aleppo boil, Biskra button, Bagdad boil, Bouton d'orient, Endemic granuloma. For the American cutaneous type: Forest yaws, Bubas, Uta. Espundia is a term applied to the naso-oral involvement in the American cutaneous type.

History of Clinical Varieties.—Kala-azar.—When the British occupied the district of the Garos, in Assam, in 1869, they found an endemic disease which the natives called "kala-azar," meaning black fever, so named from the darkened skin of the affected persons. The disease was considered to be malarial cachexia, and its history is confused with that of malaria up to 1900. With the opening up of human intercommunication, the disease spread to neighboring districts; and, on account of the high death rate, it attracted considerable attention.

In 1900, Leishman found what he considered to be degenerated trypanosomes in the spleen of a soldier who died of dum-dum fever at Netley; and he published this finding in May, 1903. In July, 1903, Donovan

found the same parasites in blood obtained by spleen puncture during life. Laveran and Mesnil considered the organisms to be piroplasms, and gave the name *Piroplasma donovani*. Ross considered that the organism belonged to a different genus, and he created the genus leishmania, the organism of kala-azar becoming *Leishmania donovani*. In 1904, Rogers cultivated the organism by adding splenic blood to citrated salt solution; and he observed that the cultural forms had a single flagellum.

INFANTILE KALA-AZAR.—Fede described a febrile splenic anemia in children in Italy. In 1904, Cathoire found peculiar bodies in spleen smears from a child that had died of an ill-defined disease in Tunis, and Laveran considered these bodies to be *Leishmania donovani*. In 1905, Pianese found bodies in the spleen of children dead of Fede's splenic anemia; and he considered these bodies identical with *Leishmania donovani*, at the same time calling attention to the similarity of the symptoms of Fede's disease and kala-azar. In 1907, Nicolle studied the disease in Tunis, and considered the parasite to be related to the parasite of Indian kala-azar but not identical with it; he suggested the name "infantile kala-azar" for the disease, and the name of *Leishmania infantum* for the parasite. Gabbi, in 1908, reported that he found the disease among adults, and he considered it to be the same as Indian kala-azar.

ORIENTAL SORE.—In 1756, Russell described Aleppo boil, and stated that the natives considered it was due to the drinking water. The disease was described by various observers from that time on, but it was over one hundred years before any one seemed to doubt that the drinking water was the cause of the disease. From 1868 to 1902, various workers described ova of worms, bacteria, fungi and protozoa in the tissues of cases of Delhi boil. In 1885, Cunningham described endocellular organisms which he considered as stages of some mycetozoal organism. In 1891, Firth confirmed Cunningham's finding, and gave the name *Sporozoön furunculosum* to the organism. In 1903, Wright found round and oval bodies in endothelial cells in smears from an Oriental sore on a boy from Armenia. These bodies were 2 to 4 microns in diameter, and Wright gave them the name *Helcosoma tropicum*. It is not possible to say whether these bodies found by Wright are the same as those described by Cunningham.

AMERICAN LEISHMANIASIS.—On his voyage to Brazil, in 1648, Pisone saw a disease, known as "bouba," which he considered distinct from syphilis. In Brazil it was thought that the disease was brought in by Negroes from the Calabar coast. Since that time there has been confusion regarding the various ulcerative conditions of the skin in Brazil.

In 1895, Moreira reported that for several years the clinicians in Bahia had noted a peculiar variety of cutaneous lesions, known as "Bahia button," and he expressed the opinion that these lesions were the same as Biskra button. He suggested the name "Bouton endemique des pays chauds," as the condition was not confined to the Orient. Adeodate also considered "Bahia button" to be the same as "oriental sore."

In 1895, Breda studied three cases of skin ulceration with mucous membrane involvement from São Paulo. He concluded that "boubas" was not syphilis, tuberculosis or infectious granuloma; but that it was a special disease. He considered that some endemic skin diseases in the Orient should be called "oriental sore," and that some endemic skin diseases in America and Africa should be called "frambœsia." He considered that "boubas" was a variety of "frambœsia" that was not limited to the skin, but also involved mucous membranes.

Different workers found different organisms in the ulcerations, and there was difference of opinion as to whether the lesions were syphilis, tuberculosis, yaws or blastomycosis. About 1908, during the building of a railroad in the state of São Paulo, in Brazil, it was noted that many of the men were affected on naked parts of the body with chronic ulcers. These ulcers were known as "Bauru ulcers," from the name of the city that was one terminus of the railroad. In 1909, Lindenberg and Carini and Paranhos demonstrated in these ulcers organisms which were identical with *Leishmania tropica*.

In 1909, Nattan-Larrier, Touin and Heckenroth reported cutaneous leishmaniasis from French Guiana; and in 1911 Darling reported it from Panama. Flu reported it from Dutch Guiana in 1911; and Minett and Field reported it from British Guiana in 1913.

In 1911, Carini, studying cases in São Paulo, noted that persons who had leishmania ulcers on the skin were at times attacked by peculiar lesions of the mucous membrane of the mouth, nose and pharynx, at times by direct continuity from lesions on the neighboring skin, at other times when the ulcer was on a remote part of the body. Carini concluded that the "buba brasiliana," described by Brede, was leishmania lesions in which the mucous membranes were involved.

Splendore concluded that Breda's "buba brasilianica" was not a good term, as "buba" was a popular term for any form of ulcer, while physicians applied the term exclusively to yaws. Splendore concluded that in Brazil there are two diseases that resemble yaws, but which have a special tendency to involve the mucous membranes. One of these conditions is a form of blastomycosis, and the other is a new form of leishmaniasis.

Escomel, in 1911, described a disease that was found in the mountainous regions of Peru and adjacent territory, and gave the name "espundia" to the disease. There was a primary lesion, the "espundial chancre," on the forearm, leg, neck, chest, back or shoulders, more rarely on the face or hands. This primary lesion began as an ulcer or as a button, and healed after a varying length of time, sometimes several years. Some time after the skin ulcer had healed, even several years, the patient developed ulceration of the mucous membrane of the nose, mouth and pharynx. Escomel was not able to find the causative organism; but he pointed out that the disease was not syphilis, tuberculosis, leprosy or glanders. Laveran and Nattan-Larrier found leishmania in material sent to them by Escomel from cases of espundia.

In Cucuta, in 1916, we were told by the physicians that rhinoscleroma

was common in that region, and one case was in the hospital at that time. Though there was no history of a chronic skin ulcer, the appearance was that of nasal leishmaniasis. No microscopic examination could be made, and leishmaniasis was not known to the physicians there. Mucocutaneous leishmaniasis has been reported from Zulia, in Colombia, by Tejera.

In 1913, Migone reported a case of kala-azar in an Italian who had lived in Brazil for thirteen years. The man died after a severe attack of diarrhea.

Geographical Distribution.—Indian kala-azar is widespread in Assam, in Bengal, in the region of Calcutta, Madras, Ceylon, Turkestan, Indo-China, China, Dutch East Indies, Arabia, Egypt, Sudan and Madagascar.

Infantile kala-azar is found in southern France and Italy, Portugal, Spain, Greece, Crete, Malta, Tunis and Algiers.

Oriental sore is found throughout northern Africa, southern Asia, as far as Greece in Europe, and in New Caledonia.

American leishmaniasis is found in Brazil, Paraguay, Dutch Guiana, English Guiana, French Guiana, Venezuela, Colombia, Panama, Yucatan and Peru.

Etiology.—THE PARASITES.—Ross was the first to recognize the fact that the organism found in Indian kala-azar was a new form of protozoön, and he gave to it the name *Leishmania donovani*. Nicolle considered the organism of infantile kala-azar to be different from the organism of Indian kala-azar, mainly because it was readily cultivated, and could be transmitted to animals; he gave it the name *Leishmania infantum*. The organism found in kala-azar in Sudan can be transmitted to monkeys but not to dogs, and the organism found in kala-azar in Transcaucasia differs somewhat from the organism of Indian kala-azar.

When Wright described the organism from oriental boil, he did not know the name "leishmania," and he gave the organism the name of *Helcosoma tropicum*. When it was recognized that the organism was a leishmania, the name became *Leishmania tropica*.

Morphology.—The appearance of all of the leishmania is very much the same in the body of man. With the Romanowsky stain, the organisms appear as round or oval bodies, 1.5 to 2 microns in diameter and 2 to 4 microns long. The cytoplasm stains blue, and two nuclei are seen. The large nucleus is about one-quarter the size of the entire organism, lies close to the border of the cell, and stains deep red. The small nucleus lies deep in the substance of the cell, appears as a point or rod, and stains more violet than the large nucleus. Leishman suggested that the small nucleus was a blephoroplast, and that the organism was related to the trypanosomes. The cytoplasm is quite frequently vacuolated, and the large nucleus may appear vacuolated. *Leishmania tropica* is frequently found as long, slender forms, and very large, vacuolated forms are common; otherwise, the different species of leishmania are morphologically identical.

Leishman suggested that the bodies he found in 1900 were related to

the trypanosomes. In Rogers' cultures of the organism of kala-azar, the organisms had a single flagellum taking its origin from the small nucleus; that is, they were the leptomonas form in the order Binucleata which includes the trypanosomes.

All of the leishmania are cell parasites, being found mainly in the endothelial cells; but they are also found in polymorphonuclear leukocytes, in eosinophils and in myelocytes. At times in smears, especially from cutaneous leishmaniasis, free parasites are found: this probably means that they have escaped from destroyed cells. The parasites have the leishmania form in the tissue; but Escomel reports the flagellated leptomonas forms in espundia; and Risa and Mustafa saw motile flagellated forms in oriental sore.

Culture.—In 1904, Rogers cultivated the organism of Indian kala-azar by drawing blood from the spleen into sodium citrate solution (1 to 2 c.c. of 10 per cent. solution in the syringe), and keeping it at 22° C. In 1908, Nicolle cultivated the organism of infantile kala-azar and of oriental sore on Novy-MacNeal medium, and later on a simplified Novy-MacNeal medium. A number of workers failed to cultivate the organism of Indian kala-azar on Novy-MacNeal medium; and this was thought to be a strong indication that the organisms were different. But in 1912, Row cultivated the organism of Indian kala-azar on Nicolle's modification of the Novy-MacNeal medium. The Nicolle modification of the Novy-MacNeal medium is known as the N. N. N.-Agar, which is made as follows:

Distilled water	900 c.c.
Agar-agar	14 grams
Sodium chlorid	6 grams

This mixture is melted, cooled to 45° C., and one part of defibrinated rabbit blood is added to two parts of the mixture, and slanted. The tubes should be tightly stoppered, so the water of condensation will not dry out. The cultures grow best at 22° C.

In the cultures, from the fourth to the seventh day, the organisms appear as long, slender forms, 15 to 20 microns long, and 2 to 4 microns in diameter. A single flagellum rises from the small nucleus (blepharoplast) and extends as a free flagellum, without any evidence of an undulating membrane; that is, the organism is a leptomonas form. In the culture there are more oval forms, and as the cultures get older, there are oval forms without a flagellum and with vacuolated cytoplasm.

The growth is scant in cultures from Indian kala-azar, more marked in cultures from infantile kala-azar, and there is a heavy growth in cultures from oriental sore. The organism of American leishmaniasis grows even better than does the organism from oriental sore. All of the differences between cultural forms of the organism from oriental sore and those from kala-azar can be accounted for by the better growth of the oriental sore organism in cultures.

Transmission to Animals.—The organism of Indian kala-azar is not readily transmitted to lower animals, and earlier attempts to transmit

the infection to monkeys, dogs, rabbits, rats, goats, guinea pigs and pigeons failed. Later, Donovan and Patton both succeeded in infecting dogs with leishmania by the injection of splenic material from cases of kala-azar; and Row produced subcutaneous nodules in monkeys by rubbing material from the spleen of a case of kala-azar into the skin, and by subcutaneous injection of a culture of *Leishmania donovani.*

The organism of infantile kala-azar is readily transmitted to dogs and monkeys. Other animals, as rabbits, guinea pigs, rats and mice, suffer a light infection. The organism of oriental sore is readily transmitted from man to man; from man to monkeys and dogs; from monkey to monkey; from dog to dog; and from cultures to man, dog, and monkey. Gonder obtained general infection of mice by intraperitoneal and intravenous injection of cultures of *Leishmania tropica,* the mice developing in addition ulcerations on the feet and tail. Row got general infection of mice by injection of culture of *Leishmania tropica;* but there were no skin ulcerations.

Spontaneous Occurrence of Infection in Animals.—Donovan examined 1,150 dogs in Madras, and did not find any of them infected with leishmania. Castellani has reported a spontaneous infection in a dog in Ceylon.

Nicolle and his associates suggested that domestic animals were connected with the spread of infantile kala-azar; and they found four dogs infected with leishmania among 253 dogs examined in Tunis. The leishmania were morphologically and culturally identical with the parasite in man. Other investigators have found dogs infected with leishmania in a number of places about the Mediterranean. The percentage of infection among dogs varied in different regions, and the regions with the highest percentage of infection among dogs were not the regions with the largest number of cases in the human. In Tunis, 1.8 per cent. of the dogs were infected; in Athens, 13.75 per cent.;* in Lisbon, 5 per cent.; in Rome, 16 per cent.; in Malta, 14 per cent.; and in Messina, 18 per cent. The organisms are found in the spleen, liver and bone-marrow. The infection appears in two forms in dogs: an acute and a chronic. In the acute form, usually attacking young dogs, the disease sets in with fever, rapid emaciation, and weakness in the hind quarters, and the dog dies in three to five months. The chronic form usually affects older dogs, and they frequently appear entirely normal. Sergent and his coworkers in Algiers, in a house where there was a child with kala-azar, found a kitten with a few parasites in the bone-marrow. Attempts to transmit the infection from dog to dog have failed.

In French Guiana, Joyeux examined 12 dogs, and all were negative.

In some regions where cutaneous leishmaniasis is present, dogs have leishmania ulcers about the face, as in Teheran and Brazil. Five of the dogs that Brumpt and Pedroso took into the forest with them developed leishmania ulcers, three of them on the face.

Relation to Insects.—Rogers found that his cultures of the organism

*Cardamatis considered leishmania as a part of the life cycle of piroplasma; and this percentage may be too high.

from Indian kala-azar grew better when he acidified the sodium citrate solution with citric acid, and he suggested that this might indicate an adaptation to the acid contents of the stomach of insects, and thus indicate insects as the transmitter. He suggested the bedbug as the transmitter; but all of his experiments were negative. Patton followed up experiments with a number of biting insects, but he got multiplication of the organisms only in the bedbug (*Cimex rotundatus*): three days after feeding, the stomach of the bug contained flagellate forms that were identical with the flagellates in cultures, and rosette forms were present. Donovan suggested that a cone-nose, *Conorhinus rubrofasciatus*, was the transmitter; but there is no experimental evidence that this is so.

Basile carried out a series of experiments to determine whether biting insects transmitted the organism of infantile kala-azar; and he found leptomonas form flagellates in the stomach of fleas that were taken on children with kala-azar and on dogs with leishmania infection. He also showed that fleas, *Ctenocephalus canis* and *Pulex irritans*, that had fed on cases of infantile kala-azar and on dogs infected with leishmania, could transmit the infection to dogs. Basile considered that this work not only proved the possibility of transmission of leishmania by fleas in the Mediterranean regions; but that it also made it very nearly certain that the leishmania of the dog in those regions is the same as the leishmania of infantile kala-azar. Later work has not confirmed Basile's finding of the transmission by fleas.

There is little experimental work on the relation of insects to the organism of cutaneous leishmaniasis. In the regions where oriental sore is found, it is commonly considered that insects are the transmitters of the infection; and house-flies are commonly incriminated. Most experiments with house-flies have indicated that the organism of oriental sore dies in a few hours in the stomach of the fly; but Cardamatis and Melissidis found typical leishmania (not flagellates) in the intestine of flies, six days after feeding, and they suggest that the infection may result from organisms contained in the feces of the fly. Mosquitoes have been incriminated. Wenyon experimented with a number of insects; and was able to find development of flagellated forms only in bedbugs and mosquitoes (*Stegomyia fasciata*). But he was of the opinion that this did not indicate that these insects were the transmitters of the infection, but that the large amount of blood they had taken in acted as a culture medium for the organisms. Wenyon thinks that house flies, and more commonly mosquitoes or phlebotomus, are the transmitters.

In South America, biting flies are commonly incriminated. The history is usually that the person was bitten while in the woods, as indicated by the name "forest yaws"; and it is commonly a tabanid fly that is incriminated. Brumpt and Pedroso think tabanidæ are the most probable transmitters of American leishmaniasis; and they suggest the name "American forest leishmaniasis." They consider that the multiplicity of the sores means that the transmitter returns repeatedly to feed; and the tabanidæ do that. In Colombia, mucocutaneous leish-

maniasis is so closely associated with the bite of a reduviid bug, that the name for the disease is "picada de pito" (meaning "magpie's bite"), pito being a local name for a reduviid bug.

It is uncertain whether the organism is mechanically transmitted by different insects, or is transmitted by some insect as intermediate host, with a cycle of development in that insect.

Immunity.—Practically nothing is known regarding immunity after kala-azar under natural conditions, as most of the cases progressed to a fatal termination, until the use of antimony in treatment. In the dog and monkey, some months after recovery from an attack of experimental kala-azar, there is immunity; but for a few weeks after recovery there seems to be increased susceptibility to infection.

An animal that is infected with, or has recovered from, kala-azar is immune to infection with the organism of oriental sore.

After recovery from oriental sore, there is increased resistance against kala-azar; but it does not amount to immunity.

During infection with oriental sore, there is decreased resistance to infection with the organism of oriental sore, as is indicated by the multiplicity of the ulcers in a large part of the cases.

On the other hand, after recovery from oriental sore, there is immunity to further infection with the organism of oriental sore; and this fact has been taken advantage of by the natives in some localities, who inoculated the children with oriental sore on a covered part of the body, in order to protect them against danger of future infection with the possibility of scar formation on the face.

Relation of the Organisms in Leishmaniasis.—There is a constantly increasing amount of evidence that the organisms causing the different clinical forms of leishmaniasis, in different parts of the world, are merely varieties of one or two species. A clinical difference between American leishmaniasis and oriental sore has been the frequency of involvement of the mucous membranes in the American variety. But Castellani and Chalmers observed two cases of oropharyngeal ulceration in Europeans who had lived for some time in India—in one case they found leishmani in scrapings from the ulcers; Christopherson observed a case of naso-oral leishmaniasis originating in Sudan; and La Cava noted a similar condition in Italy.

The earlier cultural and animal inoculation differences have been overcome. Wenyon believes that kala-azar, Indian and infantile, is due to one organism, *Leishmania donovani;* and that probably oriental sore and American leishmaniasis are caused by one organism, *Leishmania tropica.* On this basis, the name, *Leishmania infantum,* given by Nicolle to the organism in infantile kala-azar, becomes a synonym of *Leishmania donovani;* and the names *Leishmania brasiliensis,* given by Vianna to the organism in American leishmaniasis, and *Leishmania nilotica,* given by Brumpt to the organism found by Thomson and Balfour in keloid-like skin nodules in Egypt, become synonyms of *Leishmania tropica.*

The conditions caused by leishmania are most conveniently discussed

under two headings: (1) Visceral Leishmaniasis, and (2) Cutaneous Leishmaniasis, depending on whether the lesions are in the viscera or in the skin.

VISCERAL LEISHMANIASIS

(*Indian Kala-Azar—Infantile Kala-Azar*)

In the Indian kala-azar, which is found in Assam, Madras, Ceylon, China, Indo-China, Dutch East India, Arabia and Sudan, the patients are generally older children and adults. Mackie reported 195 cases from Assam, of which 100 cases were in children from six to ten years old. In the infantile kala-azar, which prevails around the Mediterranean—in Tunis, Algiers, Italy, Greece, Malta, Triest, Portugal and probably the entire Mediterranean region—90 per cent. of the patients are children under four years old.

Clinically, both forms of kala-azar are characterized by an acute or chronic febrile course, with anemia, enlargement of the spleen and later the liver, a tendency to hemorrhages, gangrene and dysenteric symptoms, and tending to end fatally.

The spleen enlarges early, and comes to reach the middle line and down to the crest of the ileum, or larger. At times the liver is enlarged and there is ascites, due, according to Rogers, to a special form of cirrhosis of the liver.

Epidemiology.—In India, there is evidence that kala-azar is a house disease, and a number of persons in a house may have the disease. In the same way, it appears that sleeping in a house where there is a case of kala-azar frequently leads to infection. On the other hand, there are instances where a person with the disease has associated with other persons for a long time without any one contracting the disease from him. Neither does the infection spread in hospitals, where vermin are not present. All of this indicates that the infection is spread by some biting arthropod, and not by contact; and the bedbug is strongly suspected of being the transmitter.

The usual history is that an infected person came into a village, and that the disease spread from the house in which he lived.

The organisms are present in the intestinal ulcerations; and it has been suggested that they are spread in the urine and feces. There is no evidence to support this suggestion; and the fact that 300 yards is sufficient distance to afford protection against infection seems to rule out flies and mosquitoes as the transmitter.

In regions where infantile kala-azar is found, the dogs are infected with leishmania; but the greatest incidence of the disease in the human does not necessarily correspond with the greatest incidence of infection in the dogs. While there are experiments which tend to show that the dog flea and the human flea transmit the infection, all recent work has failed to confirm that view.

Mechanism of the Disease Process.—In the present state of our

knowledge, it is not possible to explain the entire disease process in leishmaniasis. The organism, introduced into the body, probably by a biting arthropod, enters the endothelial cells, and multiplies there by simple fission. The infected cell breaks down and the liberated parasites invade other endothelial cells, polymorphonuclear leukocytes, endothelial leukocytes and sometimes eosinophils. The parasites are especially numerous in the endothelial cells in the spleen and liver, less numerous in the bone-marrow, where they are found mainly in the mononuclear cells. The organisms are found in smaller numbers in various other tissues. Some of the parasites, escaping from the ruptured endothelial cells, are taken up by the polymorphonuclear leukocytes, and appear in the peripheral circulation.

Maggiore considers that the anemia of kala-azar is due to alterations in the tissue of the bone-marrow; that is, the anemia is due to injury to the blood-forming tissue, and is not due to destruction of the red cells. It may well be that the leukopenia, due to reduction of the polymorphonuclear leukocytes, is a result of the same action on the bone-marrow, while the increased endothelial leukocyte count is due to the involvement of the endothelial cells in different parts of the body. The ulceration of the intestinal mucosa and the skin is in all probability due to shutting off of the blood supply from plugging of the capillaries by the proliferation and swelling of the endothelial cells. The hemorrhages are probably due to the degeneration of the endothelium of the capillary walls and to the lowered coagulability of the blood. The secondary infections and gangrene are undoubtedly favored by the decrease in the number of the polymorphonuclear leukocytes.

Symptomatology.—Clinical History.—The incubation period is, according to Rogers, from three weeks to several months. Manson saw a case in which the incubation period was apparently not over ten days.

The first symptom is an irregular fever, which usually shows two remissions in the twenty-four hours—the "double quotidian" fever of Rogers. In some cases there is a low grade continuous fever. After three to six weeks of this irregular fever, there are periods of freedom from fever; but the condition progresses, and later there is a continuous fever to the end.

Gastro-intestinal symptoms appear early; nausea and vomiting are not common; but the bowels are irregular, with a tendency to diarrhea.

The spleen enlarges, and comes to fill the abdomen, so the outline of it can be seen through the abdominal wall. The liver does not enlarge so early or so much; the spleen and liver may be painful and tender.

The skin becomes dry and furfuraceous, and becomes dark or earthy in color. The hair is brittle and falls out. A papular eruption frequently appears on the forearms, lower part of the body and legs. The eruption may itch at times; there may be areas of edema in the skin; and there may be small ulcers in the papules, or there may be large ulcers, especially on the foot or leg.

Hemorrhages are common in kala-azar. Hemorrhages in the skin

may appear as purpuric spots, especially on the face and body; or there may be extensive ecchymoses, especially where there is pressure. There may be nose-bleed, and hemorrhage from the gums or any part of the gastro-intestinal tract. There may be hemorrhage on the serous surfaces, as peritoneum, pleura and the meninges.

The early gastro-intestinal disturbances continue; and from being a simple diarrhea, the stools come to consist of blood and mucus, and a dysenteric attack may end the process.

Gangrene is common, especially about the mouth, and Christophers saw gangrene of the vulva and of the colon.

As the disease progresses, the patient becomes emaciated, until he is a skeleton, the abdomen being protuberant as a result of the enlarged spleen.

The patient gradually becomes more and more emaciated, there is great weakness, and exhausting diarrheal attacks. The course of the disease may be rapid, and the patient die in three or four months, or the disease may be more chronic, and the patient live for one or two years. It is common for some intercurrent affection, as pneumonia and septic conditions, or the dysenteric attacks, to bring the case to a close.

Laboratory Findings.—The blood shows an anemia, the red cells being as low as two million, and the hemoglobin being reduced in proportion. There is marked leukopenia, the reduction being at the expense of the polymorphonuclear leukocytes; and there is a relative, and at times an absolute, increase in the number of endothelial leukocytes and lymphocytes. There is a decreased coagulability of the blood, and Archibald found a decrease in the alkalinity of the blood in cases of kala-azar in Sudan.

Diagnosis.—Clinical Diagnosis.—The principal reason for considering the clinical diagnosis is to point out the necessity for a laboratory diagnosis.

The disease is frequently confused with malaria, the only points being the double daily rise in the temperature, and the absence of constitutional symptoms in keeping with the fever, in kala-azar. Later in the disease, the dysenteric attacks have to be differentiated from amebic and bacillary dysentery. The infantile form has to be differentiated from leukemia and various anemias.

Laboratory Diagnosis.—The blood in kala-azar shows a decrease in the number of red cells, down to two million, with a corresponding decrease in the hemoglobin percentage. There is a leukopenia; the total leukocyte count being below 3,000, often down to 1,000, or even down to 625 per cubic millimeter. This leukopenia is due to a decrease in the polymorphonuclear leukocytes, which are as low as 20 per cent., or even down to 5 per cent., of the total leukocytes. There is a relative increase in the mononuclears; and often an absolute increase, especially in the endothelial leukocytes.

The diagnosis is definitely made only by finding the parasite. Examination of the peripheral blood should be made first, as the parasites

can usually be found there on careful search. Patton examined the peripheral blood of 84 kala-azar patients, many of them in the early stage of the disease. He found leishmania in 42 of the cases on the first examination, and found the organisms in the blood of more cases on repeated examination, until, on the twentieth examination, he found the organisms in the blood of the 84th case. The organisms are found in the polymorphonuclear leukocytes and also in the endothelial leukocytes. Examination of the peripheral blood will also rule out leukemia.

The superficial lymph glands are frequently enlarged, and leishmania may be found by puncture of one of these enlarged glands.

The organisms can be found in the juice obtained by splenic puncture; but splenic puncture is contra-indicated when there is ascites, marked anemia, jaundice, strong tendency to hemorrhage, or severe complication as pneumonia. When puncture is to be done on such cases, Rogers gives 20 grains (1.3 grams) of calcium lactate on the evening before, and repeats it shortly before the puncture. The needle should be as small as can be used; a pad is bound over the splenic area after the operation, and the patient is kept in bed for twenty-four hours.

The organisms are found in the liver and bone-marrow. The bone-marrow may be punctured by drilling into the head of the tibia. Liver puncture is not as good as spleen puncture for diagnosis.

Leishmania are found in the papules and ulcerations of the skin, in blisters produced by the application of a vesicant to the skin, and in the feces, free or in shreds of mucus.

Blood-culture on Nicolle's modification of the Novy-MacNeal medium is frequently positive.

Complement-fixation has been tried, but has not given practical results.

Complications.—Secondary septic infections are common; especially cancrum oris, pneumonia and pleurisy. Apparently part of the diarrhea and dysentery is due to secondary infection of the ulcers in the intestine. Cystitis is not uncommon. As might be expected, tuberculosis is not an infrequent complication.

While the decrease in the number of polymorphonuclear leukocytes probably accounts for the frequency of secondary infections, which so commonly prove fatal, on the other hand, there are cases where a secondary infection, as cancrum oris, seems to have increased the resistance of the body to such an extent that there is improvement or even cure of the kala-azar.

Treatment.—PROPHYLAXIS.—In India, the best results are obtained by abandoning infected villages, and putting the village on a new site. At times, it may be sufficient to abandon infected houses. The evidence now is that bedbugs are the transmitter, and it is to be remembered that these bugs will live for months in a house without feeding; so it is practically necessary to destroy an infected house.

The results of treatment at Shillong led Knowles to suggest that it may be easier to thoroughly treat all cases than to carry out household removals over long periods of time.

Around the Mediterranean, it seems advisable to direct prophylactic measures toward the dog as the reservoir of the infection. Children especially should not be allowed to associate closely with a dog, and infected and stray dogs should be destroyed.

CURATIVE TREATMENT.—Since the various compounds of **antimony** have come into use in the treatment of leishmaniasis, it appears that the drug is very nearly specific for the disease. **Antimony and potassium tartrate** is commonly used in 1- or 2-per-cent. aqueous solution, injected intravenously. The first dose is 5 c.c. (1.35 fluid drams) of this solution. If the first dose is well borne, 10 c.c. (2.70 fluid drams) of the solution is given every other day.

Di Cristina and Caronia treated cases of infantile kala-azar with a 1 per cent. aqueous solution of **antimony and potassium tartrate intravenously,** with satisfactory results. They began with a dose of 20 mg. (⅓ of a grain), and increased the dose to 100 mg. (1.54 grains), giving the injections every other day. They used a total amount of 250 to 840 mg. (4 to 13 grains) to cure a case.

Knowles advises a 1-per-cent. solution of antimony and potassium tartrate in physiological salt solution for intravenous injection. The course of treatment consists of about 18 to 20 injections, beginning with 4 c.c. and increasing the dose to 12 c.c., with a two-day interval between injections. This gives a course of 2 grams of antimony and potassium tartrate, distributed over about two months, as the average course of treatment. The drug is cumulative, so it is not to be pushed toward the end of the course. The heart must be watched, and edema from weakness of the heart, as well as albuminuria, are indications to proceed carefully.

Rogers prefers **sodium antimony tartrate** to potassium antimony tartrate in the treatment of kala-azar, for the reason that the sodium salt is less irritating if any of the solution escapes into the tissues about the vein. The sodium salt is used in the same way as the potassium salt.

Rogers refers to three deaths that have followed the intravenous injection of potassium and antimony tartrate; and he calls attention to the fact that at times the solutions are cloudy, and there is a heavy precipitate in the flasks. The solution must not be used unless it is clear. Almenara says that the solution of potassium and antimony tartrate must be filtered sterile, as it cannot be sterilized by heat.

The injections of the antimony salt are continued for some weeks after the leukocyte count is normal and there is no fever.

Before antimony came into use in the treatment of kala-azar, quinin was the common drug used in treatment. Frías treated a number of cases of infantile kala-azar with **quinin, arsenic and iron**; and some of the cases recovered and remain well after three or four years.

The ulcers on the skin are to be kept clean, as it is very important to prevent secondary infections. Intestinal parasites should be gotten rid of, and the patient's strength should be built up with good food and tonics.

Prognosis.—In untreated cases the prognosis is bad; the mortality being about 95 per cent. With quinin and tonic treatment the mortality is reduced to about 75 per cent. Since the introduction of antimony treatment, the mortality has been reduced to a low figure: during 1917, 20 cases were treated by intravenous injections of antimony and potassium tartrate at the King Edward Institute at Shillong, with 15 recoveries and 5 deaths. The complications are usually fatal; though there may be improvement, or apparent cure, after some secondary infection, as cancrum oris.

Pathology.—Macroscopic.—There is great emaciation, and edema is often present. The enlarged spleen partly fills the abdomen and can be seen through the abdominal wall. There may be ulcerations and gangrene of the skin. There may be ascites. The enlarged spleen is firm, dark red in color, and the capsule may be thickened. The liver is often, but not constantly, enlarged, and the surface is smooth. The marrow in the long bones is red to dark red in color. There are frequently ulcerations in the large and small intestine. Hemorrhages may occur into the skin, any organ, meninges or bone-marrow. When complicated by secondary infection, as noma, there may be infarcts in various organs; and there may be pneumonia and pleurisy as terminal conditions.

Microscopic.—Visentini has described the microscopic changes in the organs in infantile kala-azar; and Christophers has described the microscopic changes in the organs in Indian kala-azar.

In the spleen the trabeculæ are enlarged, and there is an increase in the fibrous tissue throughout the organ. The sinuses are enlarged, and the whole organ is filled with blood, at times in the form of hemorrhagic infiltration. There is at times fatty degeneration in the cells of the reticulum and in the endothelial cells. The endothelial cells are enormously enlarged, and are packed with the parasites, and, as the cells are destroyed, some of the parasites lie free or in masses of cytoplasm.

In the liver there is atrophy, and at times fatty degeneration, of the parenchyma cells, with enlargement of the sinuses. There is a perivascular round-cell infiltration, with increase of fibrous tissue. Rogers has described a diffuse, intralobular type of cirrhosis of the liver. The endothelial cells in the blood sinuses are enlarged, and are filled with parasites, the same as the endothelial cells in the spleen. The parasites are not found in the parenchyma cells.

The bone-marrow contains the parasites, often in great numbers, in the large mononuclear cells.

Scordo found fatty degeneration in the kidneys and adrenals.

In the large and small intestine there is infiltration of the mucosa, followed by necrosis of the epithelium, this ulceration extending as deep as the muscular coat. Parasites are found in the tissues about the ulcers.

The parasites are found in the lymph glands, lung endothelium, capillaries in the testicles, where they may be numerous, in the capillary

tufts of the glomeruli in the kidneys, and in the papules and ulcerations of the skin. They have been found in the meninges and the brain, especially when there is hemorrhage into those tissues. Christophers made a thorough examination of the muscles, and did not find parasites. Visentini found the parasites in the muscles.

CUTANEOUS LEISHMANIASIS

(*Oriental Sore—American Leishmaniasis*)

Cutaneous leishmaniasis appears in somewhat different forms in different parts of the world, and there has been great confusion with the various ulcerative conditions of the skin. But with the findings of leishmania in the lesions, a great part of the confusion has been corrected. The lesions may ulcerate or not, and the South American form tends to involve the mucous membrane more than does the oriental sore.

Epidemiology.—In the tropics, cutaneous leishmaniasis generally is most common in the cool season; and in the subtropical regions, it is most common in the late summer and fall. In some regions, as Bagdad, it is not possible to remain for even a few days without contracting the infection.

It is generally agreed that oriental sore is transmitted by some biting arthropod, as house-flies, mosquitoes or phlebotomus; but in no case has such transmission been proved. The fact that oriental sore can be transmitted by direct inoculation, that it is so constantly associated with some biting arthropod, and that it usually occurs on an uncovered part of the body, is strong circumstantial evidence that some biting arthropod is the transmitter. There is some indication that the infection may be transmitted by bathing in contaminated water, as well as through contaminated clothing.

The South American cutaneous leishmaniasis is constantly associated with the bite of some bug or fly, and tabanidæ are generally incriminated. The usual history is that the lesion followed a fly bite, received while in the forest. There is no proof that flies transmit the infection, and it is to be remembered that the first appearance of the lesion resembles a fly bite and frequently itches intensely: the supposed fly bite may be the beginning of the lesion resulting from inoculation some weeks before.

The lesions are auto-inoculable. The multiplicity of the lesions may be due to multiple primary inoculations, or to auto-inoculation from scratching a single primary inoculation.

The suggestions that the dog or a lizard may be the reservoir for the virus, and that the infection may be transmitted from the reservoir to man by some biting arthropod, as phlebotomus, have no experimental evidence in their favor.

Mechanism of the Disease Process.—Unna considers that the parasites enter the hair follicles, and from there penetrate the surrounding

corium. It can well be that the parasite is inoculated directly into the corium by the biting arthropod, and that the process starts from there. The organism is a parasite of the endothelial cells, and is found in enormous numbers in these large cells in the affected area. The endothelial cells of the capillaries are swollen and proliferated, and may cause blocking of the vessels. This blocking of the capillaries, together with the abundance of endothelial leukocytes, plasma cells, and the smaller number of polymorphonuclear leukocytes collected at the site of the lesion, cause destruction of the tissue with the resulting ulcer formation. There is some evidence that the enlargement of the lymph glands is due to presence of parasites, and that fever corresponds to parasites in the blood.

The tendency of the lesion is to recovery—by what mechanism is not clear—and the ulcer heals, leaving a thin, soft scar, that is often brownish in color and may shrink considerably, causing disfigurement if on the face. There is immunity of some duration, possibly for life, following recovery.

The mucous membrane involvement may be by direct extension from a lesion on the neighboring skin, or may result from infection from a sore on some distant part of the body, either by auto-inoculation or through the blood. The mucous membrane involvement may not appear for months after the primary sore on the skin has healed. Caution is necessary in interpreting the relation of the mucous membrane involvement and the skin lesion, on account of the danger of confusion of other lesions, especially blastomycosis, with cutaneous leishmaniasis.

Symptomatology.—Clinical History.—The incubation period varies from two weeks to three or more months; the average being about two months. The patient frequently connects the lesion with the bite of some arthropod, often a fly; and, especially in South America, the bite is frequently received in the forest.

The lesion is almost always on an uncovered part of the body, as the foot and leg, hand, arm or face. At first there is a small red fleck, like a mosquito bite; and this soon develops a papule in the center, and may itch intensely. This papule enlarges gradually, without there being any inflammatory reaction around it. The epidermis becomes smooth and covered with thin scales from the hyperkeratosis; after some weeks it breaks and a serous secretion escapes and dries to form a hard crust on the surface. This crust may heap up, and appear like a syphilitic rupia. If the crust is removed, the chronic ulcer, with a yellowish secretion, remains. There may be only one ulcer; but more commonly there are several—up to twenty—partly from multiple primary inoculations, and partly from repeated auto-inoculation from the primary sore. The ulcer continues for a number of months to a year, and then heals by the formation of healthy granulations in the floor.

At times the nodule does not ulcerate, but appears as a nodule in the cutis, as large as a pea, not adherent to the underlying tissues. The nodule gradually disappears, with or without any desquamation

the surface where the nodule was located. The keloid-like nodules appear as cystadenomata of the skin, and do not ulcerate.

At other times, the ulcer appears as any ordinary chronic ulcer.

At times the lymph glands, especially in the region of the ulcers, are enlarged; but it is not possible to determine how much this may be due to secondary bacterial infection.

In South America there is a frequent involvement of the naso-oral mucous membrane, either by direct extension of a lesion on the neighboring skin, from auto-inoculation from an ulcer on some other part of the body, or through the blood stream. The lesions of the mucous membrane sometimes do not appear until as much as eighteen months after the ulcer on the skin is healed. The patient's voice is changed, and is finally lost as the involvement of the pharynx and larynx progresses. These naso-oral lesions are very chronic, often lasting a number of years, and are usually fatal.

During the progress of the condition, it is not uncommon for the patient to have attacks of fever, malaise and headache; but it is not possible to say how much of this may be due to secondary bacterial infection. Mild fever and malaise is not uncommon during the incubation period, and before the appearance of a new boil.

The duration of the various forms of leishmaniasis of the skin is usually a number of months to a year; and it is sometimes known as "year's boil."

Diagnosis.—CLINICAL DIAGNOSIS.—There has been a great amount of confusion of the various chronic ulcerations of the skin; and it is difficult to say whether some of the older cases are cutaneous leishmaniasis, yaws, syphilis, tuberculosis, blastomycosis or some of the milder skin affections. It is very important to differentiate cutaneous leishmaniasis from blastomycosis, especially as both conditions are apt to involve the mucous membranes of the nose and mouth. With the finding of the specific parasite in the lesions, the diagnosis becomes possible; and it is not possible to make a diagnosis in any other way.

LABORATORY DIAGNOSIS.—Remove the crust, and make smears from scrapings from the floor and edges of the ulcer, and stain with one of the Romanowsky stains. The parasites may not be numerous, especially in the mucous membrane lesions.

The blood may show an increase in the number of endothelial leukocytes. At times, when there is secondary infection of the ulcer, there may be a leukocytosis.

At times it is possible to obtain a culture of the parasites from scrapings from the ulcer, when inoculated onto Nicolle's modification of the Novy-MacNeal medium. Very rarely it may be possible to obtain a culture of the parasite from the peripheral blood.

Treatment.—PROPHYLAXIS.—The belief that the infection is transmitted by the bite of a fly indicates that one should protect himself against such bites; and, in South America at least, this would seem to be important when going into the forest. As it has been shown that infection can take place through inoculation of the infectious material

onto a scarified area of the skin, or through a bleb on the skin, it is important to protect such abrasions from flies. The **lesions** should early be **protected with a dressing**, as the infection is inoculable and autoinoculable.

CURATIVE TREATMENT.—It was in the treatment of cutaneous leishmaniasis in South America that the excellent results of antimony were first shown; and the use of the drug in other forms of leishmaniasis has given equally good results.

Machado and Vianna, in 1913, treated cases of cutaneous leishmaniasis with **intravenous injections** of a 1 per cent. solution of **potassium and antimony tartrate**, and obtained excellent results. Since that time, the antimony treatment has practically supplanted all other methods of treatment in all forms of leishmaniasis. The method of treatment is the same as given under kala-azar. The results have not been so satisfactory in the treatment of the lesions of the mucous membranes.

Some authorities apply a solution of **potassium and antimony tartrate** to the ulcer, in addition to the intravenous injection of the solution. A 1- to 2-per-cent. solution may be applied at intervals of one to three days; and a saturated solution is applied every four to eight days. The ulcer receives mild antiseptic dressings in the intervals. This treatment causes a slough to form, and healthy granulations then appear in the floor of the ulcer.

Mitchell treated a number of cases by **freezing with carbon dioxid snow.**

Prognosis.—The prognosis in uncomplicated cutaneous leishmaniasis is good. There may be secondary infection with bacteria, which may lead to a fatal termination. Erysipelas may result from secondary infection of the ulcers. The mucous membrane involvement is more serious, and, until the introduction of antimony in treatment, was almost uniformly fatal.

Pathology.—MACROSCOPIC.—The developed ulcer is circular or oval, an inch or more in diameter, with a raised skin margin; and covered with a thick hard crust, brownish-yellow in color, and raised above the surface. On lifting the crust, the ulcer is seen to have a steep, jagged margin, with the floor covered with pale, unhealthy granulations. There is little induration around the margin of the ulcer.

Thomson and Balfour describe the non-ulcerating, keloid-like lesions as resembling the mountains on a relief map, looked at from above. There is a parent lesion, and connected secondary growths. The lesions are pink in color, smooth and shiny, with no scaling or evidences of breaking down. They are firm, but soft, and not adherent to the deeper tissue. On puncture, they yield blood and serum or a small amount of cheesy, sebaceous-like material. The largest lesion was 35 by 15 mm.

In the involvement of the mucous membranes, the earlier appearance is that of granulations, and later there are vegetations and extensive ulceration.

MICROSCOPIC.—The characteristic of the process is the formation

of areas of cellular infiltration in the cutis, with marked change in the overlying epidermis.

Jeanselme and Rist describe marked thickening of the rete malpighii, with incomplete keratinization of the corneal layer of the epidermis; while Unna and Wright describe thinning of the overlying epidermis. It is probable that the thinning is merely a later stage of the change in the epidermis, especially as Unna describes thickening and hypertrophy of the rete malpighii and hyperkeratosis with the formation of epithelial pearls around the margin of the ulcer. There is edema of the rete malpighii, with vacuolation of the cells. There is some cellular infiltration in the rete malpighii. When the epidermis is thinned, the hair follicles are atrophied, and are transformed into horny masses.

The crust is composed of cornified epithelium mixed with fibrin, red blood-cells and leukocytes in all stages of degeneration, and cellular débris.

In the keloid-like lesions, the change in the epidermis is marked, and there is no evidence of breaking down of the epidermis. There are down-growths of columns of cells from the rete malpighii, with the formation of cell nests and epithelial whorls.

The infiltrated areas in the cutis consist of edematous masses of lymphocytes, plasma cells, endothelial leukocytes, a few giant cells, red blood-cells and fibrin, and polymorphonuclear leukocytes. The endothelial cells of the blood-vessels are swollen and proliferated, sometimes occluding the vessel. In the center of the area, the tissue breaks down to a necrotic mass. Around the margin of the infiltrated area, the cells are less numerous, being mainly lymphocytes and plasma cells, this infiltration extending especially about the blood- and lymph-vessels. In the periphery there is multiplication of the fixed tissue cells. When the epidermis breaks down over the areas of necrosis, the ulcer results.

The parasites are generally found in the endothelial cells; but they are also found in the polymorphonuclear cells. Not infrequently parasites are found free, probably from the breaking down of endothelial cells. Flagellated parasites have been reported from ulcers. Vianna found the parasites in plain muscle-fibers in the wall of a blood-vessel in the tissue near an ulcer on the nose of a dog.

In the lesions on the mucous membranes, the picture is that of granulation tissue, with a rather small number of endothelial leukocytes, but with an abundance of lymphocytes and plasma cells, and some giant cells. The parasites are not abundant in these lesions.

There is nothing characteristic in the microscopic appearance of the enlarged lymph glands. Parasites are found, usually in clumps, at times in polymorphonuclear cells: there is no infiltration with endothelial cells.

In the blood there may be an increase in the number of endothelial leukocytes. The parasites have been found in the peripheral blood; but this is generally considered to be an accidental escape of the parasites into the blood from the local lesion, rather than an indication that the ulcer is a local manifestation of a general disease. By some authori-

ties it is held that the mucous membrane involvement may be through the blood from a skin lesion, as the mucous membrane lesion may appear months after the skin ulcer has healed.

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CHAPTER XXIX

RELAPSING FEVER

By Eugene R. Whitmore, B.S., M.D.

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Synonyms.—Febris recurrens, Tick fever, Famine fever.

Definition.—The term "relapsing fever" is applied to a group of specific fevers which closely resemble each other clinically, caused by blood spirochetes, and characterized clinically by one to four or more paroxysms of fever, each lasting five to six days, with an afebrile interval of about six days.

Etiology.—Predisposing Causes.—Relapsing fever occurs epidemically, endemically and sporadically. It prevails especially under conditions of filth and overcrowding, and during times of privation and famine. In India, it is common in jails and police hospitals; while Rabinowitsch, who studied relapsing fever in Russia, finds that typhus fever is more commonly favored by conditions such as exist in asylums.

Season.—It is generally found that relapsing fever prevails more in winter; probably as a result of greater crowding, privation and insanitary conditions at that season of the year. Rabinowitsch studied an epidemic in Russia in 1906. The epidemic began in January, 1906, and gradually increased to December of that year: the number of cases fell in January, 1907, rose again in March and had decreased slightly by May, 1907. Robledo says the disease in Colombia is most frequent in March and April; and that it is not rare in October and November.

Age and Sex.—Rabinowitsch found that relapsing fever was more common among persons from 15 to 30 years of age; and that it was over three times as common among men as among women. However, he is of the opinion that this prevalence among young men is due to the fact that these are the persons who would be crowded together, under un-

hygienic conditions, as laborers; and that there is no difference in age or sex susceptibility.

EXCITING CAUSE: THE ORGANISM.—Relapsing fever is caused by organisms which are commonly classed as protozoa and placed in the flagellata; or they are classed as transition forms between the bacteria and the flagellata of the protozoa; or they are classed with the bacteria. Whether the spirochetes causing relapsing fever in different parts of the world are different species or are varieties of one species is difficult to say. For the present, the different morphological and biological differences make it advisable to consider them as different species. It is useless to discuss genera in the spirochetes until there is agreement as to whether they belong to the bacteria, to the protozoa, or are separate groups.

Morphology.—The spirochetes of relapsing fever are 8 to 40 μ, usually 17 to 30 μ, long, and 0.3 to 0.5 μ in diameter, the Central African relapsing fever spirochete being generally considered as larger than the others. In stained preparations it is not possible to make out any structure, though there are irregularities of staining in the interior that are considered by some observers to represent granules of chromatin. There is no evidence of an undulating membrane. The ends are pointed, and a flagellum on one end is described by most observers. The flagella described along the sides of the organism are considered to be artefacts. There are 3 to 6, or even 10, curves in the body.

In the living preparation, the spirochetes are seen to have three kinds of motion: (1) a corkscrew-like motion, (2) a wave-like forward and backward movement, and (3) lateral bending and looping movements. The movement of the spirochetes is most active at the height of the fever attack.

Resistance to Physical and Chemical Conditions.—The spirochetes remain alive for a day or more under the cover glass when sealed, and they remain alive for weeks in the ice-box. Novy and Knapp kept them alive for 40 days in blood drawn in the beginning of the attack of fever, and they lived 30 days on blood agar without multiplying. They remain alive for some days in the blood of leeches.

They are killed in the blood in half an hour at 45° to 48° C. They are quickly killed by chemical agents.

Development.—(*a*) *In the Vertebrate Host.*—The spirochetes appear in the peripheral blood in large numbers during the attack of fever. Whether multiplication is by longitudinal or transverse division is disputed. Shortly before the crisis the spirochetes roll up, and part of them are taken up by the endothelial cells of the spleen, liver and bone marrow. Others assume a cyst-like form, and are seen to break up into fine granules. By some authorities, it is considered that this cyst-like form is a resistant stage; and that the granules are the forms which develop the new generation for the relapse, and can also pass through a bacterial filter. Todd and Wolbach showed that *Spirochæta duttoni*, in the blood-serum of a rat, would pass through a Berkefeld filter that took out *Bacillus prodigiosus* and *Staphylococcus aureus*, at

over 50 pounds pressure; but not at atmospheric pressure. However, Todd doubts whether spirochetes are filterable in the usual sense of the term.

Spirochetes are found in the peripheral blood at each relapse, but not during the interval between relapses.

(*b*) *In the Arthropod Host.*—I. Ticks: The development of *Spirochæta duttoni* in the tick, *Ornithodorus moubata*, was studied by Dutton and Todd, and by R. Koch. Dutton and Todd found motile spirochetes in the stomach and malpighian tubes of infected ticks for five weeks after feeding; and they found that ticks, hatched from eggs laid by infected ticks, could transmit the infection to monkeys. Koch found that, four days after feeding, the spirochetes had disappeared from the stomach of the tick, and had collected in the ovaries; and that the spirochetes enter the eggs and multiply there, being visible up to the twentieth day of development of the embryo. Koch did not find spirochetes in the embryos after twenty days; but they are present, as the young ticks transmitted the infection to monkeys.

While the infection of the ovaries accounts for the transmission of the infection to the next generation of ticks, the adult tick itself is also infectious after feeding on infected blood. The form in which the spirochetes exist in the body of the tick has been a subject of discussion.

Leishman studied the development of the spirochete in the tick, and only occasionally could he find the spirochetes in the eggs. He found that the spirochetes were not present longer than ten days in the stomach of the tick; but that they broke up into small coccus-like or ovoid granules of chromatin. These granules pass to the malpighian tubes and to the ovaries, entering the unripe egg and infecting the embryo that develops in that egg. These bodies in the malpighian tubes and in the coxal glands are deposited on the skin when the tick bites.

A number of workers have studied the granules in the various organs of ticks; and some have found granules in the organs of ticks which had not been infected. Wittrock found granules in the tissues of unfed offspring of uninfected ticks. Most workers are of the opinion that the granules found in ticks are not a phase in the life-cycle of spirochetes; but Leishman has recently reaffirmed his belief that these granules are such a phase.

Marchoux and Couvey state that the spirochetes do not disappear from ticks, but that they are fine and are difficult to see. They consider that infection takes place through inoculation of spirochetes as such. Kleine and Eckard found spirochetes in the ovaries, coxal glands, malpighian tubes, cephalic glands, stomach and salivary glands of ticks; and they found spirochetes in the eggs laid by infected ticks. They found comma-shaped bodies in ticks, but infection was not produced by injecting these bodies; and they conclude that spirochetes as such are necessary for the tick to transmit the infection.

Regardless of the form in which the spirochetes exist in the body of the tick, it seems definitely agreed that infection is from contamination with the secretion of the coxal glands and feces of the tick when it

is biting. If there is a period during which the tick is not infectious, it is only the time necessary for the infectious form of the spirochete to reach the feces and coxal glands in sufficient number to produce infection. Wittrock found that emulsions of the organs of ticks were infectious at all times from one hour to ninety-six days after feeding on infected blood; and concludes that there is no cycle of development in the tick. The ticks remain infectious for eighteen months; and there is evidence that the infection may be transmitted hereditarily as far as the third generation of ticks.

II. Lice: Nicolle and Blanc have studied the development of *Spirochæta berbera* in the clothes louse. They find that the spirochetes disappear rapidly from the body of the insect, and no spirochetes are visible. The louse is not infectious until about the fifth or sixth day; but still no spirochetes are visible. On the seventh to tenth days, slender spirochetes appear in the body cavity of the louse, and the louse is still infectious. After the tenth day, the spirochetes are adult, and the louse is not infectious. No spirochetes are found after the nineteenth day. The spirochetes are in the body cavity of the louse, and infection takes place through crushing the louse on the skin. In the course of their experiments, a man was bitten 15,500 times by infected lice without becoming infected; then an infected louse was crushed and placed on his conjunctiva, and he developed relapsing fever. They got evidence of hereditary transmission only occasionally.

Rabinowitsch failed to transmit the infection with clothes lice in Russia; and Robledo failed to transmit the infection with head lice in Colombia.

III. Bedbugs: Nothing is known of the development of spirochetes in the bedbug. Tictin and Rabinowitsch found that the spirochetes remained alive in the intestine of the bugs for 5 to 7 days after feeding on infected blood; but they did not find any further development in the bug. Tictin transmitted the infection to monkeys by crushing bugs as soon as they had gorged on infected blood, and injecting the blood from the intestine of the bugs into monkeys. But when he waited 48 hours after the bug had fed on infected blood, he was not able to transmit the infection to monkeys by injection of the intestinal contents of the bugs; though he found living spirochetes in the intestine of bugs as long as 77 hours after feeding on infected blood.

Rabinowitsch is of the opinion that Tictin's experiments do not indicate that the spirochetes undergo any development in the bedbug, as the immediate injection of blood from the intestine of the bug amounted to the same thing as injecting the blood direct from the infected person. He does not accept Tictin's explanation of his failure to transmit the infection with bugs 48 hours after feeding as due to the small number (6) of bugs used. Rabinowitsch tried to transmit the infection to himself by allowing bugs to bite him immediately after, and five days after feeding on infected blood; the bugs failed to transmit the infection.

Cultivation.—Noguchi cultivated *Spirochæta duttoni, Spirochæta kochi, Spirochæta obermeieri,* and *Spirochæta novyi* on his spirochete

medium. Hata used a simplified medium in the cultivation of *Spirochæta obermeieri*. Some observers have described branching forms in cultures of the spirochetes, and have held this as an indication of the vegetable nature of the spirochetes.

Transmission to Lower Animals.—Spirochæta obermeieri can be transmitted to monkeys very readily; and it can be transmitted to rats, mice and guinea pigs by intraperitoneal injection. Rats, mice and guinea pigs usually have a mild infection.

Spirochæta duttoni is readily transmitted to monkeys, either by injection of blood or by the bite of infectious ticks. Rats, mice, rabbits and guinea pigs are readily infected by *Spirochæta duttoni*. The dog, pony, sheep and goat develop light infection.

Spirochæta berbera is readily transmitted to monkeys by the injection of blood; or by injecting crushed infectious lice. The infection is not transmitted to monkeys by the bite of infectious lice. Rats, mice, guinea pigs and rabbits are susceptible to infection with *Spirochæta berbera*.

Spirochæta novyi and *Spirochæta carteri* are both readily transmitted to monkeys, rats and mice.

Relation of the Spirochetes in Relapsing Fever in Different Regions.—While there are minor differences in the morphology and animal susceptibility of the different relapsing fever spirochetes, it is not possible to separate them into species on those differences; and it is not possible to separate them by cross immunization. But they can be separated by their reactions with sera which are specific against the different spirochetes. Thus, a highly immune serum, prepared by injecting a rabbit with *Spirochæta obermeieri*, will agglutinate and destroy *Spirochæta obermeieri;* but it has no effect on any of the other relapsing fever spirochetes.

Epidemiology.—It is generally agreed that the spirochetes of relapsing fever are transmitted by biting arthropods in different countries; but it does not appear that the spirochetes are specifically adapted to any particular arthropod in a given locality. Nuttall points out that a number of arthropods can carry the same spirochete, and that the same arthropod may carry a number of different spirochetes.

The bedbug (Fig. 1) has long been considered as the transmitter of *Spirochæta obermeieri;* but Tictin's work is the only experimental evidence in favor of such transmission. The clothes louse has also been suspected; but there is no experimental evidence that the infection is transmitted by this arthropod. Authorities have reported outbreaks of relapsing fever accompanying outbreaks of typhus, and considered that both were transmitted by lice. Hagler saw relapsing fever and typhus together in Serbia. Typhus stopped when lice disappeared; but relapsing fever continued until the wards were fumigated to get rid of bedbugs. Kuelz saw relapsing fever in Serbia, and found it impossible to prevent the disease by eradicating lice.

In Central African relapsing fever, the tick has long been considered as the transmitter of this condition; and all experimental work confirms

that opinion. The infection follows caravan routes; and the rest houses along the routes seem to be great sources of infection. Koch noted that the infection remained attached to a house for years; and he suggested that, in the absence of the human, the ticks bite the rats and mice, and so keep up the infection in the house. It is a little difficult to know how such an abandoned house is infected with rats and mice, unless the human frequents it enough so that there will be food for rats

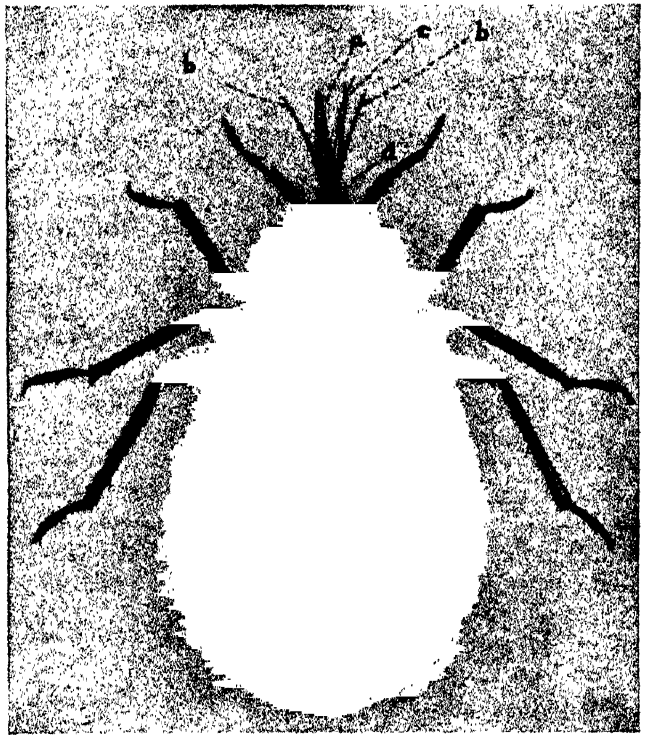


FIG. 1.—CIMEX LECTULARIUS (Female). (× 13.)

The mouth parts are turned forward, and the cutting parts are drawn out of the groove in the dorsal surface of the labium (a). The double-grooved mandibles (b) are drawn widely apart; the maxillæ, with their serrated tips, lie close together (c). The distal segment of the labrum (d) is visible.

and mice; in that case it may well be man himself that keeps up the infection in such abandoned houses.

Spirochæta berbera is transmitted by the clothes louse (Fig. 2).

It is generally considered that *Spirochæta carteri* is transmitted by clothes lice. In Persia, miana fever, which is relapsing fever, is transmitted by a tick, *Argas persicus* or *Ornithodorus savignyi*. In addition to his experience in Serbia, Kuelz saw considerable relapsing fever in Macedonia and Persia; and he is of the opinion that some other arthropod than lice transmits the infection, and he suggests fleas as the transmitter.

Mouzels, in Tonkin, found spirochetes in the stomach of mosquitoes in houses where there were cases of relapsing fever, while lice and bugs were often absent. Mouzels thinks any blood-sucking arthropod may transmit the infection.

It is not known how *Spirochæta novyi* is transmitted. Robledo is of the opinion that it is transmitted by *Argas persicus (americanus)* in Colombia; while Franco and his co-workers are of the opinion that it is transmitted by *Ornithodorus turicata* or possibly by *Argas reflexus.*

The spirochetes can pass through the unbroken skin or mucous membrane. It is generally agreed that the infection is not transmitted by biting; but that the organisms are deposited on the skin, in the feces or



FIG. 2.—PEDICULUS HUMANUS CORPORIS.
A, male; B, female. (× 35.)

in the gland secretions of the arthropod, and are rubbed into the bite wound or pass directly through the unbroken skin. In the case of louse transmission, it seems that the important way of infection is from the crushing of lice on the skin.

Infected blood, as from the menstrual flow, or from childbirth, rubbed on the unbroken skin, will transmit the infection. The possibility of infection through sexual intercourse should be borne in mind.

Spirochetes are found in the blood from hemorrhages, as from nosebleed; in the bloody stools; in the saliva; and they have been found in the sweat and in the tears, when they are numerous in the blood. Since the spirochetes are present in the saliva, it does not appear that their presence in the sputum of cases of complicating pneumonia is of special significance.

Rabinowitsch is of the opinion that bedbugs are not the only means of

transmission of the relapsing fever spirochete in Russia. He failed to transmit the infection by the bite of bedbugs and lice; and he says that bedbugs were so numerous in some places that no one could have escaped the infection if it was transmitted by the bugs. He also points out that physicians and nurses are rarely infected, though they frequently get bugs on their clothing. From these considerations, together with the fact that the spirochetes are found in the secretions and discharges, Rabinowitsch is of the opinion that infection may take place by way of the mouth in persons who live in the insanitary conditions under which relapsing fever is found.

Darling is of the opinion that persons in the Panama Canal zone contract relapsing fever by visiting native villages.

Mechanism of the Disease Process.—The parasite, entering through the unbroken skin or mucous membrane, or rubbed into the wound produced by the bite of the arthropod, undergoes some unknown form of multiplication. After a few days an attack of fever sets in. The spirochetes do not appear in the blood for some hours, or even until the second or third day after the onset of the fever. The fever is considered to be due to a toxin produced by the spirochetes. After a few days' fever, the parasites disappear from the blood; and some hours later the temperature falls to normal. Just before the attack of fever stops, the blood contains antibodies which kill and dissolve the spirochetes.

After the temperature becomes normal, no spirochetes can be found in the blood; but the blood is still infectious for another animal, and it remains infectious after being passed through a Berkefeld filter. There is discussion as to the form in which the spirochetes exist in the peripheral blood during the interval after the attack of fever. It is generally held that the spirochetes exist at this time in the "infective granule" form of Balfour, as described in the development of the spirochete in the human host. Numerous workers have found the spirochetes in the endothelial cells in the spleen and in the bone marrow; and Darling found them in the endothelial cells in the liver. This finding of spirochetes in the endothelial cells has led to discussion as to whether it is a part of the mechanism of recovery in relapsing fever; and there are numerous authorities on both sides of the question. Darling considered that the spirochetes in the endothelial cells in the liver were an indication that this was a mechanism of defense; though he noted that emulsion of a liver that contained only a trace of blood was more infectious than was heart's blood. Rabinowitsch found spirochetes free or in the cells, and is of the opinion that phagocytosis plays no part in relapsing fever; he also holds that it is a strong argument against Metchnikoff's phagocytic theory.

After a few days, in which there are no symptoms, whatever form of the organism exists in the body develops into spirochetes which are resistant to the antibodies which have been elaborated against the original strain, and multiply to produce another attack of fever. The same process is repeated, until finally the antibodies overcome the spirochetes, and the disease process is at an end.

It has been suggested that the spirochetes continue to live in the body of man for some time, as a labile infection; but there is no evidence that this happens. It is interesting that the spirochete, at each relapse, has different biological reactions than it had at the previous or the subsequent relapse, and these reactions remain fixed on transmission to other animals; but they are lost when the organism is passed through an arthropod host.

A small number of cases have no relapse. Cassaux reports that one-fourth of his patients had no relapse, and two-thirds of them had only one relapse. In Rabinowitsch's tabulation of 3,464 cases, 29.01 per cent. had no relapse; 64 per cent. had one relapse; 6.29 per cent. had two relapses; 0.59 per cent. had three relapses; 0.17 per cent. had four relapses; and 0.03 per cent. (one case) had five relapses.

Immunity.—There is immunity following an attack of relapsing fever, but the immunity is of short duration, infection being possible within forty days to six months. In Serbia, Walko saw one person have relapsing fever eleven weeks after recovery from an attack. Jarussow reports that, in the Moscow epidemic in 1908, one-third of all the cases had second attacks.

Nicolle and Blaizot report experimental work in which a monkey had relapsing fever, was infected with the same virus in less than six weeks after recovery, and was again infected with the same virus, seventy-four days after recovery from the second attack.

Apparently there is more marked immunity after infection with *Spirochæta duttoni*. Koch was of the opinion that natives in the endemic region had the disease in youth and were immune. This is not borne out, though the attack in youth may cause the succeeding attacks to be milder.

The anemia is due to the destruction of the red cells by the toxin; and this destruction of red cells, with the disturbed function of the liver, leads to the hematogenous jaundice. The leukocytosis is due to the toxin, and is polymorphonuclear: at times it may be mononuclear, but it is suggested that this is due to malaria or amebiasis.

Rabinowitsch considers the cause of the pathologic changes is the spirochetes and their products of metabolism. Thus, he says, the infarcts and hemorrhages in the spleen are due to injury of the endothelium by the toxin. Mühlens is of the opinion that further study along this line is necessary.

Death from the disease itself usually occurs in collapse during or following the crisis; or death may be due to suprarenal deficiency. Death more commonly results from some complication, as rupture of the spleen, pneumonia or myocarditis.

Symptomatology.—Clinical History.—*Period of Incubation.*—There is an incubation period of two to twelve days, usually five to eight days, during which there are no symptoms; or there may be a prodromal stage of a few hours to two or three days, consisting of headache, loss of appetite and lassitude.

Mode of Onset—Symptoms during Progress of Disease.—The attack begins suddenly, with a chill and aching in the head, back and joints.

The temperature rises rapidly to 103° to 104° F. (39.4° to 40° C.); the pulse is rapid—110 to 120; the face is flushed; there is epigastric pain; nausea and vomiting are frequently present.

The temperature remains high for five to six days, often with irregular fluctuations amounting to as much as four degrees. During this time there is nausea and vomiting; the skin is usually dry and hot, but there may be light perspiration, and the skin is yellow tinged. There may be constipation, but diarrhea is frequent in some epidemics. Nosebleed is frequent, also hemorrhages from the gastro-intestinal tract, the gums, into the conjunctiva, and from the ears. Hematuria is rare; there may be hemorrhages into the skin, and metrorrhagia. There is bronchitis, with cough, rapid pulse and respiration, and pains in the joints and muscles. There may be delirium—sometimes abrupt and violent, and rarely stupor. There may be a rose-red, macular eruption on the thorax, abdomen and legs, lasting for a day or two. Herpes is common. The spleen and liver are enlarged and tender; the urine is high colored and contains albumin. There is a rapidly developing anemia; a moderate leukocytosis, the increase being due to increase in the polymorphonuclears, and spirochetes are found in the blood.

About the sixth or seventh day the patient breaks out in a profuse perspiration, the temperature falls to normal in one to two hours, and the patient is apparently normal. The spleen and liver return rapidly toward normal in size, and the patient gains in strength.

Rarely there is recovery after one attack of fever. More commonly, after about six or seven days of freedom from fever, the *relapse* sets in with a chill, as with the first attack of fever, and the entire attack is repeated. At times the relapse is more severe than the first attack of fever, but more commonly the relapse lasts only three or four days, ending by crisis just as the first attack of fever. In about two-thirds of the cases, this relapse ends the course of the disease, and the patient returns to normal. A second relapse is not uncommon; a third and fourth relapse are much less common, and very rarely are there more than four relapses.

At times instead of the rapid rise of the temperature, there may be a gradual onset, with rheumatic-like pains, headache and constipation. The temperature curve may be irregular, or it may show a tertian or quartan intermittency. The temperature may fall by lysis, over six hours to three days. There may be a pseudocrisis on the third or fourth day, the temperature going up again for three to five days. In the crisis the temperature may fall, then rise to or above the original temperature and fall again—all in a few hours. There may be a chill at the crisis.

The spleen may not be markedly enlarged, and Robledo speaks of this in the relapsing fever of Colombia.

Meningeal symptoms may be prominent: severe headache, stiffness of the muscles of the neck and body, hyperesthesia, clouded mental condition and Kernig's sign may be present.

Reinfection during the same epidemic is not uncommon. The second attack is generally marked by shorter attacks of fever and fewer relapses.

Diagnosis.—Differential Diagnosis on Clinical History.—Malaria, dengue, small-pox, influenza and yellow fever have to be differentiated from relapsing fever, and this is very difficult from the clinical picture alone. The early stages of plague may be confused with relapsing fever. Franco and his co-workers draw a parallel between the clinical picture in yellow fever and relapsing fever, and suggest a relationship in the etiological agent in the two diseases. The enlarged spleen speaks against small-pox, influenza, yellow fever and dengue. When the meningeal symptoms predominate there may be confusion. Weil's disease may cause confusion, especially with the bilious form of relapsing fever. Typhus may cause confusion, the stupor and the dark, macular eruption being points in favor of typhus.

Laboratory Findings.—There is a polymorphonuclear leukocytosis in relapsing fever, which speaks against *dengue.*

Agglutinins and spirillicidal substances appear in the serum of the patients late in the course of the disease: these substances may be of assistance in diagnosis late in the course of the disease or during convalescence.

The finding of the spirochetes in the blood is the one definite diagnostic sign. It is to be remembered that the spirochetes are not numerous in the peripheral blood in some forms of relapsing fever, especially in the early days of the Central African form, and that the spirochetes are not found in the blood from a short time before the crisis to the beginning of the relapse.

The blood may be examined direct in a smear between slide and coverglass, with the condenser well lowered; or it may be examined by dark-field illumination. Smears may be made in the usual way, as for examination for malaria, and stained with any of the Romanowsky stains. As the parasites may not be numerous, the thick drop method may be used. The hemoglobin may be washed out and the smear fixed and stained with a Romanowsky stain; or, what is simpler, the thick drop preparation, as soon as dry, is placed in Giemsa's staining solution for half an hour, then removed and carefully rinsed in distilled water—but not flushed with it—and dried in the air. The hemoglobin is washed out of the unfixed smear by the Giemsa solution, and only leukocytes, blood platelets and spirochetes stain in the smear. The blood may be dropped into acetic acid solution to dissolve the red cells, then centrifuged to collect the spirochetes and leukocytes in the sediment.

Even if the spirochetes are not found in the blood, as during the interval, they are present in an infectious form, and the blood will produce infection when injected into a susceptible animal. Monkeys are the most satisfactory, but if monkeys are not available, some of the blood should be injected intraperitoneally into a mouse or rat. Rats and mice are readily infected with *Spirochæta duttoni, Spirochæta berbera* and *Spirochæta novyi,* when injected intraperitoneally with infected blood. Rabinowitsch found that very young rats and mice—a few days old, without hair—were very susceptible to infection with *Spirochæta*

In *Weil's disease,* though the spirochetes are in the peripheral blood in the first six or seven days of the disease, they are rarely found on direct examination, and they are smaller than the spirochetes of relapsing fever. The spirochete of Weil's disease produces characteristic lesions in guinea pigs, on intraperitoneal injection of blood, in the first week of the disease, and later appears in the urine and feces.

Complications.—Complications of the respiratory tract are the most important. Pneumonia is a severe complication. Bronchitis and pleurisy are fairly common. Marked icterus is hardly to be considered as a complication, but it makes for a bad prognosis. Dysentery is fairly common. There may be rupture of the spleen, at times spontaneously, more commonly from trauma, as from getting out of bed during the delirium. Splenic abscess has been reported. The frequent hemorrhages into any of the tissues are hardly to be considered as complications; they are more common in cases with jaundice. There may be cerebral hemorrhage. Angina is fairly common during the attacks of fever. There may be edema from heart failure or from nephritis. Kuelz says that the so-called relapsing fever edema is not peculiar to relapsing fever, but is due to deficient diet—lack of vitamins. Iridocyclitis is fairly common. Pregnant women abort almost without exception.

There is a difference of opinion as to whether the bilious typhoid fever in Egypt is a severe form of relapsing fever, with marked jaundice, or there is an added septic infection, or there are two different diseases. Rabinowitsch thinks that bilious typhoid fever is not relapsing fever. It is probable that some of these cases are Weil's disease, and Rabinowitsch saw two cases of Weil's disease in the epidemic of relapsing fever studied by him.

Clinical Varieties.—The clinical picture of relapsing fever varies a great deal, and in addition to the ordinary form, as just described, Casaux describes ambulatory, typhobilious, typhoid-like and bilious forms. When the liver is seriously affected there is a bilious form.

Treatment.—PROPHYLAXIS.—The conditions under which relapsing fever flourishes—filth and famine—should be corrected, if they exist.

Prophylaxis is aimed directly at removing the spirochetes from man as the source of infection, by curing the cases promptly, and at protecting persons from the bites of bedbugs, lice and ticks. In Africa it is necessary to avoid the native houses; and Darling is of the opinion that relapsing fever in Panama is contracted by visiting the native houses. It is worthy of note that the tick, *Ornithodorus moubata,* will not come into moist earth or where there is moisture. Stitt says the ticks bite only at night, and that a night-light will keep them away. Mosquito nets protect from adult ticks as well as from mosquitoes. As *Ornithodorus moubata* does not travel more than thirty yards away from the house, it is advised to sleep in the open, at least that distance away from the houses. Lice and bedbugs are more difficult to avoid, and the eradication of those insects is discussed in the section on Parasitic Arthropods.

Rabinowitsch advises measures to prevent infection by mouth. It is

to be borne in mind that the infection is in the discharges and secretions, and that it will pass through the unbroken skin and mucous membranes. A number of laboratory infections have resulted in this way.

GENERAL MANAGEMENT.—**Salvarsan** or **neosalvarsan** is a specific in relapsing fever. It is not necessary to give large doses, and there is some evidence that relapsing fever patients do not stand large doses of salvarsan well. Protocalis recommends two doses of 0.2 gram of salvarsan: one dose during the first attack; the second dose four or five days after the temperature has fallen. Even with this treatment, he got relapses in 25 per cent. of his cases. Levaditi found that the best time to give salvarsan was just before the crisis, as it took less of the drug to produce a cure at that time.

Brault and Montpellier found **neosalvarsan injections in oil** unsatisfactory, as the absorption was too slow; rapid absorption is necessary in order to kill the spirochetes. **Antimony preparations** have not given satisfactory results in the treatment of relapsing fever.

Cool sponging may be given for high temperature, and **aspirin** for the pain in the head, back and joints. A **hypodermic injection of morphin** may have to be given. When there are meningeal symptoms and the headache is due to intracranial pressure, **lumbar puncture** will relieve the pain. The cough may require **sedative cough mixtures.**

The vomiting may be allayed by **hot fomentations or counterirritation** over the epigastrium and by **cracked ice.** The thirst is relieved by **acid drinks,** as lemonade and cracked ice or soda water. Constipation or diarrhea may require treatment.

Complications are treated as they arise.

It is necessary to watch the patient, as he may develop delirium and get out of bed, and there is danger of death from heart failure or collapse, or from rupture of the spleen spontaneously or on slight exertion.

At the time of the crisis it is necessary to support the patient with **stimulants,** as **camphorated oil,** and to apply **external heat.**

During the attack, the **diet should be liquid.** *After the attack* is over, it is necessary to **feed the patient well,** as the anemia is marked. **Fresh air and rest** complete the recovery.

Prognosis.—Before the introduction of salvarsan treatment of relapsing fever, the mortality was from 2 to 5 per cent. In China and Indo-China the mortality was often as high as 25 to 40 per cent.; and in the epidemics in India and China in 1912-1913, the mortality was as high as 70 to 80 per cent. Alcoholic liver and weakened heart muscle are apt to be badly affected in relapsing fever. Severe jaundice makes for a bad prognosis, as the mortality is about 40 per cent. in such cases. Of the complications, pneumonia is severe, the mortality being 35 to 40 per cent., or even as high as 70 per cent. As most of the deaths are due to complications, death is not very common in children on account of the rarity of complications. Persons living in the conditions under which relapsing fever thrives are apt to be lowered in general resistance, and this makes for a bad prognosis, as well as for the frequency with which other diseases

are found with relapsing fever. The long course of the disease is one of its worst features.

Pathology.—Rabinowitsch has made an extensive study of the pathology of relapsing fever.

Macroscopic.—The skin is frequently jaundiced, especially in the African relapsing fever, and all the organs may be bile stained. The appearance of the organs will vary with the stage of the disease in which death takes place.

The spleen is enlarged, Rabinowitsch reporting one case in which it weighed 1700 grams. The capsule is tense and thin. On section, the spleen is soft and diffluent, dark red in color, filled with blood, the follicles are enlarged, and infarcts are numerous. The kidneys are enlarged and congested. The liver is enlarged and congested, the capsule is tense, the lobules are indistinct: there may be a layer of fibrin over the surface of the liver. The heart is soft and flabby. There is congestion of the lungs and brain.

Metastatic abscesses may be found in the liver, kidneys, spleen and various parts of the body.

Microscopic.—Early in the attack the vessels in the spleen are intensely congested and there are some hemorrhages in the spleen pulp. The follicles are enlarged, and there is an increase in the lymphocytes throughout the spleen pulp, with macrophages containing red blood cells and lymphocytes.

As the attack progresses the hemorrhages increase and amount to infarcts; at the same time the follicles become less prominent and the lymphocytic infiltration less marked.

At the time of the crisis, or two or three days after it, the hemorrhagic areas show considerable change: the red cells are in all stages of disintegration, there are homogeneous areas of fibrin, the endothelium of the vessels is swollen and lost, the macrophages are filled with cells and cellular débris, and karyorrhexis is marked in the areas of lymphocytes. The spleen rapidly returns to normal in microscopic appearance after this time.

Spirochetes are not found in the spleen in the beginning of the attack, but they are numerous shortly before the crisis, partly free and partly in the endothelial cells.

In the kidneys the epithelium of the tubules is swollen and cloudy, and as the condition progresses the change in the epithelium becomes more marked until the outline of the cells is lost and there is nothing but granular débris. There is not infrequently infiltration of red cells in the interstitial tissue; more rarely an abundance of red cells between the layers of Bowman's capsule.

The liver parenchyma is swollen and cloudy: the blood sinuses are filled, and there is pigment in the endothelial cells as well as in the parenchyma cells. There may be round cell infiltration about the portal vessels. Rabinowitsch considers the increase in interstitial tissue and the fatty change in the parenchyma cells as due to a previous chronic

condition, as alcoholism. Darling found spirochetes in the endothelial cells of the liver.

The heart muscle always shows marked changes. Frequently the striations are lost; the nuclei are pale or do not stain, and the cell shows marked vacuolation, or is reduced to a mass of granular débris. The muscle cells often contain pigment and at times there is pigment and red cells between the muscle fibers.

There are areas of softening in the bone marrow. There is nothing characteristic in the mucosa of the gastro-intestinal tract.

The metastatic abscesses appear throughout any of the organs.

History.—Hippocrates described an epidemic of relapsing fever in Thasos. Fever with relapses was known in London and Ireland in the eighteenth century, and during an epidemic of fever in England, in 1826 and 1827, it was recognized that there were two types of fever that had been included in "typhus fever." There were repeated epidemics of the milder type of typhus fever, and in 1843, Henderson recognized that this mild fever was not typhus. In 1868, during an epidemic in Berlin, Obermeier found "fine motile threads" in the blood of relapsing fever patients, and he published his findings in 1873, giving the name "Spirillum febris recurrentis" to the organism. Obermeier's finding was confirmed in other countries of Europe; but relapsing fever came to be more and more rare in Europe, and the organism did not receive any great attention. Cohn gave the name *Spirochæta obermeieri* to the organism of relapsing fever in Europe. Hindle says *Spirochæta recurrentis* is the proper name for this spirochete.

In North America, relapsing fever was observed in Philadelphia in 1844 and was supposed to have been brought in by Irish immigrants, so the disease was considered to be identical with European relapsing fever. During the next thirty years, the disease was pretty well known in the eastern states, and in 1874 an epidemic was observed among some Chinese laborers in California. Since that time the disease has been reported from Central and South America, and the West Indies. In 1906 a number of workers studied the spirochete of American relapsing fever and considered it different from the spirochetes of relapsing fever in Europe, Asia and Africa. Shellack gave the name *Spirochæta novyi* to the spirochete of American relapsing fever.

In 1857 Livingston described "human tick disease" from Portuguese South Africa, and stated that the natives considered the disease was transmitted by the bite of ticks. From 1901 to 1904, a number of observers studied and described the tick fever of Central Africa. Novy and Knapp gave the name *Spirochæta duttoni* to the organism of relapsing fever in Central Africa. Some authorities separate the spirochetes of relapsing fever of East and West Africa, giving the name *Spirochæta duttoni* to the spirochete in West Africa, and the name *Spirochæta rossii* to the spirochete in East Africa. *Spirochæta kochi* is a synonym of *Spirochæta rossii.*

In 1853 Griesinger described a "bilious typhoid" fever in Egypt, and since that time there has been confusion as to whether bilious typhoid

is a severe form of relapsing fever that is found in North Africa, or there are two diseases; one of them relapsing fever, and the other bilious typhoid of unknown cause. Sergent and Foley considered the spirochete of relapsing fever in North Africa to be a distinct species, and named it *Spirochæta berbera*.

Relapsing fever had been known in India since the eighteenth century. Lyall studied an epidemic in the Punjab in 1852 to 1853; and Carter found spirochetes in the blood of cases in Bombay in 1877. Hill described relapsing fever in China in 1904; Imbert described it in French Indo-China in 1910; and Schneider described it from northern Syria in 1912. Mackie gave the name *Spirochæta carteri* to the spirochete of relapsing fever in India.

Geographical Distribution.—There have been extensive epidemics of relapsing fever in Ireland, and there were severe epidemics in Russia in 1865 and in 1881. There have been lesser epidemics in England, Scotland, Germany, Denmark, Norway and the Balkan States. The disease has not been so common in Europe in recent years; but it was fairly prevalent on the eastern front during the recent war.

The disease is constantly present in India, French Indo-China and China. The cases reported from the Philippines seem to have been in persons who came from an endemic area, and the infection may have originated outside the Philippines. It is endemic in Syria and Arabia.

The disease is endemic in Portuguese South Africa and German East Africa; and there was an extensive epidemic along the caravan route from Dar-Es-Salaam to Muanza in 1903-1904. It is endemic in the Sedan. Other endemic centers in Africa are Uganda, Congo Free State, Nyassaland and Rhodesia.

In former years there was confusion regarding bilious typhoid fever in Egypt, but it is certain that relapsing fever is prevalent in Egypt, Tunis and Algiers.

The disease has not prevailed in epidemic form in the United States since 1869; but it is endemic in the southwestern part of the United States, in Mexico, Panama, Colombia, Venezuela, Cuba, Peru, Bolivia and Chili.

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CHAPTER XXX

TRYPANOSOMIASIS

(African Trypanosomiasis—American Trypanosomiasis)

By E. R. Whitmore, M.D.

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Under this heading are included two diseases, found in different parts of the world, and having different clinical courses, both caused by trypanosomes.

African trypanosomiasis is an endemic disease in some parts of Africa, while *American trypanosomiasis* is an endemic disease in some parts of South America.

AFRICAN TRYPANOSOMIASIS

Synonyms.—Sleeping sickness; Negro lethargy.

Definition.—A chronic disease caused by *Trypanosoma gambiense* and *Trypanosoma rhodesiense,* characterized anatomically by an inflammatory condition of the lymphatic system, with enlargement of the lymph-glands and meningo-encephalitis and meningo-myelitis. Clinically the disease is marked by irregular fever, emaciation, lassitude, weakness, tachycardia, erythema and edema of the skin, nervous and mental disturbances; and later, at times dementia, and commonly a protracted lethargy—sleeping sickness.

History.—John Atkins, in 1734, described "the sleeping distemper" which he had seen among the natives on the Guinea coast in 1721. In 1803, Winterbottom described the disease on the west coast of Africa, near Sierra Leone. He noted the enlargement of the cervical glands, and says that this enlargement of the glands was known to the slave-traders, and when present in a negro was a sign for refusal of a slave. Other observers described the disease from different parts of Africa; and, in 1869, Guerin saw the disease in Martinique, in slaves who had been brought there from Africa. A case was brought to London in 1891; and two cases were brought there in 1900. Several cases have come to the United States and have been studied here.

In 1901, Ford found a parasite in the blood of a patient with a peculiar type of fever from Gambia; and in 1902, Dutton recognized the parasite to be a trypanosome and gave it the name *Trypanosoma gambiense*. In 1902, Castellani found trypanosomes in the spinal fluid of cases of sleeping sickness in Uganda and gave the organism the name *Trypanosoma ugandense*. The findings of Todd and Castellani were confirmed by different observers; and Castellani and Nabarro showed that *Trypanosoma gambiense* and *Trypanosoma ugandense* were the same, and that sleeping sickness was only a stage in the febrile disease in which Todd and Dutton had found trypanosomes in the blood.

In 1903, Bruce and Nabarro showed that *Trypanosoma gambiense* was transmitted by a biting fly, *Glossina palpalis*. Kleine showed experimentally that *Trypanosoma gambiense* undergoes a cycle of development in *Glossina palpalis*.

In 1910, Stephens and Fantham reported that trypanosomiasis in Rhodesia was caused by a trypanosome that was different from *Trypanosoma gambiense;* and they gave the name *Trypanosoma rhodesiense* to the new trypanosome. In 1912, Kinghorn and Yorke showed that *Trypanosoma rhodesiense* was transmitted by *Glossina morsitans,* a biting fly closely related to *Glossina palpalis*. A number of observers, notably Bruce and his co-workers, hold that *Trypanosoma rhodesiense* is a variety of *Trypanosoma brucei;* while a number of other observers, as Laveran, hold that it is a distinct species.

Geographical Distribution.—The disease was first described at Sierra Leone; but it was soon found to extend far south of there. It has been carried by infected men into neighboring regions, until now it is found in a broad strip of territory, extending from 20° north to about 12° south of the equator, on the western coast of Africa, and extending inland to Uganda and Rhodesia. The disease has been carried to the West Indies, but did not spread there, as the arthropod host was missing. It is probable that the focus in Rhodesia has been an endemic focus for some time, and that it is not due to the spread of the West Coast disease.

Etiology.—Predisposing Causes.—*Race* is not a predisposing factor. *Sex* seems to play no part in predisposition, though Manson notes that females are more liable to infection. In the same way, *age* does not seem to play any part in predisposition, though some observers hold that young children are more liable to infection. The disease is most common in

young adults, probably because their occupation and habits lead to greater exposure to infection.

Occupation is of considerable importance, as persons in certain occupations are especially exposed to the bites of infected flies. Fishermen and persons who live or work along the shores of lakes and streams are especially exposed to infection with *Trypanosoma gambiense,* as *Glossina palpalis* lives on the borders of such waters. Porters who travel through the fly-zones are especially liable to infection, on account of their great exposure to the bites of infected flies.

EXCITING CAUSE: THE ORGANISM.—(*a*) *Trypanosoma Gambiense.*—*Trypanosoma gambiense* is the cause of African trypanosomiasis, except in Rhodesia. This organism appears the same in the spinal fluid as in the blood of man.

Morphology.—In the blood it is 16 to 30 microns long and 1.5 to 2 microns in breadth, though it varies greatly in size—is polymorphic, short plump forms being 14 to 20 microns long, and long slender forms being 23 to 32 microns long. The anterior end is usually drawn out to a point along the flagellum, but it may be rounded; the posterior end is usually rounded, but it may be drawn out to a point. The undulating membrane is small; the flagellum is well developed. The nucleus is oval and is situated about the middle of the body; the blepharoplast is oval and is situated at the posterior end, often just in front of a distinct vacuole. There is often a number of granules in the cytoplasm about the nucleus.

Cultivation.—*Trypanosoma gambiense* is difficult to cultivate. Thomson and Sinton cultivated it on the Nicolle modification of the Novy-MacNeal medium—the N. N. N. medium—using rat's blood. They mixed two parts of rat blood with one part of a one per cent. citrate solution; and mixed equal parts of agar and citrated blood. The medium was heated to 45° C. for two hours to destroy the complement, and was allowed to stand for two days at 25° C. for the water of condensation to collect. The cultures were kept at 22° to 24° C.

Occurrence in Lower Animals.—Spontaneous infection occurs frequently in antelopes. Yorke and Blacklock found one ox infected with *Trypanosoma gambiense;* and Kleine and Eckard found one ox, one sheep and one goat infected. The infected animals are not sick as a result of the infection.

Experimentally, monkeys are readily infected; parasites appear in the peripheral blood in from 18 to 20 days, the animal is quite sick, and dies in a few weeks to a few months. White rats are susceptible; the course is usually chronic, and marked by periods of latency when no parasites are found in the blood, and periods when the parasites are numerous in the blood. Mice usually have a chronic infection; but when the strain is carried in rats or mice for some time, it becomes more virulent and kills in 3 to 6 weeks. In rabbits and guinea pigs, the infection runs a chronic course with few parasites in the blood. Dogs are susceptible, and the infection may run a fairly acute course. Horses, cattle, goats, sheep and hogs are susceptible; but the infection is light.

Development in the Vertebrate Host.—The development of *Trypanosoma gambiense* has been studied especially in the blood of the rat. After inoculation, the parasites multiply by longitudinal division until they are very numerous in the peripheral blood. Then the parasites undergo a change in structure, becoming less numerous in the peripheral blood, and numerous in the lungs, spleen and bone-marrow. The nucleus of the parasite contracts and flattens, a large clear vesicle forms beside the nucleus, and a cytoplasmic sheath forms around both. The other structures of the parasite disappear, and these bodies lodge in the spleen and bone-marrow, where they remain during the latent period—ten days or more—when no parasites are found in the peripheral blood. These are the "latent bodies" of Moore and Brienl. At the termination of the latent phase, the other structures of the trypanosome are developed anew and the latent body becomes a trypanosome which multiplies by longitudinal division, the parasites re-appearing in the peripheral blood.

Fry and Rankin observed extrusion of granules from trypanosomes. When the trypanosomes are about to disappear from the peripheral blood, many of them extrude granules, usually from some point near the middle of the body; and these granules take on the leishmania form. They may now elongate and form trypanosomes, or they may divide before forming trypanosomes.

Wolbach and his coworkers, working with *Trypanosoma gambiense* in the blood of animals, conclude that it does not pass through bacteria-proof filters. Trypanosomes do not pass through the placenta.

Development in the Arthropod Host.—When *Glossina palpalis* feeds on blood containing *Trypanosoma gambiense,* the trypanosomes pass through the stomach of the fly, and in twenty-four hours lose their infectivity for the vertebrate host and multiply in the posterior part of the midgut. In ten to twelve days slender forms develop, and from the twelfth to the twentieth day they move forward to the proventriculus. From here they pass to the salivary glands, become attached to the walls of the gland ducts, and develop into crithidia forms which divide and form small trypanosomes similar to those in the blood of the vertebrate host; and these small forms are injected with the saliva into the subcutaneous tissues of the vertebrate host when the fly bites. Just how the trypanosomes get from the proventriculus to the salivary glands of the fly is not quite clear, though it is generally considered that they pass along the hypopharynx into the salivary glands. Trypanosomes are not found in the juice of the body cavity of the fly. The development in the salivary glands requires two to five days.

The development in the fly is favored by high atmospheric temperature—24° to 29° C. (75.2° to 84.2° F.)—while low temperature—15° to 21° C. (59° to 69.8° F.)—delays or prevents development, but does not kill the trypanosomes. Under favorable conditions the development in the fly is complete in twenty to thirty-four days, and the fly remains infective the rest of its life.

Trypanosoma gambiense completes its cycle of development in a small percentage of *Glossina palpalis* which feed on infected blood, as only

about 6 to 8 per cent. of the flies become infective. The infection is not transmitted to the pupa of the fly.

(*b*) *Trypanosoma Rhodesiense.*—*Trypanosoma rhodesiense* is the cause of trypanosomiasis in Rhodesia.

Morphology.—*Trypanosoma rhodesiense* resembles *Trypanosoma gambiense* in size, form and polymorphism. The nucleus is generally situated well to the posterior end, near the blepharoplast; but it may be situated near the middle of the body as in *Trypanosoma gambiense;* and in the short plump forms it may even be behind the blepharoplast. The posterior position of the nucleus is best shown in the blood of rats.

Cultivation.—Thomson and Sinton cultivated *Trypanosoma rhodesiense* in the same way they cultivated *Trypanosoma gambiense.*

Occurrence in Lower Animals.—Spontaneous infection occurs frequently in wild animals, as the antelope, hartebeest, water buck, impala and wart-hog. Kinghorn and Yorke found one dog infected.

Experimentally, the same animals as given under *Trypanosoma gambiense,* are susceptible to infection with *Trypanosoma rhodesiense. Trypanosoma rhodesiense* is generally more virulent than is *Trypanosoma gambiense;* and it causes severe disease in sheep and goats, killing them in forty to forty-five days.

Development in the Vertebrate Host.—The development of *Trypanosoma rhodesiense* in the vertebrate host is practically the same as that of *Trypanosoma gambiense.* Fantham has studied the development of the latent forms in the lungs. The blepharoplast moves close to the nucleus, and the rest of the body is lost, leaving a rounded body containing the nucleus and the blepharoplast. This rounded body becomes surrounded by a capsule, and becomes a cyst 2 to 4 microns in diameter—the latent body or preflagellar stage. After a time these bodies increase in size and length, and develop into trypanosomes again.

Development in the Arthropod Host.—When *Glossina morsitans* feeds on blood containing *Trypanosoma rhodesiense,* the trypanosome goes through the same cycle of development as does *Trypanosoma gambiense* in *Glossina palpalis.*

The development of *Trypanosoma rhodesiense* is affected by atmospheric temperature in the same way as is that of *Trypanosoma gambiense.* Under favorable conditions *Trypanosoma rhodesiense* completes its cycle of development in *Glossina morsitans* in fourteen days; but only about 5 per cent. of the flies become infective.

There is a difference of opinion as to whether *Trypanosoma rhodesiense* is a distinct species or is a variety of *Trypanosoma brucei,* which is the cause of nagana, the tsetse-fly disease of horses and cattle in Africa. Both trypanosomes are transmitted by *Glossina morsitans.* Laveran found that sheep immunized to *Trypanosoma brucei* were susceptible to infection with *Trypanosoma rhodesiense.* Chalmers says that animals immunized to *Trypanosoma brucei* are killed by *Trypanosoma rhodesiense,* and vice versa. On this basis, it is held that *Trypanosoma rhodesiense* is a distinct species. Bruce does not consider cross inoculations as reliable for differentiation, and depends on morphology, action on animals,

and manner of development in the fly, in the separation of species. On this basis, it is held that *Trypanosoma rhodesiense* is *Trypanosoma brucei.*

(*c*) *Other Trypanosomes.*—Macfie gave the name *Trypanosoma nigeriense* to a trypanosome found in the blood of young persons in Nigeria. This trypanosome is less virulent than is *Trypanosoma gambiense,* and is transmitted by *Glossina tachnoides.* Bruce is of the opinion that *Trypanosoma nigeriense* is *Trypanosoma gambiense.*

Castellani and Chalmers express the opinion that more than one species of Trypanosoma is included in the species *Trypanosoma gambiense;* and they note that the Uganda strain appears to be different from the Gambia strain.

Trypanosomes that cause disease in lower animals may cause occasional cases in man. Thus, there have been laboratory infections in man with laboratory strains of *Trypanosoma brucei.*

Epidemiology.—(*a*) Source of Infection.—*Man* is an important source of infection. As men may have trypanosomes in the blood for several years without being too sick to go about their usual occupation, it is easily understood that man spreads the disease along caravan routes, and from place to place. Mayer gives the following percentages of apparently healthy persons who have *Trypanosoma gambiense* in the blood: 0.6 per cent. in Gambia; 4.6 per cent. in Congo; and 28.7 per cent. in Uganda.

But man is not the only source of infection. Where infected areas have been depopulated, infected flies were still found in the area a year or more later. Wild animals are frequently found infected with *Trypanosoma gambiense* and *Trypanosoma rhodesiense,* and remain in good condition. So it is evident that *lower animals* act as reservoirs for the infection. While domestic animals are occasionally found infected, it does not appear that they play an important part as reservoirs for the infection. Antelopes act as reservoirs for infection with *Trypanosoma gambiense;* while the antelope, water buck, hartebeest, wart-hog and impala act as reservoirs for infection with *Trypanosoma rhodesiense.*

The relative importance of man and lower animals as sources of infection varies in different regions. Yorke and Blacklock consider man as the chief source of infection with *Trypanosoma gambiense* in Sierra Leone; but they think domestic animals may be of some importance. Human trypanosomiasis may be very chronic in Sierra Leone, and trypanosomes may be found in the blood when examining for some other organism, as malarial parasites. They consider that wild animals are the chief source of infection in South Central Africa. Duke says that antelopes are the reservoir for *Trypanosoma gambiense* on the uninhabited islands of the Victoria Nyanza Lake.

(*b*) Mode of Transmission.—The infection is transmitted by the *bite of infected tsetse flies, Trypanosoma gambiense* being transmitted by *Glossina palpalis,* and *Trypanosoma rhodesiense* being transmitted by *Glossina morsitans.*

The flies may transmit the infection mechanically for a short time after feeding on an infected animal. Then there is a period, corresponding to the length of time necessary for the cycle of development in the fly, during which time the fly cannot transmit the infection. Following this period, the infection is transmitted by the bite of the fly.

Carpenter studied the habits of *Glossina palpalis* with special reference to its rôle in the transmission of *Trypanosoma gambiense*. The females live about four months, and the males live about eight months. There are no natural enemies; and the pupæ are found at the base of trees and under fallen logs, only a few yards from the water's edge and a few feet above it, out of the way of birds. The flies feed on blood, especially on lizards, having a special liking for certain lizards; they also feed on crocodiles and birds. Of mammals, they feed on the antelope, hippopotamus and otter. Lamborn says that some wasps are parasitic on the pupa of glossina, and that dragon flies prey on the adult flies.

Tsetse flies also breed in shaded places, in sand along river beds, where the water leaves the sand uncovered in the dry season.

The female tsetse fly gives birth to one large larva at a time; this larva immediately bores a couple of inches into the sand, and changes to a pupa. In about a month the adult fly emerges from the pupa.

Tsetse flies bite during the day, even in sunlight; and will follow human beings some distance. Both males and females bite and can transmit trypanosomes.

Sexual intercourse has been considered to be a mode of transmission of the infection. Koch noted infection of fifteen women in a fly-free area, and considered that they were infected by their husbands who had returned from working in fly zones. Bernard noted infection of prostitutes in the same way. It is known that trypanosomes can pass through an unbroken mucous membrane; and dourine, a trypanosomiasis of horses, is transmitted by sexual intercourse. Neiva showed that *Trypanosoma equinum, Trypanosoma evansi,* and *Trypanosoma equiperdum* can be transmitted from guinea pig to guinea pig by the instillation of a drop of infected blood into the conjunctival sac.

Mosquitoes are suggested as transmitting the infection, as children are often infected though not exposed to the bite of tsetse flies.

Martin and Leboeuf suggest *tattoo wounds* as sources of direct infection.

But the all-important mode of transmission is through the *bite of infected tsetse flies.*

(*c*) Susceptibility.—All races and ages, and both sexes are susceptible to infection.

Symptomatology.—Generally the bite of a glossina leaves only a small papule which itches for a short time and then disappears. At times, possibly due to contamination with pyogenic bacteria, there is an inflammatory area at the site of the bite, with a swelling of the neighboring lymph-glands. These infected bites may cause painful furuncle-

like swellings on various parts of the body; they are usually single, but there may be as many as five.

It is usual to describe the symptoms under two stages: (1) trypanosome fever, and (2) sleeping sickness. Martin and Leboeuf describe the symptoms under three stages: (1) *incubation,* (2) *invasion* and (3) the *developed disease;* and they divide the third stage into three periods: (a) *beginning*—organisms in the blood but not in the spinal fluid; (b) *infection of the nervous system*—when the organisms enter the spinal fluid, and (c) *terminal period.* The stage of invasion and the first period of the stage of the developed disease, in the Martin and Leboeuf description, correspond to the usually described stage of trypanosome fever; while the second and third periods of the developed disease in the Martin and Leboeuf description correspond to the usually described stage of sleeping sickness.

(1) INCUBATION.—The stage of incubation, from the bite of the fly to the appearance of trypanosomes in the blood, is ten to twelve days. The period from the bite to the development of symptoms may be as short as ten days; but more commonly it is two to three months. The inhabitants of some infected regions consider that the incubation period may be long, and that a man may develop the disease up to seven years after leaving an infected region.

(2) INVASION.—The stage of invasion is represented by the first symptoms of the disease. The resistance of the body has been overcome, and the organisms circulate in the blood. This stage begins with irregular remittent or intermittent fever of 39.4° to 40° C. (103° to 104° F.), and in whites is commonly accompanied by an erythematous rash. There is nervous excitement, insomnia and prostration. After about a week, the fever and symptoms disappear, though the pulse may remain rapid.

These symptoms may be absent in natives; and they may reach the period of infection of the nervous system without having fever.

(3) THE STAGE OF THE DEVELOPED DISEASE.—(*a*) The *first period* is of variable length, and trypanosomes are found in the blood but not in the spinal fluid.

After an afebrile period of a few days to two or three weeks the fever returns, but is generally not as high as in the first period—38.3° to 38.9° C. (101° to 102° F.). After about a week, the fever again disappears; and these febrile and afebrile periods continue to alternate.

Headache is common, and may be persistent; but it is not very severe. There may be neuralgic pains, with cramps in the calves of the legs, and pains in the feet. A very common symptom is superficial and deep hyperesthesia, and a slight blow or pressure will produce sharp pain. The patient is very susceptible to cold.

There are insomnia, weakness, anemia and emaciation. Photophobia is not uncommon; and there may be iritis and cyclitis.

In the white person there is commonly an erythematous eruption from the beginning of the fever. This eruption appears as poorly defined, pinkish patches, appearing especially on the chest. These

patches may be ring-shaped or crescentic, and are frequently seen better at a little distance from the patient.

The erythematous eruption is often not seen in the negro. Here the skin is often dry and scaly, at times with severe pruritus. There is frequently a papular eruption that may itch considerably. The eruption may be vesicular, or may ulcerate or be pigmented. It is these types of eruption to which Martin and Leboeuf refer as trypanids, and compare them to syphilids.

Areas of localized edema are not uncommon, sometimes with a large erythematous patch. These areas of edema often appear over the sternum, on the arms, and on the internal surface of the thighs, and are fleeting.

The heart is rapid—about 120 per minute; and this tachycardia commonly continues through the afebrile period.

There is loss of sexual power; the menses may be suppressed or they may continue for almost the entire duration of the disease.

There may be dysenteric crises, which may dominate the picture.

The lymph-glands are enlarged and movable, and about the consistence of a ripe plum. The lymph-glands in the posterior cervical triangle are very commonly enlarged; other superficial lymph-glands less commonly. This enlargement of the lymph-glands is an important clinical sign; and the natives recognize that a person with enlarged posterior cervical glands will have sleeping sickness.

The spleen is often enlarged; and the liver may be enlarged.

Mental symptoms are not prominent. Whites may be sad or irritable, and may be neurasthenic. They show loss of attention, and are apt to make errors in figures and in writing. Natives often show no mental changes; but they may continue to do their work as automatons, may be expansive or morose, and may lose their self-respect and become lax in discipline.

This period lasts from a few months to seven years. Natives may go through the entire period, with trypanosomes in their blood, without being sick.

(*b*) The *second period* begins with the entrance of the trypanosomes into the subarachnoid space.

All symptoms are increased in severity. The febrile periods are more frequent; there is marked nervousness; and the headache increases and may be severe. There may be ringing in the ears, or deafness.

The patient becomes dull and apathetic; is tired by the least exertion; the gait is weak and shuffling; and the entire figure is relaxed and drooping, thus adding to the appearance of apathy and moroseness. The puffy eyelids tend to fall shut; there is a state of physical asthenia. With this, there is a state of mental and intellectual asthenia; the patient does not enter into conversation; answers slowly when spoken to and even simulates sleep to avoid conversation. He becomes careless in his habits. The appetite is good, but the patient will not go to the trouble of getting food, and he may go to sleep with food in his mouth. The digestive apparatus is undisturbed.

The condition is one of intellectual asthenia and lethargy, rather than actual sleep. When spoken to, the patient is easily aroused, but he will yawn and stretch, as though he had just wakened; and he may even be angry at being disturbed.

Mental symptoms are quite common. At night, there may be mental disturbance amounting to delirium or mania. The patient may have fits of excitement or anger, in which he is quarrelsome or destructive; after the fit is over, he returns to the lethargic state. There may be delusions of grandeur; hallucinations of sight, hearing, smell or taste. There may be melancholia, but suicide is rare. There may be amnesia, catatonia, echomimia, echolalia, negativism or mutism. There may be impulse to steal; and the patient may collect all sorts of worthless things.

There is a tremor of the muscles, especially noticeable in the tongue, lips and hands. There may be epileptiform attacks. Rigidity and muscular contractions are rather common. There may be hemiplegia or paraplegia. The reflexes are generally normal; though the deep reflexes may be exaggerated early, and lost later. There is loss of coördination in walking; and Romberg's symptom is often present. The pupils are equal and react to light and accommodation. Control of the sphincters is retained to near the end. There may be hyperesthesia or anesthesia.

The edemas increase, especially about the face; and may extend to the glottis.

This period lasts from three to six months.

(*c*) In the *third period* the condition is one of complete decrepitude. The general weakness and emaciation increase; there is marked tremor; contractures; and the lethargy is profound. The patient is neglectful and oblivious; will eat dirt; saliva dribbles from the mouth; and there is incontinence of feces and urine. The patient falls when he tries to walk. The blood-pressure falls; there is cardiac arhythmia; the temperature is subnormal; decubitus appears on different parts of the body; the patient passes into a comatose condition and dies.

Death may result from an epileptiform or apoplectiform attack, or from cachexia; but more commonly it results from a complication, as pneumonia, meningitis or dysentery.

This period lasts two to three months.

The disease may last from eighteen months to several years. After involvement of the nervous system, the disease usually does not last over four to eight months; though it may be prolonged to two years or more by treatment.

The entire clinical course is variable. Lethargy is the most striking characteristic, and this form is most common; but the disease may resemble general paralysis. About one-sixth of Martin and Ringenbach's cases had psychoses. The course may be rapid or slow; and there may be periods of latency followed by relapse.

There may be no enlargement of the glands throughout the disease. While the pulse is usually rapid—100 to 140 per minute—it may be as

slow as 50 per minute, probably due to irritation of the vagus as it passes through the subarachnoid space.

The course of the Rhodesian form of the disease is more rapid than that of the Gambian form, often lasting not over four or five months; and the lethargy may not appear.

Diagnosis.—CLINICAL DIAGNOSIS.—The disease may escape diagnosis for a long time. The history is important, especially a history of residence in an endemic area and of having been bitten by tsetse flies. In the early stage of the fever there is apt to be confusion with *malaria;* but chills and sweats are rare in the fever attacks, and the fever is not affected by quinin. The enlarged lymph-glands, erythema and headache may cause confusion with *syphilis;* and the danger of confusion is increased by the fact that the Wassermann reaction is not infrequently positive in the blood of cases of trypanosomiasis—possibly cases of the two diseases together.

While *enlarged cervical lymph-glands* is an important sign, it must be remembered that such enlarged glands are frequently met with in persons who are free from trypanosomes. Mayer says that in Uganda, from 50 to 75 per cent. of the natives have enlarged lymph-glands; but only 28.7 per cent. of the healthy persons harbor trypanosomes. There may be no enlargement of the lymph-glands throughout the disease.

In an endemic area the irregular fever, the rapid pulse, the asthenia, the headache, the eruption, the enlarged cervical lymph-glands (Winterbottom's sign), the deep hyperesthesia (Kerandel's sign), and the tremor of the tongue (Low-Castellani sign) make it possible to arrive at a clinical diagnosis with a fair degree of accuracy.

In addition to malaria and syphilis, there may be confusion with *filariasis, dysentery, relapsing fever* or *liver abscess;* and any of these conditions may exist with trypanosomiasis. In *beriberi* the lymph-glands are not enlarged, and the heart is involved.

After involvement of the central nervous system, the lethargy, emaciation and edema, and tremors and muscular contractures are of importance in diagnosis.

The various mental states are difficult to differentiate from such mental states due to other causes. The pupils are normal.

In all cases, it is important to make a laboratory examination for trypanosomes; and only in this way can a definite diagnosis be made.

LABORATORY DIAGNOSIS.—*Blood.*—Trypanosomes may be found in the peripheral blood, especially during attacks of fever; but trypanosomes are not numerous in the peripheral blood, and long search is necessary—even then it is frequently impossible to find them.

Citrated blood may be repeatedly centrifuged and the sediment examined on the third centrifugalization; or the leukocyte layer may be examined after centrifuging citrated blood in narrow tubes. In obtaining trypanosomes from the blood of cattle, Teague and Clark defibrinated the blood with sticks, strained it through gauze, mixed it with an equal volume of water, allowed it to stand a few minutes, centrifuged and examined the sediment.

Trypanosomes are considered to be more numerous in the erythematous areas on the skin than in the general circulation. The erythematous areas may be scarified and blood films from the scarified area examined.

There is secondary anemia, the red cells falling to as low as two million per cubic millimeter. The leukocyte count is often disturbed by secondary infections. In uncomplicated cases, the leukocytes are normal in number or rise to 10,500 per cubic millimeter. There is an increase in the mononuclear elements, the lymphocytes rising to 37 per cent. of the total count.

There is auto-agglutination of the red cells, but it is not specific. Various serum reactions—agglutination, precipitin, complement fixation, trypanolysis and attachment—have been tried; but the results are not very satisfactory.

Gland Puncture.—Trypanosomes are especially numerous in the lymph-glands. An enlarged lymph-gland is punctured with a dry syringe; a small amount of gland juice is aspirated and examined for trypanosomes. This is the most satisfactory method of direct microscopical diagnosis.

Spinal Fluid.—After involvement of the central nervous system, trypanosomes are found in small numbers in the spinal fluid by centrifuging about 10 c.c. and examining the sediment.

Dubois and Van den Branden tried the reaction of Boveri on the spinal fluid in cases of trypanosomiasis in the stage of nervous system involvement. The reaction is positive in this stage of the disease; but it is not specific, being due to the presence of proteids.

Early in the disease the spinal fluid is normal. After involvement of the central nervous system it is often slightly turbid and contains serum albumin and serum globulin; lymphocytes are fairly numerous, and there are larger vacuolated cells.

Animal Inoculation.—When trypanosomes are not found on direct microscopic examination of the body fluids, 10 c.c. of blood or spinal fluid may be injected into a susceptible animal. Monkeys are the most satisfactory animal for the purpose, but may not be available. The most satisfactory of the available animals is the guinea pig, injected intraperitoneally. Dogs are satisfactory. Rats and mice are not satisfactory as they are frequently infected with trypanosomes in nature; and this might lead to confusion.

Complications.—Acute infectious conditions are the usual complications, as pneumonia, purulent meningitis and dysentery. Pleurisy, pulmonary gangrene and tuberculosis are also met with. The secondary bacterial infections produce secondary lesions throughout the body; and these infections have also caused confusion regarding the etiology of the disease.

Iritis and iridocyclitis are quite frequently met with—especially in Rhodesian trypanosomiasis—and in four of Daniels' cases, it was the eye lesions which led the patient to seek medical advice. Orchitis is less frequent. These conditions are hardly to be considered as complications, as they are due to the action of the trypanosomes.

Abortion, premature birth, stillbirth and death a few days after birth are the rule in trypanosomiasis.

Treatment.—GENERAL MANAGEMENT.—If possible, the patient should be removed to a **temperate climate,** should be given **rest** and an **abundance of good food,** placed under **good hygienic conditions,** and **protected from the cold,** as persons suffering from trypanosomiasis feel the cold very keenly.

Atoxyl generally gives good results in the treatment of trypanosomiasis; and trypanosomes disappear from the blood in six to seven hours after an intramuscular injection of 0.5 gram (7.7 grains) of the drug: the patient may have a febrile reaction at this time. There are several methods of giving atoxyl, Martin and Leboeuf advising 0.5 gram (7.7 grains) intramuscularly, to be repeated in 48 hours; after an interval of 10 days the same two doses are to be given, with the 48-hour interval; and treatment is to be continued in this way. A few cases of optic neuritis have resulted from the use of atoxyl.

Other arsenicals have not given very satisfactory results; though **Fowler's solution** may be given by mouth when treatment by injection cannot be carried out.

Tartar emetic has proved to be a valuable drug in the treatment of trypanosomiasis; and trypanosomes disappear from the blood in five to ten minutes after an intravenous injection of 50 milligrams (10/13 grain) of the drug. Tartar emetic is given intravenously in doses of 50 to 100 milligrams (10/13 to 1 1/2 grains) dissolved in 75 to 150 c.c. (2 1/2 to 5 ounces) of water. One difficulty with tartar emetic is the severe pain and inflammation that is caused by the escape of the solution into the tissues around the veins. Van den Branden undertook to overcome this difficulty by giving the tartar emetic intravenously in oil: he could give 150 milligrams (2 4/13 grains) of tartar emetic (3.75 c.c. [1 fluidram] of oil) this way; but there were severe symptoms—especially violent coughing (possibly fat embolism)—when 200 milligrams (3 grains) of tartar emetic (5 c.c. [1⅜ fluidrams] of oil) were given. Antimony salts may produce a fall of blood-pressure and dyspnea; so it is advisable to give a **hyperdermic injection of caffein** a few minutes before giving the antimony.

Tartar emetic is usually **combined with atoxyl,** in order to prevent the formation of drug-resistant strains of the trypanosome. A series of ten daily injections of tartar emetic is given, with an interval of a month before the next series. Atoxyl is given in 0.5 gram (7.7 grain) doses every five or six days, or 0.2 gram (3 grains) every three days.

Daniels and Newham had difficulty in treating Rhodesian trypanosomiasis with atoxyl and tartar emetic; and they obtained satisfactory results from the subcutaneous injection of **antimony oxid** in a case in which atoxyl and tartar emetic had failed.

Masters recommends antimony oxid, alone or combined with **soamin.** He dissolves antimony oxid in equal parts of glycerin and water by heating it gently, 1 c.c. of the solution containing 0.65 mg. (1/100 grain) of antimony oxid. He gives 2 to 3 c.c. of the solution intramuscularly

every other day until 26 milligrams (2/5 grain) are given. If trypanosomes do not disappear from the blood he gives 0.77 gram (11.8 grains) of soamin every five days, continuing the antimony oxid injections. Masters considers that soamin given in large doses is more effective than when given in numerous small doses.

Numerous other drugs have been used, but have not given satisfactory results, or have not been used in enough cases to determine their value.

Treatment must be continued until the patient's pulse, temperature and weight are normal and until at least two animal inoculations prove negative. If treatment is discontinued too soon, the patient will relapse; and relapse is serious and increases the danger of involvement of the nervous system. Treatment can do no more than prolong life.

PROPHYLAXIS.—Prophylaxis is based on the premises that (1) man is an important source of infection, spreading it from place to place, and that certain wild animals serve as reservoirs of the infection and keep it up in endemic areas; that (2) the infection is spread from man to man or from reservoir to man by the bites of tsetse flies; and that (3) both sexes and all ages and races are susceptible to the infection.

(1) *Source of Infection*—**Early diagnosis and treatment** of cases is important. Persons ill with trypanosomiasis should be **segregated** in treatment camps, or treated in localities where they are not exposed to the bites of flies.

Many persons have trypanosomes in their blood for years without being sick. These persons are a very important source of infection, as they continue at their occupation and travel from place to place. In order to detect such cases, it is necessary to make **systematic examinations of persons exposed** and of all suspects coming into a locality. In order to carry out these examinations, it is necessary to have segregation camps in which exposed persons, suspects and travelers are held until they can be examined. Servants are given health certificates, and travelers are given medical passports.

It is important that all infected persons found be given **prompt treatment** in order to free their blood of trypanosomes as soon as possible.

Depopulation of infected districts has not resulted in eradication of the infection, as the wild animals in the district served as reservoirs and kept up the infection in the flies.

Destruction of the wild animals that act as reservoirs in a district has not given satisfactory results.

(2) *Mode of Transmission.*—**Destruction of the tsetse flies** has given good results, where it could be carried out satisfactorily. Various traps have been tried, but without much success. Some success has been obtained in **catching flies** by men wearing white clothes and having on their backs a square of black cloth covered with bird-lime. In their work in the island of Principe, Da Costa and his co-workers caught 470,000 flies in this way in three years. Shircore has suggested **revolving screens,** like the ordinary revolving exit and entrance door, covered with bird-lime and set up along caravan routes, for the catching of *Glossina morsitans* as they follow the porters through the screens.

Koch advised killing crocodiles and destroying their eggs, as an attack on the fly through its food supply. But the flies feed on the blood of other animals, so that this method is not satisfactory.

The best results follow **destruction of the breeding and resting places of the fly.** The flies require considerable moisture and a temperature not above about 25° C. (77° F.). They breed in a narrow strip of ground, well covered by vegetation, close to the edge of the water. Clearing a strip about fifteen feet wide along the edge of the water will to a great extent prevent breeding. But the **trees and stumps should be removed,** as Lamborn has shown that the flies breed in the decaying vegetation around fallen trees and under logs. As the flies rest in the shade of the forest and will follow humans some distance, it is advisable to clear a strip 100 yards wide along the water, especially at crossings, and 300 yards wide around villages. Da Costa and his coworkers eradicated the disease from the island of Principe by clearing and draining and by catching flies.

As the pupæ are one or two inches in the ground, among roots or under logs, they are difficult to destroy. Minchin suggested the breeding of jungle-fowl for the destruction of the pupæ.

(3) *Personal Prophylaxis.*—It is necessary to instruct the people regarding the disease, and to secure their coöperation in any preventive work that is to be undertaken. Misery and famine are to be relieved. **Occupations which expose to fly bites should be avoided, also areas in which the flies live. Travel in the fly regions should be undertaken at night. Whites should live at a distance from natives, and persons in occupations where they are specially exposed should live at a distance from other people.**

White clothes should be worn, as white does not attract the flies. The face, hands and ankles should be protected from the bites of flies by **nets, gloves and boots or leggings,** in spite of the discomfort from the heat.

Repellants, as **citronella oil,** are of some value.

Vaccination does not offer much hope. There is no evidence of immunity after trypanosomiasis, such as there is after some bacterial diseases. Schilling and Rondini allowed suspensions of trypanosomes to stand for some hours at incubator temperature, and then injected the suspensions into animals. These animals were protected against infection on injection of infective blood seven days later. Laveran could not confirm this work, and considers that in general there is not satisfactory evidence of protection.

Prognosis.—The prognosis is bad. The progress of the disease may be slow, and there may be long periods of latency; but the tendency is toward death. It is not known whether the cases reported by Todd, from Gambia, are cases of recovery or only long periods of latency. The disease in Gambia is less acute than in Uganda or French Congo.

With the use of organic arsenic compounds, when taken early, the prognosis is not so bad, even when the patient cannot be removed from the endemic area. Greggio studied the effect of treatment on the length

of life of patients. Of 51 patients who began treatment in 1907, 20 were alive in 1915. Most of the deaths occur in the first year of treatment (124 of 183 deaths) and the great majority in the first two years (157 of 183 deaths). Some patients die after as much as 7 1/2 years after the beginning of treatment. Of 59 patients found in 1911, 26 were treated and 33 were not treated. Of the treated, 16 were alive in 1916; of the untreated, 9 were alive in 1916.

When the patient can be removed to a temperate climate early in the disease, and can be given good food, rest and proper treatment, the prognosis is fairly good.

Relapse occurs if treatment is discontinued too soon; and the prognosis of relapse is bad.

The prognosis is almost hopeless after the nervous system becomes involved, though treatment may prolong life.

Mechanism of the Disease Process.—The trypanosomes injected into the subcutaneous tissues by the bite of the fly, multiply and circulate in the peripheral blood.

Schuberg and Böing injected trypanosomes (*Trypanosoma lewisi and Trypanosoma brucei*) into the skin of animals, and studied the manner in which the trypanosomes entered the tissues. The trypanosomes very quickly enter the lymph spaces of the corium, and then pass through the connective tissue to the neighboring lymph-glands. Here they multiply enormously and are found in large numbers in the glands on the same side of the body before they are found in the peripheral blood.

In the human, the trypanosomes probably multiply and travel in the lymphatics, and the toxin causes inflammatory reaction in the lymph-vessels, glands and follicles. The trypanosomes enter the blood stream early, producing a general infection; and later they enter the cerebrospinal fluid.

Wolbach and Binger conclude that the lesions in trypanosomiasis are due to the trypanosomes which invade the connective-tissue structures of all organs, the reticular tissue of lymph-glands and the spleen, and the substance of the brain. Martin and Leboeuf draw the following parallel between syphilis and trypanosomiasis: (1) local lesions; (2) eruption, etc. (trypanids); (3) nervous system. They consider the early lesions due to toxin from the trypanosomes and the later lesions due to changes in the tissues.

Early in the disease there is round-cell infiltration of the tissues and organs; and later there is an increase in the connective tissue. The round-cell infiltration about the blood-vessels in the central nervous system compresses the vessels and causes anemia of the brain. This, with the presence of trypanosomes in the brain tissue, gives rise to the cerebral changes which give the clinical picture of lethargy, or sleeping sickness.

The course of the disease caused by *Trypanosoma rhodesiense* is the same as that caused by *Trypanosoma gambiense,* except that the rhodesian disease is generally more severe than is the disease caused by *Trypanosoma gambiense.*

IMMUNITY.—Recovery appears to be the result of the general resistance of the body, rather than any specific immunity. It is not known whether persons who recover are immune; but there does not appear to be immunity in recovered animals.

Schilling doubts whether there is spontaneous recovery in human trypanosomiasis, but there may be long periods of latency. There are anti-bodies—precipitins, trypanolysin, opsonins and substances which produce agglomeration of trypanosomes—in the blood of infected animals; and these antibodies prevent superinfection.

Heckenroth and Blanchard found that the serum of infected animals is almost always protective, and that it very exceptionally produced agglutination, rarely produced attachment, and frequently produced lysis, of the trypanosomes.

Todd reports that of twelve cases of trypanosomiasis in natives of Gambia in 1911, four were living and in good condition at the end of 1918; the others had died at irregular intervals. Todd considers that this proves there is some immunity to human trypanosomiasis; but it is not determined whether it is a sterilizing immunity or a tolerance immunity.

CAUSES OF DEATH.—The disease may run a rapid course and cause death from inanition in a few months.

Secondary bacterial infection is very common, and death is often due to purulent meningitis, pneumonia, or dysentery.

Pathology.—MACROSCOPIC.—The body is emaciated, and the enlarged lymph-glands are visible in the neck and groins.

On opening the body there is nothing markedly abnormal. The bronchial and mesenteric glands are enlarged; all of the lymphatic glands are congested, and they may be hemorrhagic. The organs are pale; the heart is soft and flabby; the liver and spleen may be slightly enlarged; the kidneys show nothing.

The important lesions are in the brain. The cerebrospinal fluid is increased in quantity; the meninges are congested; and there is diffuse pachymeningitis with adhesions. The arachnoid is cloudy, and the subarachnoid space contains a yellowish, turbid exudate. The brain tissue is usually firmer than normal, is congested, and may be edematous. The gyri are flattened, and there is excess of fluid in the ventricles.

Lesions of complications are very common; especially pneumonia and dysentery, and, less frequently, purulent meningitis.

MICROSCOPIC.—The main change is the round-cell infiltration around the blood-vessels in the meninges and brain; the so-called coat-sleeve infiltration. The infiltrating cells are mainly plasma cells; but lymphocytes are numerous, and mast cells are also present. There are isolated areas of plasma cells in the nervous tissue. The nerve cells show chromatolysis. Later there is increased formation of fibrous tissue with thickening of the meninges and the adventitia of the blood-vessels. Mayer says that the change in the brain resembles that in paresis, but the genesis of the change is just the reverse: in trypanosomiasis, the interstitial inflammatory change is primary, and the parenchymatous

changes result from this; while in paresis the primary change is the degeneration of the parenchyma.

The changes are less marked in the spinal cord; the lining of the central canal often shows proliferation of its cells. There are no changes in the peripheral nerve fibers.

All organs show the round-cell infiltration, the condition being well marked in the lymph-glands, the spleen and the heart muscle. In the lymph-channels, the infiltrating cells are in more or less dense clumps; while they lie singly or in small groups in the stroma of the organs. In the lymph-glands, the cellular infiltration leads to formation of connective tissue.

Trypanosomes are found in the lymph-glands from the beginning of the disease, and are usually fairly numerous there. As soon as the disease is established, trypanosomes are found in the blood, though not in great numbers. When the central nervous system becomes involved, trypanosomes are found in the cerebrospinal fluid, but they are always very scarce there. Wolbach found trypanosomes in the neuroglia cells in the brain. Vianna found cysts, like those of *Trypanosoma cruzi*, in the muscles of cases of sleeping sickness and in animals infected with *Trypanosoma gambiense*. Trypanosomes disappear from the tissues and fluids in a few hours after the death of the host.

AMERICAN TRYPANOSOMIASIS

Synonyms.—Chagas' disease; Opilacão (in part).

Definition.—An acute or chronic disease, caused by *Trypanosoma cruzi*, and characterized anatomically by enlargement of the thyroid gland and of the lymph-glands, and by meningo-encephalitis. It is characterized clinically by symptoms of thyroid and suprarenal insufficiency.

History.—In 1909, Chagas was on a malaria expedition in the northern part of the state of Minas Geraes in Brazil, and he found there a cone-nose bug that was known as "barbeiro" by the natives. This bug lived in the houses, and at night, after the lights were out, would come out and bite the occupants. Chagas recognized the importance of studying such a bug as to its possible rôle in the transmission of disease; and on studying the bugs he found, in the hindgut, flagellates of the Crithidia form. It was a question whether this was a flagellate limited to the intestine of the bug, or was a stage in the cycle of development of some flagellate from a vertebrate host.

He sent some of the bugs (*Triatoma megista*) to the Oswaldo Cruz Institute in Rio de Janeiro, where the bugs were allowed to bite monkeys, whereupon the monkeys developed trypanosomes in their blood. Chagas studied the trypanosomes, and found that the bugs were actually the intermediate host of the trypanosome, and that it was eight days from the time bugs were fed on the monkey until the bugs could transmit the infection.

Chagas then returned to Minas Geraes to search for the disease transmitted by this bug. He found that the people in whose houses the bugs lived were in poor health, and some of them had physical findings that are known to indicate trypanosomiasis; enlarged lymph-nodes, edemas and a peculiar puffiness of the face. He remembered that he had seen similar cases which did not yield to quinin. But he could find nothing in the blood of these persons. Finally he saw a child with fever, enlarged lymph-nodes, puffiness of the face and enlargement of the thyroid gland; and he found numerous trypanosomes in the peripheral blood, identical with the ones which the bugs had transmitted to the laboratory animals. Then he was able to produce trypanosomiasis in guinea pigs by the injection of blood from the chronic cases in which he had not found trypanosomes in the patients' blood. Chagas named the trypanosome *Trypanosoma cruzi*.

In 1919, Tejera found cases of the disease in Venezuela, and showed that *Rhodnius prolixus*, a Reduviid bug related to Triatoma, was the transmitter of the disease there.

Geographical Distribution.—The disease is fairly common in the state of Minas Geraes, Brazil; and is also found in São Paulo and at Bahia. It has been found in the states of Trujillo and Zulia, Venezuela. It exists in the eastern part of Peru.

Etiology.—PREDISPOSING CAUSES.—The disease is more severe in children than in adults. It appears to be more common in children; possibly because the bugs have a better opportunity to bite them.

EXCITING CAUSE: THE ORGANISM.—*Trypanosoma cruzi* is the cause of the disease. This organism is 18 to 20 microns long and about 1.5 microns in breadth. The flagellum is not much longer than the body; the undulating membrane has few undulations; the anterior end is pointed; the posterior end is usually pointed, but may be rounded; the blepharoplast is large and is situated close to the posterior end; the nucleus is situated about the middle of the body.

Trypanosoma cruzi appears in the peripheral blood of the human in two forms: (1) Small, slender forms, with a large blepharoplast, and an oval nucleus. This form is actively motile, and moves rapidly across the microscopic field. (2) Larger forms, with a smaller spherical blepharoplast and a spherical nucleus. This form has an active motion, in the form of the letter S, but scarcely changes its position in the microscopic field. Chagas considers the first form as neutral and the second form as sexual; but Brumpt considers the first form as young and the second form as adult trypanosomes.

Virulence.—The virulence varies. Guinea pigs die in from 5 to 10 days when bitten by infected Triatoma; but on repeated passage the virulence is lowered until the duration of the disease is about two months. Passage through monkeys raises the virulence again. The virulence is raised by passage through mice.

Cultivation.—Chagas cultivated *Trypanosoma cruzi* on Novy-Mac-Neal medium. The culture grew readily, and developed crithidial forms which lived two months. The first and second subcultures grew;

and guinea pigs were infected by injection of cultures. The organism grows readily in the beginning but is difficult to carry in culture; and no one seems to have obtained growth beyond the second subculture.

Occurrence in Lower Animals.—Armadillos commonly have *Trypanosoma cruzi* in their blood, even when they are far from human habitations; and Chagas found 40 to 50 per cent. of armadillos infected in regions where Chagas' disease is found. The animals are not sick. Cats are occasionally found infected in houses where there are cases of the disease.

Experimentally, monkeys are susceptible, but the susceptibility is commonly limited to young monkeys and to certain species: marmosets are susceptible. The incubation period is from 10 to 14 days, and the monkey dies in from 3 to 4 weeks.

Mice are susceptible, the incubation period at first being from 10 to 14 days; but with repeated passage through mice the virulence is raised and the incubation period is reduced to about 6 days. In the beginning, the mice generally recover; but after the strain has become more virulent, the mice die in from 2 to 4 weeks.

In rats, the incubation period is from 6 to 18 days, and the animals usually recover. In rabbits, the incubation period is about 2 weeks, and the infection is transient. The disease is usually chronic in guinea pigs, and recovery is frequent; but the infection may be acute and cause death. Dogs are susceptible.

Development in the Vertebrate Host.—When blood containing *Trypanosoma cruzi* is injected into a susceptible animal, part of the trypanosomes circulate in the blood as trypanosomes, and part of them enter the muscle fibers and the neuroglia cells and there develop the leishmania form. When the trypanosomes from the digestive tract of the invertebrate host are injected into a susceptible animal, all of the trypanosomes enter the muscle fibers and neuroglia cells and there develop the leishmania form. These leishmania forms multiply until the cells containing them are converted into cysts containing these forms. In four or five days the leishmania forms begin to assume the trypanosome form; the cysts formed of the muscle fiber or neuroglia cell rupture, and the trypanosomes gain access to the blood, appearing in the peripheral blood as long, slender, actively motile trypanosomes. About the eighth day the larger trypanosomes appear in the peripheral blood.

Development in the Arthropod Host.—The cycle of development in *Triatoma megista* is typical of the development in other arthropods. The large trypanosomes taken into the stomach of *Triatoma megista* in any stage of its development (larva, nymph, or adult) pass to the intestine, assume the crithidia form, lose the flagellum and become spherical in about twenty hours, and divide. They then develop a flagellum and, in about forty-eight hours, appear as crithidia forms in the midgut, and multiply rapidly. In ten days to several weeks they develop into metacyclic trypanosomes in the hind-gut. These metacyclic trypanosomes persist in the intestinal contents of the bug for a long time, probably

throughout the life of the bug. In bedbugs, the infection lasts only about two months.

In keeping with his belief that there are sexual and neutral forms of the trypanosome in the blood of the vertebrate host, Chagas describes two methods of development in the arthropod host: (1) the asexual method as described above, giving rise to parasites in the hind-gut; and (2) a sexual method of development, giving rise to parasites in the hind-gut, in the body cavity, and in the salivary glands.

Twice Chagas saw flagellates in the body cavity, and three times in the salivary glands of bugs he caught. The infection is not transmitted to the young through the egg.

Epidemiology.—(*a*) SOURCE OF INFECTION.—***Man*** is a source of infection, especially children during acute attacks of the disease when trypanosomes are fairly numerous in the peripheral blood. In the chronic cases, trypanosomes are scarce in the peripheral blood, though they are present in 5 or 10 c.c. of blood.

Chagas found trypanosomes in the blood of a *cat*, in a house in which there were triatomes; and Torres considers that the cat acts as a reservoir for the infection.

Chagas considers that the *armadillo* serves as a reservoir for the infection. Armadillos are common around human habitations; and Chagas found 40 to 50 per cent. of armadillos, caught in regions where Chagas' disease is found, infected with *Trypanosoma cruzi*.

(*b*) MODE OF TRANSMISSION.—Chagas found *Triatoma megista* to be the transmitter of the infection in Minas Geraes; and Torres says that larvæ and adults of *Triatoma megista*, feeding on man and cats, is the only way in which *Trypanosoma* is transmitted in Brazil.

The triatomes live in the houses which have cracks in the walls; they also live in outbuildings, especially chicken houses, where they live on the blood of chickens. *Triatoma megista* may live in the burrows of armadillos; but *Triatoma geniculata* is the bug usually found in such burrows. The larvæ of *Triatoma megista* are about the size of an ordinary bedbug; and larvæ, nymphs and adults bite and spread the infection. The bugs do not bite until night, after the lights are out, when they come out and bite the sleeping people. The bite is not painful; and Chagas saw about twenty larvæ, nymphs and adult bugs biting a child that was sleeping calmly. The bugs do not come out in the day, but they will bite if a person leans against the wall for any length of time. They spread very rapidly from house to house, and from town to town.

Tejera found *Rhodnius prolixus* to be the transmitter of the infection in Venezuela. This bug has very much the same habits as *Triatoma megista*. It lives in the grass houses, and especially in the grass roofs of houses, where it multiplies abundantly; but it is rarely found in houses with tile roofs. It comes out at night, after the lights are out, to bite. It is frequently found in the burrows of armadillos and other animals.

Chagas showed that the infection can be transmitted by the ***bite***

of *Triatoma megista*. Torres transmitted the infection to kittens by the bite of *Triatoma megista*, the bugs being confined in tubes, and biting through the gauze covering the end of the tube, so that soiling with feces was prevented. Of 35 bugs tested in this way, 19 transmitted the infection, and 13 failed to transmit it. Torres failed to get infection by depositing the feces of infected bugs on the unbroken skin of animals; and he is of the opinion that the infection is transmitted in nature by the bite of the bug.

Brumpt is of the opinion that the usual mode of infection is through the *dejections* of the bug. The bugs defecate freely when biting; and, as they commonly bite on the lips and cheeks (hence the native name "barbeiro," the barber), the dejections of the bug may soil the buccal mucosa, although there may be no evidence of it. Brumpt considers that the infection may also pass through the unbroken skin or through the wound made by the bite. He failed to transmit the infection to monkeys by the bite of infected bugs or by placing the feces of infected bugs on the skin; but a monkey was infected by placing the feces of infected bugs in the conjunctival sac. In another set of experiments, there was one infection through the unbroken skin. Mayer and da Rocha-Lima could not determine experimental transmission of the infection through the bite of infected bugs or ticks.

Tejera succeeded in infecting mice by allowing infected *Rhodnius prolixus* to bite them; but of four mice bitten, only one became infected, and that mouse had only a few trypanosomes in its blood. He infected mice by the instillation of intestinal contents of infected bugs into the conjunctival sac, into the anus, and on the genital mucosa.

While *Triatoma megista* is the transmitter of the infection in Brazil, and *Rhodnius prolixus* is the transmitter in Venezuela, *Trypanosoma cruzi* is not strictly adapted to these two arthropod hosts, but may complete its cycle of development in a number of other arthropods, and they may transmit the infection. In nature, it completes its cycle of development in *Triatoma megista, Triatoma geniculata* and *Rhodnius prolixus; Triatoma megista* and *Rhodnius prolixus* transmitting the infection to man, and *Triatoma geniculata* transmitting the infection in armadillos. Brumpt succeeded in infecting other species of Triatoma, including *Triatoma sanguisuga* from Texas; bedbugs; and a tick, *Ornithodorus moubata*. Neiva transmitted the infection to dogs, through the dog tick, *Rhipicephalus sanguineùs*, from experimentally infected dogs. Brumpt considers that the common bedbug, *Cimex rotundatus*, of Brazil, may be as important as *Triatoma megista* in the transmission of the infection.

The distribution of *Trypanosoma cruzi* does not correspond to the distribution of Chagas' disease. In Brazil, armadillos are infected, though far from human habitations; and *Triatoma geniculata* transmits the infection from armadillo to armadillo. Kraus and Rosenbusch found triatomes infected with *Trypanosoma cruzi* in the mountainous regions of Argentina, but they did not find any cases that they could be sure were Chagas' disease. Maggio did not find Chagas' disease; but he

found triatomes infected with flagellates which behaved in every way as *Trypanosoma cruzi* when injected into animals.

Brumpt discusses this difference in the distribution of *Trypanosoma cruzi* and Chagas' disease. Bugs, living on lower animals, may become adapted to life on man; so, some bugs (*Triatoma megista and Rhodnius prolixus*) can keep the infection going in man. Other bugs do not become adapted to life on man, but keep the infection going in lower animals (as with *Triatoma geniculata* and armadillos; and probably the bugs in Argentina transmit the infection in some lower animal).

(*c*) SUSCEPTIBILITY.—There is no difference in sex or race susceptibility. Young children are more susceptible than are adults; and the disease commonly runs an acute course in children, while in adults the disease is commonly chronic from the beginning.

Symptomatology.—Chagas divides the disease into two clinical forms: acute and chronic. In the acute cases the symptoms are severe, and the parasites are found on direct examination of the blood.

ACUTE FORM.—This form of the disease generally affects children under one year of age; and it is seen in children only a few months old.

The period of incubation is about ten days. The disease begins with fever, the temperature going as high as 40° C. (104° F.); the fever is continuous, with a slight morning remission at times. There is a peculiar puffiness of the face; and, early in the disease, on palpation, the skin of the face gives a characteristic crepitation, which has been likened to that produced by rubbing sheets of gelatin together. The thyroid gland is enlarged, also the lymph-glands, especially in the axillary and inguinal regions. The liver is somewhat enlarged; and the spleen can be felt below the border of the ribs. There may be serous effusion into the pleural, pericardial and peritoneal cavities.

Trypanosomes are found in fair number in the peripheral blood during the fever.

Chagas divides the acute form into two groups: (1) the meningo-encephalitic form, in which there is nervous system involvement with resulting idiocy, paralyses or imbecility; and (2) a group in which the nervous system is not involved.

The acute form lasts ten to thirty days; and the child may die—at times with the clinical picture of meningo-encephalitis—or the disease may pass into the chronic form. Chagas says that spontaneous recovery does not occur at this time.

CHRONIC FORM.—The acute form may pass into the chronic form, or in adults the disease may be chronic from the beginning.

Chagas divides the chronic form into five clinical forms, according to the predominant symptoms: (1) the *pseudomyxedematous form;* (2) the *myxedematous form;* (3) the *cardiac form;* (4) the *nervous form,* and (5) chronic forms with *persistent acute and subacute manifestations.*

(1) In the *pseudomyxedematous form* there is a slight mucous infiltration of the subcutaneous tissue, without the solid edema and parchment-like skin, or skeleton changes of myxedema. There is a violet—

or blue—bronzing of the skin. The thyroid and lymph-glands are enlarged. Convulsions are common.

(2) In the *myxedematous form* there are the solid mucous infiltration of the subcutaneous tissue, the mental deterioration or arrested development, and the skeletal changes of myxedema. The parchment-like, dry skin pits on pressure. The lymph-glands are enlarged, and the thyroid gland is atrophied. Inflammations of the eyes, as conjunctivitis, are common.

(3) The *cardiac form* is an important one; and Chagas considers that the symptoms are due to the presence of the parasites in the muscle fibers, with the inflammatory reaction when the parasites escape from the muscle fibers, and the resulting myocarditis. Marked arhythmia is an important symptom, especially in children; while extrasystole is common in older persons. Heart-block, with the pulse below 30 per minute, is not uncommon. Sinus irregularity is common in children, possibly due to vagus disturbance or to the myocarditis. Mackenzie's rhythmus nodalis may occur.

There is danger of death in asystole in cases of the cardiac form.

(4) In the *nervous form* there is great variation in the localization of the symptoms, on account of the irregular scattering of the foci of parasites in the brain. Diplegias are the most common. There may be paralysis or a spastic condition of the lower extremities, with athetosis in the upper extremities; there may be choreiform movements, or contractures in the lower extremities may be present. The reflexes may be increased. There may be disturbances of speech, amounting to aphasia, or pseudo-bulbar paralysis. There may be paralysis of the ocular muscles. There may be convulsions when there is extensive involvement by foci in the cerebral cortex. Other convulsions appear to be due to hypothyroidism, and thyroid extract relieves them; these cases are in children or older persons with arrested development (infantilism).

(5) In the *form with acute and subacute exacerbations,* there is fever and other acute symptoms in addition to the symptoms of any one of the chronic forms. In adults it is usually the cardiac form, and there are enlarged thyroid and evidences of suprarenal insufficiency. There are few parasites in the blood.

The exacerbations are not like severe acute attacks; and Chagas thinks they may be due to re-infection.

Under the name of *metaschizotrypanotic manifestations* Chagas includes the cases of infantilism with long-standing goiter and other sequelæ of the disease.

Diagnosis.—Clinical Diagnosis.—In the endemic area, the physical findings of enlarged thyroid, with a myxedematous condition of the skin, irregularity of heart action, bronzing of the skin and paralysis, would lead one to suspect Chagas' disease. The acute cases may be mistaken for *malaria,* while the chronic cases may be mistaken for *uncinariasis;* examination of the blood and feces is necessary for differentiation.

The chronic cases may be mistaken for *goiter*, which is common in many parts of South America; and the question has been raised whether the thyroid changes are a part of Chagas' disease, or are endemic goiter in persons with Chagas' disease. While Kraus and Rosenbush found triatomes infected with *Trypanosoma cruzi* in the mountainous regions of Argentina, they did not find any acute cases of Chagas' disease, but they found cases of cretinism and goiter.

Chagas holds that the thyroid involvement is characteristic of the disease. He saw the disease, with thyroid involvement, in four children, all less than three months old and exclusively breast fed, thus ruling out goiter due to drinking water. Thyroid involvement is always present; and the thyroid is always enlarged, except in the myxedematous form, where the thyroid is atrophied and the symptoms of thyroid insufficiency are very marked. Thyroid enlargement is found in children and adults in Triatoma infested houses, and not in houses free of Triatoma.

The nervous form must be differentiated from *syphilis*.

A definite diagnosis is possible only on the finding of the trypanosome.

Laboratory Diagnosis.—In the acute cases trypanosomes are found in the blood in fair number. When brain symptoms develop, the number of trypanosomes increases in the peripheral blood until death. When the disease goes on to the chronic form the number of trypanosomes decreases in the peripheral blood, until they are no longer found except during acute or subacute exacerbations.

Trypanosoma cruzi is very fragile; and it is difficult to make a smear in which the trypanosomes are not torn. Tejera mixes a few drops of blood with some 10 per cent. sodium citrate solution to prevent coagulation, then puts a small drop of the citrated blood on a clean slide, exposes it one-half minute to the vapor of a 2 per cent. osmic acid solution, and then smears out in the usual way. He stains fifteen minutes by Pappenheim's panoptic method.

Trypanosomes may not be found in the peripheral blood longer than two to three weeks after the onset of fever; but they can be demonstrated in the blood of chronic cases by the injection of 5 to 10 c.c. of blood into a guinea pig or a young monkey. Mice and rats are suitable for demonstrating the trypanosome by injection of blood, but mice may have *Trypanosoma duttoni* in their blood, and rats frequently have *Trypanosoma lewisi* in their blood; and these trypanosomes might lead to confusion.

The guinea pig is the most satisfactory of the available animals for demonstrating *Trypanosoma cruzi* by the injection of blood. At times the trypanosomes are so scarce in the peripheral blood of the pig that they cannot be found on direct examination of the blood. Chagas advises examining for parasites in the endothelial cells of the capillaries in the lungs of the pig. Brumpt suggests xeno-diagnosis, that is, allowing *Triatoma megista* to bite the pig, and, as the digestive tract of the bug is a good culture tube for the parasites, they will multiply there and can be found by examining the intestinal contents of the bug.

When parasites are not found in the blood, a postmortem diagnosis may be made by examining for the parasites in the tissues, especially the heart muscle, the muscles of the legs, arms and back, and the brain.

The blood shows secondary anemia. In the acute cases there is a slight leukocytosis, with an increase in the percentage of mononuclears; in the chronic cases, there is no change in the leukocyte count. The Wassermann reaction is negative.

Complications and Sequelæ.—There are no special complications. The sequelæ are important, as so many of the cases occur in young children. The sequelæ are enlarged thyroid with hyperthyroidism, infantilism, cretinism, paralysis, idiocy and aphasia.

Treatment.—No treatment has any effect on the course of the disease. Symptomatic treatment, especially for the hypothroidism, may lessen the severity of some of the symptoms.

PROPHYLAXIS.—(*a*) *Source of Infection.*—Persons suffering with the disease should be **protected from the bites of Triatoma and Rhodnius.**

Armadillos (and possibly other wild animals) and cats act as reservoirs for the infection; but no practical results can be expected from destruction of these animals.

(*b*) *Mode of Transmission.*—The best results are obtained by **preventing Triatoma and Rhodnius from living in the houses and feeding on the people.** Tejera's finding that *Rhodnius prolixus* lives and breeds in the grass roofs of houses—but not in houses with tile roofs—and the finding of *Triatoma megista,* especially in the poor houses in Minas Geraes, indicates that **better construction of houses** would go far toward eliminating the bugs from human habitations.

Triatoma is said to be attracted by articles made of leather.

Sulphur fumigation and whitewashing of the houses have been recommended for the destruction of the bugs.

(*c*) *Susceptibility of the Population.*—The bugs bite at night, and the adults can fly; so it is necessary to **sleep under nets,** as well as to **prevent the bugs coming up the legs of the bed or along the hammock ropes.**

Nothing is to be expected from vaccination.

Prognosis.—In the acute cases the prognosis is bad, as they die or pass into the chronic form. The prognosis is bad in the cardiac form, and sudden death may occur. The sequelæ are permanent.

Mechanism of the Disease Process.—The trypanosomes inoculated by the bug—either by the bite, or from the feces through the mucous membranes or skin—enter the tissue cells, especially the muscle and neuroglia cells, lose their flagellum and assume the leishmania form. These leishmania forms multiply by simple fusion until the infected cells come to have the appearance of cysts filled with the parasites. After a time the cells rupture, and trypanosomes appear in the peripheral blood. The multiplication of the parasites in the muscle fiber simply separates the fibrils and bulges the sarcolemma, without other damage to the fiber. There is no inflammatory reaction about the in-

fected cell until it ruptures or the parasite dies, the inflammatory reaction being due to the toxin set free.

The toxin causes the early symptoms of the acute form; and it causes the fatty degeneration of the liver, the meningitis, and the changes in the thyroid and suprarenal glands. The myocarditis is due to the damage done to the heart muscle by the development of the parasites in it, and the waxy degeneration of the muscle fibers caused by the toxin. The changes in the brain substance are due to the localization of the parasites in the brain, as well as to the toxin.

IMMUNITY.—Nothing is known regarding immunity in man. Mayer and da Rocha-Lima found that rats, guinea pigs and rabbits were immune after recovery from infection; and Brumpt found that recovered mice were immune eight months after recovery. Serum from Mayer and da Rocha-Lima's immune animals did not protect other animals against infection when injected twenty-four hours before or at the time of inoculation. Mayer and da Rocha-Lima found that relapse occurred; and one guinea pig relapsed after a latent period of eight months.

CAUSES OF DEATH.—Failure of the heart is a common cause of death. In the acute cases, death may result from asthenia or from meningo-encephalitis.

Pathology.—MACROSCOPIC.—There may be bronzing of the skin; and there is often a myxedematous condition of the subcutaneous tissues. The axillary and inguinal lymph-glands are considerably enlarged, the cervicals less so. The thyroid gland is generally enlarged and hard, but it may be atrophied.

There is a yellowish serous fluid in the pleural, pericardial and peritoneal cavities. The mediastinal lymph-glands are enlarged; the pericardium is congested, and may be hemorrhagic; the heart shows an intense myocarditis.

The liver is enlarged and fatty; the spleen is moderately enlarged, congested and soft. The mesenteric lymph-glands are enlarged; the suprarenal glands are congested.

The most marked changes are in the meninges and the brain. The cerebrospinal fluid is increased in amount; the dura is congested and is adherent to the bone. The pia is thickened and edematous, and there may be a gelatinous exudate in the subarachnoid space. There are areas of meningitis. There may be areas of chronic encephalitis. There may be adhesions over the spinal dura.

MICROSCOPIC.—In the *heart*, the parasites are abundant in the muscle fibers, many of the fibers forming cysts filled with the parasites. When a cyst ruptures, some of the parasites are found free; others in phagocytes. In acute cases there is diffuse inflammatory reaction in the interstitial tissue; in chronic cases there are localized areas of inflammatory reaction. The small blood-vessels of the heart show perivascular round-cell infiltration. There may be pericarditis or endocarditis; but no parasites are found in the lesions.

The *thyroid gland* shows sclerosis and round-cell infiltration, the acini

being small or dilated to form cysts; and there are frequently areas of calcification. There is increase in the number of cells in the interstitial islands of cells. No parasites are found in the thyroid.

The *liver* shows marked fatty degeneration; and in acute cases the degeneration may be as marked as in yellow fever. The *suprarenals* are congested and fatty, and show inflammatory reaction; later they show degeneration. The parasites are not usually found in the suprarenal glands; but they may be found either in the cortex or the medulla. The *kidneys* may show inflammatory reaction.

In the *central nervous system,* the meninges and blood-vessels show a mild perivascular round-cell infiltration, of the same type as is seen in African trypanosomiasis. In the brain, there are scattered foci, seen with low magnification, in which the parasites are collected. The neuroglia cells are packed with parasites, and swell to form cysts, without any reaction around the cell. When the cell ruptures, there is a collection of mononuclear and polymorphonuclear cells which take up the parasites. No parasites are found in the nerve cell.

The *skeletal muscles,* especially of the legs, arms and back, are commonly invaded by the parasites. As long as the parasites remain in the muscle fibers there is no inflammatory reaction. When the fiber ruptures, and the parasites escape, there is inflammatory reaction around the area, and the inflammatory cells pass into the ruptured muscle fiber. There is round-cell infiltration about the blood-vessels in the muscles.

The *testicles* show inflammatory reaction, and the epithelial cells lining the seminal tubules are infected with the parasites; and parasites may be found in the spermatozoa. There is round-cell infiltration of the interstitial tissue, and there is round-cell infiltration about the blood-vessels. Vianna found trypanosomes in the semen of two of six infected guinea pigs.

The *ovaries* are sclerotic and contain cysts, but no parasites are found.

The parasites are found in the endothelial cells in the capillaries of the *lungs.* Da Rocha-Lima found the parasites in fatty and connective tissues, the spleen, bone marrow, lymphatic glands, and in the unstriped muscle in the walls of the *intestine* and the *arteries.*

Secondary infections are not common.

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CHAPTER XXXI

ENTAMEBIC DYSENTERY

By Sidney K. Simon, A. B., M. D.

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Definition.—Entamebic dysentery is a widespread disease of infectious origin, caused by invasion of the structures of the large bowel by the *Entameba histolytica*, a specific protozoal organism belonging to the group of Rhizopoda. The clinical course of the disease is marked by a considerable irregularity and inconstancy of symptoms. There is an acute or subacute phase, characterized by frequent, scanty evacuations, often containing mucus and blood, by abdominal pain, tenesmus and general bodily depression. This phase is followed by variable periods of latency, during which the clinical phenomena remain, for the most part, in abeyance. Anatomically, the most characteristic feature is an undermining of the submucosal layer of the large bowel. Subsequently, extension of the ulcerative process takes place into the mucosa and, with less frequency, into the muscular and peritoneal coats. Remote infections, usually ending in suppuration, occur not uncommonly in the liver spleen and even in the brain, the specific organism reaching

these organs by way of the blood stream from the original focus of infection in the intestinal tract.

Nomenclature.—The disease has been described in the past under a number of different names, and even at the present time disagreement still manifests itself in respect to the nomenclature. The term "amebic dysentery" was first used by Councilman and Lafleur in 1891 and, although prior to that time ameboid organisms had been repeatedly discovered in dysenteric stools, the condition itself had not been recognized as a distinct clinical entity. The further classification, made in recent years, describing the organism as a separate species, under the genus "*Entameba,*" has justified the change of the original title into the more correct form "entamebic dysentery," while the general state of infection induced by the specific organism should be designated more properly as "entamebiasis," than as "amebiasis." In this manner, an intestinal entamebiasis is to be regarded as synonymous with entamebic dysentery, although the latter designation is to be preferred, because of its longer and more general usage.

Such titles as "amebic colitis," "entamebic colitis" or "entamebic enteritis," commonly used in the past, should be discarded entirely, since they serve to create confusion. Likewise, the use of the word "tropical," in connection with the disease, is to be especially condemned as misleading. While it is true that infections with the *Entameba histolytica* are frequently encountered in tropical or sub-tropical countries, the fact must not be overlooked that bacillary dysenteries also occur with great frequency in the tropics. Moreover, it is now fully recognized that entamebic dysentery is a disease of world-wide distribution, with little respect for locality. There can be no justification, therefore, for the inference that the special type of dysentery caused by the *Entameba histolytica* is necessarily of tropical origin.

ETIOLOGY

Predisposing Causes.—While the direct cause of entamebic dysentery and of other allied morbid conditions lies in infection with the *Entameba histolytica,* certain factors undoubtedly play a part in rendering the tissues more susceptible to invasion by the specific organism. It is to be recalled in this connection that the mere presence of the parasites within the lumen of the intestinal tract does not in itself imply actual tissue invasion. Conditions favorable to the vegetative state of the organism must exist in each instance before penetration of the intestinal wall is possible on a measureably large scale. In some individuals, a definite degree of immunity against the invasion of the organism has been shown to exist, even in the face of persistent parasitation of the intestinal tract with the pathogenic entameba. The following causes are to be considered as predisposing factors in the disease:

Meteorological Conditions.—The rate of prevalence of the disease in any locality is, to a considerable extent, influenced by meteorological

conditions. In endemic regions, the maximum number of cases occur during the *wetter seasons* of the year, that is, during the late summer or fall, while comparatively few cases, on the other hand, are met with during the colder and dryer months from December to May. In the Philippines, for example, Strong observed that the greatest number of cases appeared between June and September, the majority shortly after the heavy rains had begun. Rogers, likewise, concluded that the prevalence of dysentery in India closely corresponds with the rainy season of the year, the curve declining steadily with the cessation of the rains late in October. Heavy, and especially prolonged, rainfall favors the transmission of the infection in two ways:

(1) By preserving the life of the cyst, which succumbs readily, if deprived of a liberal amount of moisture.

(2) By causing the cyst to be washed out of the soil and out of stagnant pools, thus opening up new avenues of infection.

The influence of *temperature* upon the spread of the disease is of less importance than precipitation, although outside of the body encysted organisms undoubtedly thrive best in a hot, as well as a moist, atmosphere. Relapses of the disease occur more or less independently of meteorological conditions. Acute relapses, for example, frequently occurred during the very coldest periods of the winter, in the case of some of the author's patients. Brown believes, in fact, that the tendency to relapse is augmented in cool weather, inasmuch as the general clinical manifestations of dysentery are evoked in a certain measure by the lowering of the surface temperature of the body.

In a careful record of cases, the author has found that the incidence of the disease is greatest during April and May, with a steady decline during the summer months, and a further rise in the early fall, extending well into November. This bears out Brown's contention that relapses are especially prone to occur during the cool spring or autumn weather, rather than during the periods of summer heat.

ALTITUDE.—Entamebic dysentery is essentially a disease of low-lying and poorly drained soils. As greater altitudes are reached, the infection becomes less manifest. The effect of altitude on the incidence of the disease is shown in a characteristic way in high mountainous regions situated in the tropics. In the valleys and lowlands, and particularly along the undrained stretches of sea-coast, a far greater number of cases are encountered than is the case upon the mountainsides, even within the same degree of latitude. In the tropics both the native population and the resident foreigners are, as a rule, cognizant of the better sanitary conditions which prevail in general in the greater altitudes, and are prone to select these regions as residences whenever possible, in preference to the valleys or the sea-coast.

GEOGRAPHICAL DISTRIBUTION.—Until rather recent times the disease was universally associated with the tropics. While the transmission of entamebic infections is fostered by certain climatic and sanitary conditions incidental to warm countries, it has been shown that the infection

is capable of being disseminated with great facility in many regions outside of the tropics as well. The malady is therefore not to be considered as indigenous to any particular locality, but, on the contrary, is to be viewed as a widely distributed infectious condition, reaching out into practically every part of the habitable world.

In strictly tropical countries as India, Egypt, Asia Minor, Sumatra, Siam, Central America, parts of South America, the southern provinces of China, and the Philippines, all types of the disease are extensively prevalent among the native population, and many victims are claimed each year among resident foreigners as well.

In the United States, the disease has shown a steady increase during the past fifteen years, and sporadic cases have now been reported from practically every section of the country. In the South, and especially in that portion bordering on the Gulf of Mexico, where semitropical conditions prevail, the disease is endemic. An acute outbreak of the malady was noted by Craig in 1916 among the American soldiers stationed on the Mexican border. During the recent world conflict, a number of sporadic cases made their appearance among the Allied troops in France. The infection was no doubt brought to that country by members of the Colonial soldiery, who served as carriers. Further extension has been noted more recently in France and in England among the civilian population, and it is highly probable that the number of cases in the United States will continue to increase during the next few years as a result of the return to our shores of troops who have acquired the infection overseas.

RACE.—No class of individuals may be considered immune to entamebic infection. In fact, racial susceptibility does not play a very prominent rôle in the etiology of the disease. In the tropics, it is true, the natives seem more prone to infection than do the whites, but this is the result largely of the different standards of sanitation and hygiene which prevail among these races in all warm countries. When individuals have been exposed to the infection for long periods of time, a certain degree of immunity is established. For this reason, a greater degree of virulence is exhibited in the case of foreigners who have recently taken up their abode in the tropics.

Out of a series of 217 cases compiled from his own records, the author found 165 whites and 52 negroes to be affected. This ratio of approximately three to one corresponds with the population figures for the City of New Orleans and vicinity, from which most of the cases were derived.

SEX.—In the same series of 217 cases as above, 180 were males and only 37 were females. A similar disproportion between the sexes has been noted by other observers. Futcher, for example, found 108 males and only 11 females in his 119 cases. Among Strong's 200 patients, no fewer than 177 were males. Men undoubtedly suffer more exposure to the infection than do women, because of their more active life and the greater chances which they incur in outdoor occupations.

AGE.—Among the author's patients, the oldest recorded was sixty-eight years and the youngest, fourteen years, with an average of thirty-four years for the entire 217 cases. In view of the similarity of these figures to those of other observers, the greatest susceptibility to the disease would seem to lie between the third and fourth decades of life, which corresponds to the period of greatest economic activity. No stage of life is, however, to be regarded as immune to the disease. Kartulis, from his observations in Egypt, became convinced that entamebic dysentery occurs with almost equal frequency at all ages. Nevertheless, the malady is without doubt comparatively rare in infancy and early adolescence.

De Buys found only 4 cases among 300 children in an outdoor pediatric clinic in New Orleans. He states, however, that although entamebic dysentery is undoubtedly a rare disease in children, this is not because those of tender years are less susceptible to infection, but is due rather to the fact that they are exposed to a much lesser extent to the etiological factors which bring about infection in the adult.

Cannata was similarly able to find but 100 children between the ages of two and fifteen affected with the disease, out of a total of 6,000 examinations made in one of the endemic centers in Brazil.

All authorities are agreed that the prognosis is favorable in children, since complications are usually lacking.

OCCUPATION.—Occupation plays a considerable rôle in the etiology of the disease. The worker who is compelled to seek employment in heavily infected regions, and those whose occupation is especially apt to bring them into contact with a contaminated water supply are, without doubt, subjected to greatly increased chances of infection.

In the author's series of cases, the greater number appeared among individuals engaged in such occupations as logging, ditching, truck farming, railroad construction, civil engineering and others fields of work which carried the individual into swampy regions.

Wenyon, in the course of a large series of examinations conducted among British troops in the tropics, found that camp cooks showed the highest relative percentage of infection with *Entameba histolytica*. Among 398 cooks examined, 9 per cent. were found to harbor encysted organisms in the stools. Contrasted with this, the general percentage of infection among 1,979 troopers in the same camps was found to be only 5.3. Wenyon acknowledges his inability to explain the greater susceptibility to infection shown by cooks, unless the cause may be traced to the large number of flies which, in the tropics, are always to be found in the neighborhood of the cook-houses of army camps.

UNSANITARY CONDITIONS WITHIN THE HOME.—Overcrowding and unsanitary conditions within the home in general predispose to this and to other infections, by helping to impair the resisting forces of the body. House-screening is a highly necessary sanitary measure in the tropics, since the large number of flies and other insects found in these regions become important factors in the transmission of disease. Wenyon has

shown that the cysts of the *Entameba histolytica* may be swallowed by flies, and redeposited upon food and drinking water without losing their viability. It is especially necessary, therefore, that kitchens and dining halls in all tropical and subtropical regions be safeguarded against the access of flies and insect life in general.

Overfatigue.—This attains some importance as a predisposing factor, especially in times of war, where groups of individuals who are otherwise exposed to entamebic infection are in addition forced to undergo prolonged and unaccustomed physical strain. It is a matter of common observation that when troops are engaged in active military operations, the susceptibility to entamebic infection is greatly increased, while a decrease in the number of cases is shown during periods of relative inactivity in military camps. Similarly, in civil life, individuals who harbor infection with the *Entameba histolytica* more readily suffer relapses of the malady when subjected to undue physical or mental strain than is the case with those who are spared the effects of overfatigue.

The Influence of Foods and Diet.—Since the soil becomes the chief repository for the protozoal cysts after they are discharged from the body, a special element of danger is occasioned by the use of vegetables and fruit which have come into intimate contact with the soil during growth. Infection in tropical countries is undoubtedly conveyed in no small part by this means alone. In the case of individuals already affected with the disease, dietary indiscretions are not infrequently followed by a prompt outbreak of symptoms. In the same way, the sudden appearance of the entamebic form of dysentery among soldiers in the field can be traced, not uncommonly, to a poorly equipped or inefficient commissary.

Exciting Cause: The Organism.—Classification.—The direct causal agent of entamebic dysentery and its allied morbid states is the *Entameba histolytica*, a protozoal organism belonging to the genus *Entameba*, a subclass of the *Sarcodina* or *Rhizopoda*. The *Rhizopoda* embrace a large number of species, the majority of which are free-living and incapable of carrying on a parasitic mode of existence in man or in the lower animals. Several attempts have been made within recent years, notably by Hartmann, Calkins, Craig and others, to establish some uniform basis for the classification of the entire order of *Ameba*, including the parasitic amebæ of man. Though complete agreement is lacking, Calkins',classification has been the one most generally accepted. Calkins divides the old genus Ameba into seven distinct genera, as follows: *Ameba, Vahlkamfia, Nagleria, Craigia, Trismastigameba, Entameba and Parameba.*

Of these, according to Craig, only two contain true parasitic species, namely, the *Entameba* and the *Craigia*, while another, the *Vahlkamfia*, may become parasitic for a brief period of time. In the following discussion, only those organisms will be considered which possess some special significance in clinical medicine.

(1) Genus Entameba (Leidy, 1875; Emend, Cassigrandi and Barbagallo, 1895).
Species: *Entameba histolytica* (Schaudinn, 1903; Emend, Walker, 1911).
Entameba coli (Lösch, 1875; Emend, Schaudinn, 1903).
Entameba nana (Wenyon, 1915).
Entameba gingivalis (Gros, 1849; Emend, Prowazek, 1904).

The genus *Entameba*, first correctly interpreted by Cassigrandi and Barbagallo, comprises a group of strictly obligatory parasites inhabiting the intestinal tract of man as well as that of the lower animals. The characteristic features of this genus, as contrasted with other genera of ameba, are mainly as follows: They are of relatively small size varying between 5 and 80 microns in diameter. The cytoplasm, or cell-body, is separated into two distinct portions, the ectoplasm and the endoplasm, which become especially prominent when the organism is in motion.

The ectoplasm forms a densely reticulated structure and presents a glass-like and refractile appearance. The endoplasm, on the other hand, is coarsely granular, and its consistency is more fluid and plastic than that of the ectoplasm. A number of non-contractile vacuoles are usually contained within the meshes of the endoplasm in addition to a variable amount of granular material which consists, for the most part, of food particles, crystals and bacteria. The nucleus occupies an eccentric position within the endoplasm and, in some species, cannot always be made out distinctly in the living parasite. Its structure becomes distinct, however, in stained specimens, and is found to vary considerably, even in the same species. These variations are brought about by relative differences in the amount of chromatin, which is distributed in various forms to the body of the nucleus as well as to the nuclear membrane. Reproduction takes place in the vegetative stage either by simple division or by schizogony, with the production of a varying number of daughter cells. An important reproductive phase likewise occurs within the cyst. Cultivation of the organisms contained in this group on artificial media has, up to the present time, never been successfully accomplished.

The genus *Entameba* contains several species, of which, according to Craig, no less than twenty-six have been described at various times as parasitic in man. Many of these species have been shown to be identical, the confusion which arose in the past being due to the variations in morphology which occur during the different stages of the life cycle of the organisms.

Entameba histolytica.—This species is now universally recognized as the exciting cause of a characteristic series of morbid lesions occurring, for the most part, in the large intestine, but also, although to a lesser extent, in other organs, such as the liver, the spleen and the brain. The pathogenic nature of the organism now known as *Entameba histolytica* was first clearly recognized by Schaudinn, in 1903, although other research workers, principally Jurgens, Councilman and Lafleur, Strong

and Musgrave, had, at an earlier period, studied and described disease-producing amebæ under the terms *Ameba coli* and *Ameba dysenteriæ*.

Schaudinn drew a sharp line of distinction between pathogenic and non-pathogenic entamebæ. For the former he proposed the name *Entameba histolytica*, because of its marked tissue-invasive power; while for the latter, the name *Entameba coli* was suggested, on account of the frequent presence of this organism as a harmless parasite in the colon. Schaudinn's classification has been accepted by practically all observers, although some of his original interpretations concerning the morphology and life cycle of the organism have since been proven to be erroneous.

In 1907, Viereck announced the discovery of a supposedly new species of pathogenic entameba which he had observed in the stools of a dysentery patient from Africa. This species was entitled *Entameba tetragena*. A few months later, Hartmann and Prowazek published a

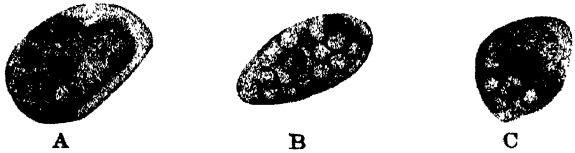


FIG. 1.—ENTAMEBA HISTOLYTICA. (After Roemer. From C. F. Craig, "The Parasitic Amebæ of Man," J. B. Lippincott Co.)

A. Entameba histolytica, showing nucleus and two red blood-corpuscles.

B and C. Entameba histolytica filled with red blood-corpuscles. Note the well-defined ectoplasm and endoplasm.

description of the same organism under the name *Entameba africana*. In accordance with the rules of priority, established for scientific nomenclature, it became necessary to retain the term *tetragena* in preference to that of *africana*. The vegetative forms of this supposedly newly discovered species proved to be smaller than those of the *Entameba histolytica* and displayed a nucleus much richer in chromatin, and therefore more visible in the living parasite. True encysted forms were likewise described as a part of the life cycle of this organism, containing from one to four nuclei. For a number of years, the *Entameba tetragena* was looked upon as a distinct pathogenic species, but in 1911 Walker, and shortly after, Darling, Craig and others succeeded in establishing its identity with the *Entameba histolytica*. It is certain that Schaudinn had entirely overlooked this important phase in the life cycle of the *Entamebd histolytica* (the so-called *tetragena* stage) and had erroneously considered the budding process, often observed in senile races, as the sole method of reproduction.

Another phase occurring during the cycle of development of the pathogenic entameba, first described by Elmaissian in 1909 as *Entameba minuta*, was also, for a time, looked upon as a separate species. These forms had previously been confused with those of *Entameba coli*, but they can be differentiated from this latter organism by the character of the nucleus and other properties which establish its direct connection

with the *Entameba histolytica. Entameba minuta* is, therefore, now generally regarded as a further step in the life process of *Entameba histolytica* (the so-called *minuta* stage) which immediately precedes that of encystment (also referred to at times as the precystic stage). It is thus apparent that the *Entameba histolytica,* as originally described by Schaudinn, is a decidedly polymorphic organism, possessing a number of complex morphological forms during its free and active state, and a distinct reproductive phase within the cyst, ending in the formation of four daughter amebæ.

The following features are characteristic of the free stage of *Entameba histolytica* as a whole: the size varies from 15 to 80 microns in

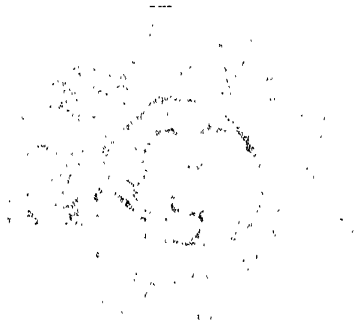


FIG. 2.—PHOTOMICROGRAPH OF ENTAMEBA HISTOLYTICA.

Showing the clear ectoplasm, with a large number of red blood-corpuscles contained within the parasite. (After Viereck. From C. F. Craig, "The Parasitic Amebæ of Man," J. B. Lippincott Co.)

diameter, with an average of from 25 to 40 microns. Under favorable conditions, the organism exhibits great activity, the endoplasm being extruded in a peculiarly explosive manner, forming characteristically elongated and finger-shaped pseudopodia.

The clear and highly refractile ectoplasm is of dense structure, which enables it to penetrate the intestinal wall without difficulty. One of the notable features of this species is the clear-cut demarcation between the ecto- and endoplasm, which is distinguishable even when the organism is at rest.

The endoplasm is light grayish or pale green in color, and, in addition to a well-defined nucleus, contains coarse granules and a number of non-contractile vacuoles of various sizes. Marked predilection is shown by this organism for red blood-corpuscles, which are ingested and retained within the endoplasm mainly for the purpose of nutrition. The nucleus is of vesicular type and ring-shaped, and because of a relative deficiency in chromatin, is not always visible in the larger *histolytica* forms. During the *tetragena* and *minuta* stages, the nucleus is, however, clearly outlined as a rule, and is found to occupy an eccentric position

in the endoplasm. The motility is greatest during the *histolytica* stage, and it is during this stage that the organism is enabled to enter the tissues and carry on its complete life cycle beyond the lumen of the gut. Reproduction takes place by binary fission with the formation of two daughter cells. Several generations of vegetative cells are produced, as a rule, before encystment finally occurs. In the older strains, spores or buds may frequently be observed. These spores eventually become detached from the parent cell, which fact led Schaudinn to believe that they represented a form of reproduction, a view which is now known to be erroneous. The reproductive phase within the cyst constitutes practically the sole means of preservation of the species, since the trophozoites succumb rapidly outside of the body, and therefore rarely serve as infectious agents in the new host. The cysts of *Entameba histolytica* range from 10 to 20 microns in diameter, and are therefore re-

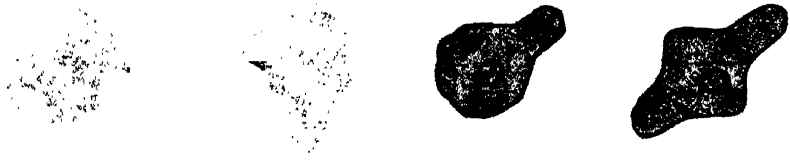


FIG. 3.—CHANGES IN THE FORM OF ENTAMEBA COLI DURING AMEBOID MOTION. Note the lack of differentiation of the ectoplasm and endoplasm and the distinct nucleus. (From C. F. Craig, "The Parasitic Amebæ of Man," J. B. Lippincott Co.)

latively smaller than those of *Entameba coli*. The cytoplasm of the cyst is finely granular, and is enclosed within a dense and highly resistant cyst wall. The number of nuclei varies from one to four, depending upon the stage of maturity of the cyst.

In addition to the nuclei, variable amounts of chromatin are, at times, present within the cytoplasm, as well as a number of clear vacuoles, some of which contain glycogen.

Entameba coli.—This is the most widely distributed of all the intestinal protozoa. The frequency with which this organism is found in the stools varies in different localities, but on the whole the percentage ranges considerably higher than that of the *Entameba histolytica*.

According to Craig, a considerable number of healthy individuals throughout the world harbor *Entameba coli* in their feces. As evidence of this fact, Craig found that in 200 healthy American soldiers stationed at San Francisco, 65 per cent. showed cysts of *Entameba coli* in the stools. Vedder likewise examined the stools of American soldiers in the Philippines and found 50 per cent. to be infected with non-pathogenic entamebæ, while over 75 per cent. of Philippine Scouts revealed the same organisms in their feces. Schaudinn himself had discovered similar infection in 50 per cent. of healthy individuals examined in West Prussia, while along the shores of the Adriatic, 66 per cent. gave evidence of infection. These figures have been confirmed more or less by numerous other observers.

The harmless character of the *Entameba coli* has been demonstrated experimentally in both man and the lower animals. In the human experiments conducted by Walker and Sellards, in the Philippines, it was noted that out of 20 individuals successfully parasitized with the organism, not a single one showed clinical manifestations, nor did pathological lesions develop, as far as could be ascertained. Other investigators have found it impossible to produce dysentery in the lower animals following ingestion of either the free or the encysted forms of this parasite. The fact that the organism is found not infrequently in the dejecta of diarrheal patients has suggested, in the minds of some, a possible causal relationship between it and the disease process. This is entirely disproved by the well-established fact that the organism appears in a large percentage of healthy individuals who never exhibit any evidence of intestinal derangement.

Schaudinn, in 1903, was the first to differentiate this species definitely from that of the *Entameba histolytica*. The vegetative forms are, as a rule, smaller than those of the pathogenic entamebæ, averaging from 25 to 35 microns in diameter. The movement is likewise more sluggish, and the pseudopodia are blunter and of frailer consistency, an important differential factor between the two species, since the *Entameba coli* is thereby rendered incapable of penetrating the mucous membrane of the intestinal tract. It is impossible to distinguish between the ectoplasm and the endoplasm, unless the organism is in motion. The endoplasm is finely granular and colorless and contains a number of non-contractile vacuoles. The nucleus of this species is relatively rich in chromatin and can therefore usually be made out with great clearness in unstained preparations. The organism does not ingest red corpuscles, differing markedly in this respect from the vegetative forms of the *Entameba histolytica*.

The writer is thoroughly in accord with Wenyon's view that differentiation between the two species is never certain, in unstained preparations except by means of the presence or absence of red blood-corpuscles within the endoplasm. In this connection, it must not be overlooked that some of the smaller strains of *Entameba histolytica* remain free of red blood-cells, so that their absence in a suspected entameba is not necessarily to be regarded as conclusive evidence of the non-pathogenicity of the organism. In stained specimens, differentiation is rendered comparatively easy by a careful study of the nuclear structure.

Marked differences likewise exist in the encysted forms of the two organisms, *Entameba histolytica* and *Entameba coli*. The cysts of the *Entameba coli* are generally spherical, and range in size from 12 to 22 microns. They are thus comparatively large in size and contain, at full maturity, from 8 to 16 nuclei, which may be clearly recognized, especially in preparations stained with iodin. The cytoplasm of the cyst is distinctly vacuolated, although the vacuoles themselves, in this species, do not often contain glycogen. In addition to reproduction within the cyst, the organism undergoes reproduction in the vegetative state, by simple division resulting in the formation of two daughter cells.

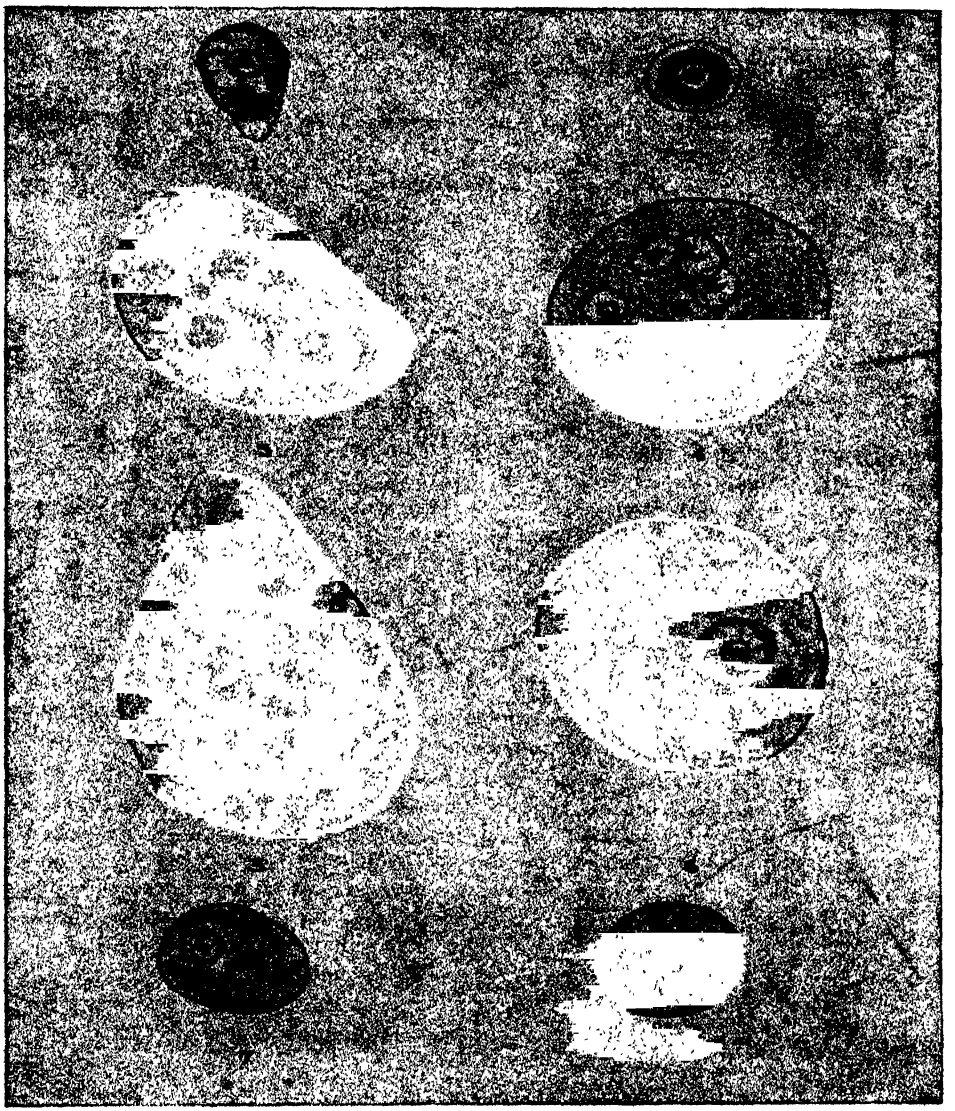


FIG. 4.

FIG. 4.—FORMS OF AMEBÆ. (After drawing by Teodosis S. Espinosa. From E. L. Walker and G. W. Sellards, "Experimental Entamebic Dysentery," Philippine Journal of Science, Aug., 1913, viii, No. 4, 331.)

(Fixed and stained preparations at the magnification of Zeiss 1/12; oil immersion objective ocular 3; tube length 160 mm., with camera lucida.)

1. Motile form of a typical ameba, cultivated from the Manila water supply. Note the small size, central arrangement of the chromatin in the nucleus, and the contractile vacuole.

2. Encysted form of the same species of ameba. Note the small size and single nucleus with central arrangement of chromatin.

3. Motile form of Entameba coli, from stool of a healthy person. Note the dense granular structure of the cytoplasm, the relatively large amount of chromatin and its peripheral arrangement in the nucleus.

4. Encysted forms of Entameba coli, from stool of a healthy person. Note the large size, the relatively thick cyst wall, the 8-ring form nuclei, and the absence of "chromidial bodies."

5. Motile form of Entameba histolytica, from the stool of an acute case of entamebic dysentery. Note the reticulated structure of the cytoplasm and the scanty chromatin in the ring-form nucleus.

6. The "tetragena" type of motile Entameba histolytica, from a chronic case of entamebic dysentery. Note the structure of the nucleus. It contains a heavier peripheral ring of chromatin—a part of which is detached from the nuclear membrane—than in the typical histolytica, and there is a central karyosome, consisting of a central granule surrounded by a circle of chromatin granules.

7. The precystic stage of Entameba histolytica, from a "carrier" case. Note the small size, dense cytoplasm, and heavy peripheral ring of chromatin in the nucleus, which causes it to resemble a small Entameba coli.

8. Encysted form of Entameba histolytica, from a convalescent case of entamebic dysentery. Note the small size, the cyst wall, the 4-ring form nuclei, and the "chromidial body."

Entameba nana.—The vegetative forms of this organism were first recognized by Wenyon in 1915, during the course of a routine series of stool examinations made on British troops stationed in Egypt. They were originally interpreted by him as typical forms of *Ameba limax* although the failure to obtain cultures on artificial media was sufficient to throw doubt upon this interpretation. Subsequently, Wenyon succeeded in identifying the organism as a distinct species of parasitic entameba, a view which has now been universally accepted.*

The organism received its name because of its uniformly small size, the free forms measuring only from 5 to 10 microns in diameter. Movement is rather sluggish, and the clear hyaline pseudopodia terminate in blunt rounded tips. The endoplasm contains an unusually large number of vacuoles, in addition to the food particles and other extraneous material. The organism is incapable of ingesting red blood-corpuscles. The nucleus is clearly discernible in the living parasite. In stained specimens no central granule is present, the chromatin being distributed over the nuclear membrane in relatively large masses, forming irregular clumps. At times, a number of small filaments are to be observed passing directly across the nuclear space from the clump of massed chromatin to the opposite pole. This type of nucleus is absolutely characteristic of the *Entameba nana,* and is likewise present in many of the cysts. Reproduction takes place in the free state in the usual manner. The cysts are either oval or spherical in shape, and, like the trophozoites, are smaller in size than those of *Entameba histolytica* or *Entameba coli.* The cyst wall is thin, and the cytoplasm contains numerous small vacuoles, in many of which bacteria are found. As in other species, food in the form of glycogen is stored in some of the vacuoles for the nutrition of the cyst, and these stain a deep brown with iodin. In some strains, an especially large glycogen vacuole is present, entirely obscuring the nucleus. It is highly probable that the so-called *iodin cysts* are, in reality, types of encysted *Entameba nana,* with especially large vacuoles, liberally supplied with glycogen. The number of nuclei in the cysts varies from 1 to 4 and the characteristic nuclear structure serves as a definite means of differentiation from the encysted forms of other entameba.

The distribution of *Entameba nana* has not as yet been completely determined. Wenyon found the organism to be one of the commonest types of intestinal protozoa in Egypt.

In a recent article, Kofoid states that *Entameba nana* is of wide geographical distribution, infections with this organism exceeding in frequency infections with *Entameba histolytica* and with *Entameba coli.* In the course of a detailed examination of feces from American troops returned from overseas duty, this author found cysts of *Entameba*

* Dobell has recently taken the position that this organism does not belong in the genus *Entameba,* on account of the peculiarity of its nuclear structure, as exhibited both in the free and in the encysted state. He has insisted upon a reclassification of the organism under the genus Endolimax (Kuenen and Swellengrebel, 1917), represented by a single species, namely, *Endolimax nana* (Wenyon and O'Connor, 1917, Brug, 1918).

nana in 417 out of 1,500 men examined, or 28 per cent., while infection with the *Entameba coli* and *Entameba histolytica* comprised 23 per cent. and 9.3 per cent. respectively. All authorities agree that the *Entameba nana* is devoid of pathogenicity, occupying a position, in this respect, similar to that of *Entameba coli.*

Entameba gingivalis.—Gros discovered this organism, in 1849, and assigned to it the name *Amœba gingivalis.* In 1904 Prowazek made a complete study of the ameboid organisms occurring in the human mouth, and came to the conclusion that they belonged to a distinct species, for which he proposed the name *Entameba buccalis.* The identity of the various buccal amebæ has been completely proven, so that under the

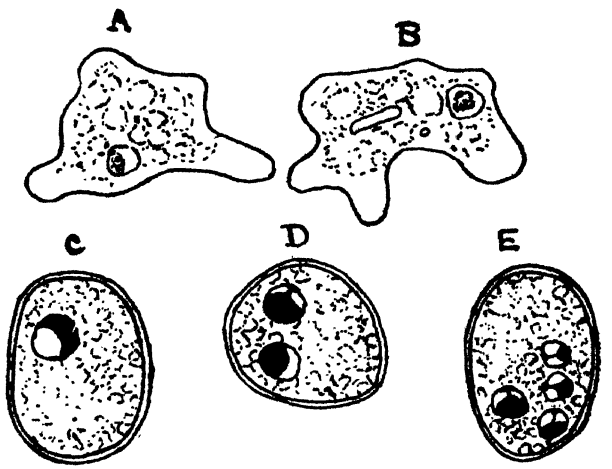


FIG. 5.—ENTAMEBA NANA.

A and B. Vegetative forms as seen in fresh preparations.

C, D and E. Cysts in various stages of development, showing one, two and four nuclei. (After Wenyon and O'Connor.)

rules of priority the correct terminology for the organism should remain *Entameba gingivalis.* This parasite has achieved considerable prominence in recent years because of its supposed connection with the lesions of pyorrhea alveolaris and other purulent conditions of the buccal cavity.

Barrett and Smith, as likewise Bass and Johns, have claimed a direct etiological relationship between this species and pyorrheal conditions of the gums. At the present time most authorities believe that although the *Entameba gingivalis* is a constant invader of the mouth and of the peridental tissues, it is doubtful whether the organism itself is the direct etiological factor in pyorrhea alveolaris. On the other hand it is by no means certain, as has been insisted upon in some quarters, that the actively motile parasites of this species are entirely devoid of pathological significance.*

* The tissue-invading property possessed by this organism most probably serves as a means for the introduction of bacteria into the peridental tissue as well as for the carrying of the bacterial organisms constantly into new areas.

The relationship between the organisms *Entameba gingivalis* and *Entameba histolytica* has been completely disproved by carefully conducted experiments which have been made upon lower animals. In man, infection of the intestinal tract has never been traced to the *Entameba gingivalis*. This distinctly buccal parasite is of relatively small size, measuring from 6 to 35 microns in diameter. The ectoplasm and endoplasm are indistinguishable during the resting stage of the organism. Under favorable conditions, motility is very active, the pseudopodia being thrust out, as in *Entameba histolytica*, in the form of elongated, sharp projections. The endoplasm contains non-contractile food vacuoles, in conjunction with a considerable amount of granular material but, in most instances, the nucleus is invisible in the living parasite. This organism, like the *Entameba histolytica*, is phagocytic

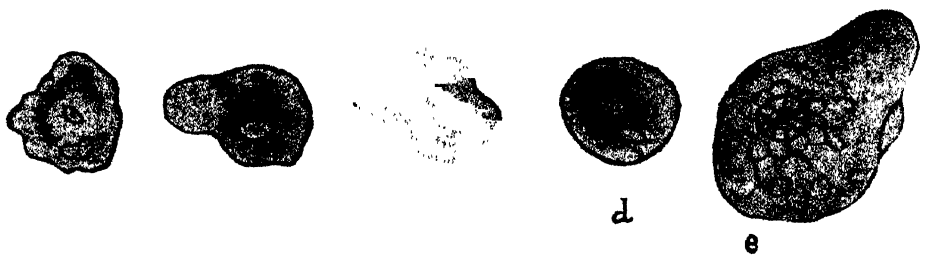


FIG. 6.—ENTAMEBA GINGIVALIS.

a-d, The same specimen observed during five minutes. (× 1,000.)

e, The organisms fixed and stained with iron-hematoxylin. (× 1,500.) (After Leyden and Löwenthal.)

for red blood-corpuscles. Reproduction usually occurs by simple division. Schizogony is rare. The cysts measure from 8 to 10 microns and contain but one nucleus. It is doubtful whether reproduction ever occurs in this species during the encysted stage.

The distribution of *Entameba gingivalis* is universal. The organism has been found not only in the structures of the mouth proper, but also in the tonsillar crypts and in purulent collections situated within the salivary glands and ducts.

(2) GENUS CRAIGIA.

Species:

Craigia hominis (Craig, 1906; Emend, Calkins, 1912); *Craigia migrans* (Barlow, 1915).

The organisms included in this genus were first described by Craig in 1906, under the name *Parameba hominis*. Calkins, in 1912, called attention to the erroneous nature of this classification, and proposed that a new order be created, for which he suggested the name *Craigia*. Two species have been identified, both of which are parasitic for man, namely, *Craigia hominis* (Craig, 1906; Emend, Calkins, 1912) and *Craigia migrans* (Barlow, 1915). The feature which differentiates these or-

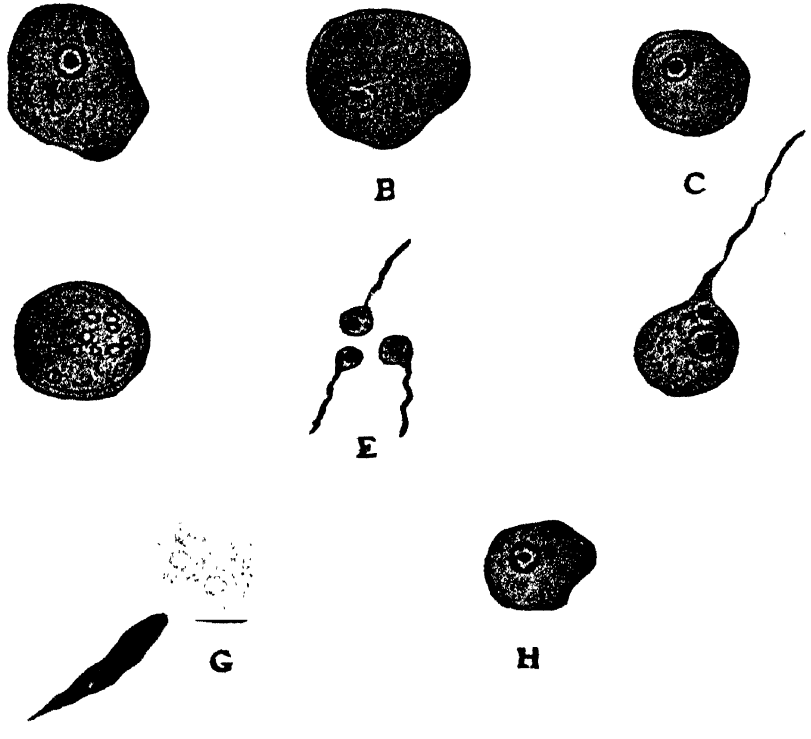


FIG. 7.—CRAIGIA HOMINIS. (After Craig. From pencil drawings, × 1,200.)

A. Typical organism in amebic stage. Note structure of nucleus and accessory nuclear body

B. Absence of accessory nuclear body and different type of nucleus.

C. Cyst showing one nucleus.

D. Cyst showing granular appearance of cytoplasm and the presence of numerous nuclei.

E. Young flagellate form.

F. Fully developed flagellate form. Note absence of undulating membrane, the single flagellum, the nucleus, and accessory nuclear body.

G. Dividing flagellated form, the flagellum being partly divided, while nucleus and accessory nuclear body have divided.

H. Flagellate forms after loss of flagellum and just before becoming ameboid.

ganisms from other species of ameba depends upon the existence of two distinct vegetative phases, including both an ameboid and a flagellate stage. The ameboid forms vary from 10 to 25 microns in size. The ectoplasm is distinguishable from the endoplasm only when the organism is in motion. The endoplasm is finely granular and contains a nucleus of modified *limax* type. Not infrequently, in the larger parasites, a

small accessory nuclear body is visible, which Craig, in his original description, considered identical with the so-called nebenkörper of the *Parameba eilhardi*, as described by Schaudinn. Because of this accessory nucleus, Craig believed that he was dealing with another species of parameba. Reproduction takes place in the ameboid stage by simple division, with the formation of two daughter amebæ. Encystment eventually occurs, and in the process of reproduction within the cyst a number of swarmers are produced, each having a single flagellum. The flagellate forms grow rapidly, and upon reaching full development, measure from 10 to 20 microns in diameter. The single flagellum is relatively long and resembles a corkscrew in shape. The nucleus is spherical, and is situated posteriorly near the origin of the flagellum.

Reproduction takes place in the swarmer stage, likewise, by simple division. As a result of this reproductive phase, new generations of ameboid forms are subsequently developed.

According to Craig, the flagellate forms of this organism are often erroneously confused with other types of flagellate protozoa, such as the *Trichomonas intestinalis* or *Cercomonas intestinalis*. Craigiasis, in Craig's opinion, has a wider distribution than is generally suspected. Clinically, the condition is accompanied by either diarrhea or dysentery, which may alternate with periods of constipation.

In examining the stools of several patients suffering from a severe form of diarrhea, in Honduras, Barlow ran across an organism similar in many respects to the *Craigia hominis*. He noted a number of distinctive features, however, which entitled this organism to separate classification as a new and distinct species (*Craigia migrans*). The young flagellates of this species are very small (from 3 to 5 microns), and as many as 40 swarmers have been observed in one cyst. Reproduction does not occur during the flagellate stage, the organism merely passing from this form into that of an ameba.

Barlow feels certain that the *Craigia migrans* is the cause of many cases of tropical diarrhea and dysentery, and claims to have been able, in a number of instances, to trace a causal relationship between this parasite and abscess of the liver.

In some quarters, the status of both species of *Craigia* has been called into question, and doubt has been expressed concerning their identity as distinct organisms. Among others, the author has never been able to confirm their presence in many hundreds of diarrheal stools examined.

(3) Genus Vahlkamfia. (Chatton, 1912, Emend, Calkins, 1912). Species: *Vahlkamfia lobospinosa* (Craig, 1912).

In most instances, amebæ belonging to the so-called *limax* group are to be included in this genus. These parasites are essentially free-living forms, finding a suitable habitat, as a rule, in small bodies of fresh or stagnant water and in moist soil. The features which characterize this class of ameba have been summarized by Calkins as follows:

"Minute free-living or commensal rhizopods, moving with finger form single pseudopodia, or with irregular ectoplasmical outbursts to form local or general hyaline ectoplasm."

The nucleus is either single or double, containing finely-defined chromatin forming a membrane-like contour with a definite karyosome.

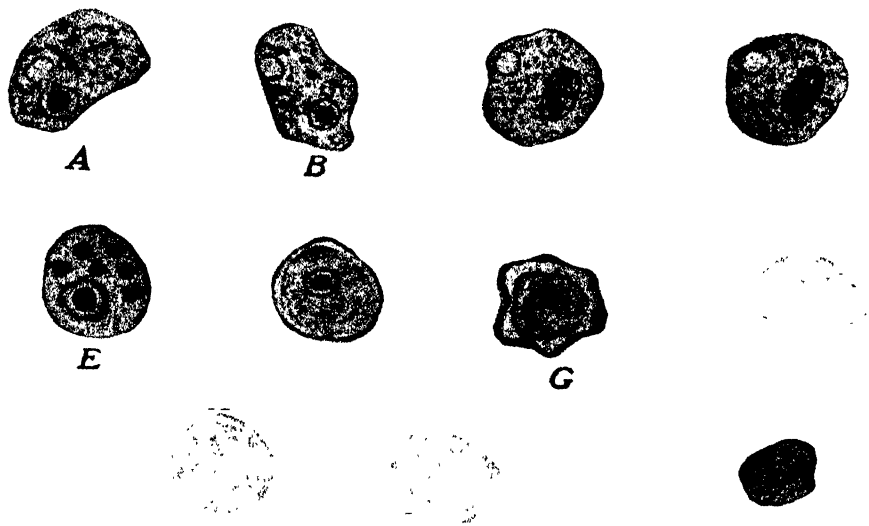


FIG. 8.—VEGETATIVE FORMS OF VAHLKAMFIA LOBOSPINOSA. (After Craig. From pencil drawings, × 1,200.)

A. Shows large contractile vacuole near the nucleus, and typical nucleus; note the large, deeply staining karysome.

B. The contractile vacuole near the periphery of the cytoplasm.

C. Division of the nucleus; note the polar bodies and equatorial plate.

D. Nuclear division.

E. Organism containing yeast-cells; note the granular appearance of the nuclear membrane.

F. Typical young cyst.

G. Old cyst; note thick cyst-wall which is folded in places—a very characteristic appearance of the old cysts.

H, I, J. Cysts; I and J degenerated cysts, the nucleus having disappeared.

K. Young organisms shortly after liberation from cyst.

Reproduction takes place by simple division. The cysts are uninuclear. The food is mainly bacteria. The organisms belonging to this genus may, in most instances, be cultivated upon artificial media—a point of importance in differentiating this group of parasites from true parasitic entamebæ.

One species of Vahlkamfia, namely that designated by Craig in 1912 as *Vahlkamfia lobospinosa*, may, however, for a short period of time,

become parasitic in the intestinal tract of man as well as in some of the lower animals. In every instance, when an ameba has been cultivated from the feces or from drinking-water, careful investigation of the cultivated organism has proved its identity with the genus *Vahlkamfia* or other free-living types of ameba. The presence of this organism in the intestinal tract of man is brought about through the ingestion of contaminated food or water, and their existence in the animal host is to be interpreted merely in the light of a temporary and harmless commensal. The cysts are easily distinguishable from those of the parasitic Entameba, due to the presence of a large central mass of chromatin within the nucleus.

The genus *Vahlkamfia* is especially prevalent in tropical countries, where the organisms propagate freely in undrained soils and in stagnant pools of water.

Experimental Entamebiasis.—IN MAN.—In 1913, Walker and Sellards conducted a series of feeding experiments in man, with different species of amebæ and entamebæ, which has helped materially in the solution of many important clinical problems. Previous to this Cassigrandi and Barbagallo, also Schaudinn, had ingested encysted amebæ, which they subsequently reobtained from their own stools without evidence of disease having been produced. The importance of Walker and Sellards' tests lay in the fact that they were able to bring about true entamebic dysentery in 4, or 22.2 per cent., out of 18 men experimentally parasitized with the *Entameba histolytica*. These men were Filipinos confined to the Bilibid Prison in Manila, who had been under observation for years without having shown infection with intestinal parasites at any time. Twenty men in all were allowed to ingest the encysted forms of *Entameba histolytica*. Of these, 17 became parasitized after the first feeding, while in 1, infection was acquired only after three successive feedings. Of the 4 men who subsequently developed dysenteric symptoms, the incubation period turned out to be twenty, ninety-five, eighty-seven and fifty-seven days respectively, yielding an average of 64.8 days for the series. Another important point brought out in these experiments involved the complete identity of the *Entameba histolytica* and the *Entameba tetragena*, which, prior to that time, had been considered as distinct species. Two of the men were fed motile entamebæ of the *histolytica* type, obtained from a case of acute entamebic dysentery. In both instances, parasitation occurred within four days, when typical *tetragena* cysts were discovered in the stools. In the case of one man who was fed *tetragena* cysts from a convalescent case of entamebic dysentery, cysts were recovered within two days. The cysts persisted in the stools for a further period of twenty days, after which symptoms of acute dysentery developed, presenting typical *histolytica* organisms in the feces. In the course of further experiments, the non-pathogenicity of *Entameba coli* was definitely proven. This conclusion was based on the fact that of 17 men successfully parasitized with the *Entameba coli*, not a single one developed disease symptoms. In addition, the fact was clearly established that the parasitic entamebæ could not be cul-

tivated upon Musgrave and Clegg's or other artificial media. Altogether, Walker and Sellards' work is to be regarded as the greatest single advance made in our knowledge of entamebic disease, since the publication of Schaudinn's classification of the organisms in 1903.

In Lower Animals.—Experimental reproduction of entamebic dysentery in the lower animals, by inoculation with infected material, can be accomplished with comparatively little difficulty. Cats have proven to be the most susceptible of the lower animals, and have been selected almost exclusively for experimental purposes, although the disease may also be reproduced in dogs, monkeys and rats. Several methods of inoculation are employed: (1) by the injection of infected dejecta directly into the rectum of the animals; (2) by the oral administration of material containing the parasites, especially in the encysted form; (3) by direct inoculation into the cecum after laparotomy. The latter method proved very successful in the experiments of Baetjer and Sellards. These authors were able to obtain typical entamebic lesions in 50 per cent. of the cats inoculated in this manner. Their method consisted in the performance of a laparotomy as an initial step. Subsequently, the infected feces were injected directly into the cecum, under strict aseptic precautions. In this manner, the organisms were carried through several strains extending over a period of many months. The animals subsequently died from sepsis, due to the increased virulence of the bacterial organisms present in the transfers. Ten animals in all were experimented upon, in five of which typical lesions promptly developed.

When the disease is reproduced experimentally in lower animals, by means of rectal injections, the lesions tend to localize in the rectum. In addition, the incidence of infection through the rectum is considerably lower than is the case when inoculation is undertaken by feeding through the mouth. The cause of this is obvious when one considers the greater degree of infectivity possessed by the encysted forms in contrast to the free or vegetative forms. Rectal inoculation with cysts is impossible, while the feeding of unencysted organisms to the animal fails to bring about parasitation of the intestinal tract in practically every instance, because of the rapid destruction of the frail trophozoites in the presence of the digestive juices.

The incubation period in lower animals ranges from four to twenty days. The entamebæ which are recovered from the intestinal tract do not differ morphologically from the type of organism associated with the disease in man.

The comparative ease of inoculation in cats, dogs and certain other animals has suggested the possibility of the spontaneous occurrence of entamebic infection among the lower animals in general. Cases with characteristic symptoms and lesions have been reported in monkeys by Eichhorn and Gallagher, Macfie, Mathis, Wells and others, and in dogs by Ware. For some unexplained reason, spontaneous entamebic dysentery in cats has been noted with extreme rarity. As a result of a series of successful inoculation experiments in rats, Lynch was led to

investigate the possible presence of the disease among these animals in certain infected quarters in Charleston, S. C. He found three rats with typical lesions of intestinal entamebiasis, in the negro quarters of that city. The organisms recovered from the feces were indistinguishable from those of *Entameba histolytica*. Lynch believes that rats may become infected by eating human feces which contain encysted parasites, and considers this rather ubiquitous animal a possible disseminator of entamebic infections both in man and in the lower animals.

Cultivation of the Parasitic Entamebæ.—The cultivation of parasitic entamebæ on artificial media is a subject to which much thought and attention has been given by research workers in recent years. As early as 1879, Cunningham claimed success in cultivating dysenteric amebæ, stating that such cultures produced dysentery in cats. Subsequently, Gross (1882), Kartulis (1890), Frosch (1897), Cassagrandi and Barbagallo (1897), each in turn reported success in attempts made by them to obtain cultures of dysenteric entamebæ. These cultures were made in symbiosis with various bacteria, but in the light of our present knowledge, it is certain that the cultures of amebæ were not of the parasitic type. In 1904, Musgrave and Clegg published a report of extensive investigations which they had made with the cultivation of amebæ taken from the intestinal tract of man and the lower animals. They employed a special culture medium made up of alkalinized agar to which pure cultures of bacteria were added as symbionts. These authorities claimed to have produced the typical clinical symptoms of dysentery in monkeys with the use of such cultures, and believed that they had succeeded in cultivating true pathogenic entamebæ. The conclusions arrived at by Musgrave and Clegg were later confirmed by Walker (1908). It is the opinion of practically all observers at the present time that amebæ cultivated under such conditions bear no relationship to the parasitic entamebæ of the human intestinal tract. As early as 1911 Craig stated his belief that the parasitic amebæ of man had never been cultivated, an attitude which he has since consistently maintained. Whitmore, Bourret, Mathis and Kumagawa have likewise acknowledged failure in their attempts to cultivate pathogenic entamebæ. It may be recalled that Walker and Sellards, as a result of the human experiments, arrived at the conclusion that *Entameba histolytica* was a strictly obligatory parasite of the intestinal tract which could not be cultivated upon artificial culture media. The amebæ which these authors succeeded in cultivating from the stools of patients suffering with dysentery conformed morphologically to the *limax* or free-living type. In the tropics, the spores of free-living amebæ are constantly present in all supplies of drinking-water, as well as in the atmosphere and moist soil. These bodies are thus constantly swallowed by individuals residing within the tropics, and reappear unchanged in the stools, from which cultures can be made without difficulty. The cultivation of free-living amebæ from the dejecta is, on the other hand, rarely successful in temperate climates, yielding further proof of the fact that the ameboid organisms cultivated from the stools are of the non-parasitic type.

Very recently, Cutler has claimed complete success with a special method devised by him for the cultivation of the *Entameba histolytica.* The media employed in these experiments are of two varieties: (1) An egg medium is used, consisting of the white and yolk of one egg thoroughly shaken up with 300 c.c. of distilled water, to which a few drops of blood are added. This mixture is brought to the boiling point in a water bath and this degree of temperature is maintained for half an hour. Divided quantities in test-tubes are finally sterilized in an autoclave. (2) A so-called blood-clot medium is used, which is prepared by adding 500 c.c of human blood-clot to 1 liter of water and boiling for one hour. Subsequently, 5 per cent. sodium chlorid and 1 per cent. peptone are added to the filtrate. This preparation is sterilized in the autoclave for twenty minutes each day for three successive days. As in the case of the egg medium, a few drops of blood are added shortly before use. Cutler found that both media proved equally successful for the cultivation of *Entameba histolytica.*

Cats injected with the cultures developed typical symptoms of entamebic dysentery, and at necropsy the characteristic intestinal lesions of the disease were found to have been reproduced. It was found that inoculation was necessary daily, as otherwise the cultivated amebæ showed a tendency to pass into the encysted stage. Slight acidity, it was noted, served to destroy the organism. Although Cutler's experiments have not as yet been confirmed, his work bears the stamp of true scientific research, and further investigations along the line he has indicated should undoubtedly be undertaken.

SYMPTOMATOLOGY

The *clinical course* pursued by entamebic dysentery is in general one of wide variability. In regions where the disease prevails endemically, all grades of severity are constantly to be observed, ranging from the mildest degrees of bowel derangement to the most evident attacks of acute fulminating dysentery. On the other hand, fairly extensive ulcerative lesions may be present in the intestine without producing definite symptoms. Nevertheless, even in such cases, careful questioning will usually reveal a history of some slight departure from the normal bowel functioning, generally intermittent in character.

The irregularity and inconstancy of clinical manifestations exhibited by the disease are determined by a number of factors in the main, as follows:

(1) The location and extent of the lesions in the large intestine.

(2) The reaction of the individual to infection with the organism (host reaction).

(3) The varying changes in morphology exhibited by the organism during the evolution of its life cycle, within the human body.

Of these factors, the changes in morphology which the organism undergoes exert by far the most marked effect upon the clinical course

of the disease. During the *histolytica* stage of the organism, rapid extension of the lesions occurs, producing active clinical symptoms. It is at this period that the patient experiences acute or subacute recurrences of the disease, varying in severity.

When the environment is rendered unsuitable for the *histolytica* type of the organism, the smaller and less active *tetragena* trophozoite is developed as a result. This type of organism is therefore ordinarily found in the stools during convalescence from acute attacks. A further change in morphology is found to occur during the quiescent stage of the disease, when clinical manifestations remain for the most part in abeyance. At this time, examination of the hardened and formed stool will reveal, for the most part, the *minuta* forms of the organism, as described by Elmaissian. The *Entameba minuta* or *Entameba tetrogena* although incapable of extensive tissue damage, may nevertheless carry on an indefinite existence within the tissues. Reproduction occurs during each of the various phases of the vegetative cycle of the organism resulting in the constant formation of new generations of daughter cells. A state is finally reached in which further regeneration of the vegetative cell becomes impossible. It is then that the cyst is produced, which serves as a means for the further perpetuation of the species within a new host.

The clinical aspects of entamebic dysentery may be conveniently grouped for consideration under the following headings:

(1) Acute entamebic dysentery.
  (*a*) Acute primary form.
  (*b*) Acute or subacute relapsing form.
(2) Chronic entamebic dysentery.
  (*a*) Active or relapsing type.
  (*b*) Latent type.
  (*c*) Atypical type.

Acute Entamebic Dysentery

Incubation Period.—In the vast majority of cases, infection of the intestinal tract with the *Entameba hystolytica* covers a protracted period. The initial onset of the disease does not, in fact, bear any direct relationship to the inception of the infection.

In the case of the human subjects experimented upon by Walker and Sellards, the incubation period, as determined from the time of ingestion of the organisms to the first appearance of intestinal symptoms, yielded an average of 64 8/10 days. In one case, the earliest evidence of bowel derangement appeared twenty-three days after parasitation of the individual with the organism had been confirmed. The longest period of incubation in the 4 cases was ninety-five days. In 14 of the 20 individuals experimented upon, typical *tetragena* cysts were present in the stools, although no clinical disturbances were manifested. It may be stated, therefore, that at the present time no criterion

is at hand for the determination of the incubation period of entamebic dysentery in any individual case.

Clinical Types.—The acute attacks may be divided clinically into two groups, depending entirely upon the manner of their origin:

(1) Those cases in which the onset is spontaneous, that is, without revealing a history of previous infection.

(2) The relapsing form which occurs as a manifestation of a previously established chronic infection.

The clinical course is markedly similar in both types, although the variations differ sufficiently in character and degree to justify separate consideration.

Acute Primary Entamebic Dysentery.—In this type, the onset is spontaneous and the course of the disease is frequently of a highly acute and fulminating character. The patient is attacked suddenly, often in the midst of good health, and without a previous history of entamebic dysentery.

Where persons have been crowded together under unfavorable sanitary conditions, as in military camps, jails, asylums, etc., the disease may assume epidemic proportions. Sporadic cases of highly acute primary entamebic dysentery also occur, especially in heavily infected regions. The epidemic form is most frequently noted among troops who have been brought into infected districts during times of active warfare. The statement, credited to Macreador, that dysentery is one of the great scourges of war and has killed more soldiers than either powder or shell, can scarcely be regarded as an exaggeration. The recent great world conflict proved to be no exception in this respect, since both bacillary and entamebic dysentery appeared in sporadic and epidemic form on the battle fronts and theaters of war, for the most part in tropical or semitropical countries. A large number of the British forces sent into these regions succumbed to the ravages of the disease.

Considerable difference of opinion arose regarding the particular type of infection which prevailed. According to the majority of observers, it would seem that the bacillary type predominated, although another group were equally positive that the *Entameba histolytica* was present as the chief infectious agent. As proof of the confusion which existed at the time, a statement was credited to Sir Ronald Ross in August, 1915, to the effect that emetin hydrochlorid should be used hypodermatically in all cases of acute dysentery, without regard to the microscopical findings in the stools. This advice was generally followed, apparently with good results. A review of the data which became available at a later period, collected from all regions where epidemics of acute dysentery occurred, proved that in many instances double or cross-infections prevailed.

As a matter of fact, in all highly acute attacks of entamebic dysentery, whether sporadic or epidemic in type, infection with organisms of the *Bacillus dysenteriæ* group is nearly always superimposed. When double infection thus occurs, the predominant type of organism will be found to vary during different periods of the disease. During the earlier

stages, the bacilli usually predominate to such an extent as to exclude the protozoal parasites completely from the stools. In the course of four or five days, as the acute symptoms subside, the *Entamebæ histolyticæ* make their appearance in rapidly increasing numbers, in connection with an inhibition of growth on the part of the bacillary organisms. It is because of this fact that differences of opinion frequently arise in regard to the bacteriological findings in certain cases of acute dysentery. In most instances, pure infections with the *Bacillus dysenteriæ* group of organisms undoubtedly form the basis of the larger number of cases of the dysenteries of war time.

When double infection exists, as frequently occurs in tropical regions, the *Entameba histolytica*, in the opinion of most observers, must be considered of primary importance in determining the treatment.

The course of acute primary dysentery is nearly always a rapid one and is ushered in by diffuse abdominal cramps and a diarrhea of a watery nature. The evacuations soon assume a distinctly dysenteric character, distinguished by the passing of increased amounts of mucus and blood. The dejecta may eventually fail to contain any fecal material.

Tenesmus is a marked feature of all forms of dysentery, and in the highly acute entamebic forms may reach such a degree of severity that the patient dare not leave the bed-pan for more than a brief period. Severe toxemia often develops at an early stage, usually signifying a mixed infection with the Flexner-Harris, or Shiga bacilli. The temperature range is rarely high in the beginning, but may become greatly elevated, reaching from 103° to 105° F. (39.44° to 40.55° C.) during the later stages of the disease, especially in the presence of a marked toxemia. The abdominal wall is retracted and rigid in most cases, becoming sensitive to touch, particularly in the right or left lower quadrants.

In fulminating cases, the symptoms become progressively worse, resulting in a fatal termination within less than a week, as a rule. In the cases which show a favorable outcome, a tendency to improvement becomes evident about the fourth or fifth day of the illness. The intestinal turmoil gradually abates, resulting in less frequent evacuations, which contain decreasing amounts of mucus and blood. Relief from tenesmus is also noted. The stools, however, often retain their dysenteric character for many days—or even for weeks—after the more acute manifestations have ceased. It is important to remember that in the initial stage of this type of dysentery, the pathogenic entamebæ may not appear in the evacuations, and only come into evidence at the termination of the more acute manifestations. The type of parasite which is present in all acute varieties of the disease is the large and actively motile trophozoite, which is practically always found to contain large numbers of red blood-cells within the endoplasm. After recovery from the acute attack, the encysted forms often persist in the stools for variable periods as evidence of continued infection. The patient then becomes a convalescent carrier of the infection and may or may not succumb to further acute attacks.

Acute or Subacute Relapsing Stage of Chronic Entamebic Dysentery.—Under ordinary conditions, entamebic dysentery is essentially a

chronic disease, extending over periods of months or years, and characterized by intermittent outbreaks of intestinal disturbances. These outbreaks occur with great irregularity, and the clinical symptoms which accompany them likewise vary considerably, both in intensity and in duration. Usually there is a history of one or more previous attacks, although it must be understood that the infection may exist in a latent form for a long period prior to the initial onset of symptoms. These attacks are to be viewed in the light of acute relapses, dependent upon a previously established and chronic infection. For convenience of description, the relapses may be divided from a clinical standpoint into the following types: highly acute or fulminating; subacute or moderately severe; mild.

(1) HIGHLY ACUTE OR FULMINATING TYPE.—In this type, the clinical manifestations closely resemble attacks of acute primary entamebic dysentery, as described above. The onset is as a rule quite sudden, and the clinical picture is in general that of a highly acute infection of the intestinal tract. The evacuations are frequent in number, and consist for the most part of a bloody and mucous exudate from the lower bowel. Tenesmus and straining are often extreme and, in fact, the patient soon becomes glued to the bed-pan or commode, so to speak. Acute abdominal pains are present, which are commonly referred to either the right or left lower abdomen. Fever is a variable symptom in such attacks, although in some instances it may reach a high level. The prominence of the toxic element invariably indicates mixed infection with organisms of the *Bacillus dysenteriæ* group. In the earlier stages, confusion is often created by failure to detect the active, *histolytica* type of organisms in the stools, since their growth is inhibited to a great extent by the bacillary infection. With the subsidence of this element, which takes place usually within four or five days from the onset of the disease, the pathogenic entamebæ make their appearance in increasing numbers.

An unfavorable prognosis must be rendered in those cases in which infection with the *Bacillus dysenteriæ* remains predominant. As a result of the persistent bacillary invasion, the walls of the large intestine become greatly thickened, and extensive sloughing is not uncommon. Should the inflammatory process reach the serous coat of the intestine, a localized peritonitis appears, which may rapidly spread through the entire peritoneal cavity. The advent of this complication brings about increased abdominal distention with considerable rigidity and tenderness of the abdominal wall itself. Although the entire thickness of the bowel wall may eventually become gangrenous as the final stage in this fulminating pathological process, perforation of the gut is of rare occurrence. Death may take place within a few days of the onset, due to the overwhelming sepsis. The prompt use of **emetin hydrochlorid** at the outset of an acute entamebic dysentery will, in most instances, prevent the appearance of such formidable secondary infections. In endemic regions, all types of acute bowel derangement should be looked upon with

suspicion, and the stools should be persistently searched for the possible presence of the pathogenic entamebæ.

(2) Subacute or Moderately Severe Type.—Fortunately, the relapsing stage of a chronic entamebic infection is seldom as acute and fulminating in character as in the preceding type. Ordinarily, recurrences of acute manifestations in the disease pursue a much milder clinical course. The onset is more insidious, and is accompanied by a simple diarrhea lasting a few days, before the stools finally assume their true dysenteric character. The patient rarely takes to his bed at first, and only does so when the frequency of the bowel movements and the abdominal pain and tenesmus render rest in the prone position imperative.

At this time, a mild degree of fever is also usually present, but this is seldom found to exceed from 101° to 102° F. (38.3° to 38.9° C.), In some cases, fever and other constitutional disturbances are altogether absent. The number of stools varies from five to fifteen within twenty-four hours. The stools contain large amounts of mucus intimately mixed with blood of a bright red or dark brown color. The fecal element is seldom completely lacking as is the case in the highly acute types. It is exceptional to find large quantities of fresh blood in the passages. The severity of the tenesmus depends, to a great extent, upon the location of the lesions in the large bowel, becoming more noticeable when the rectum is involved than when the lesions are situated higher up. The course of this moderately severe type of relapse is a variable one, in some instances lasting but a few days, while in others it extends over a period as long as two or three weeks. There may be repeated relapses of this nature with only short intervals of recovery, so that the patient drifts into a state of almost constant bowel derangement, persisting for many weeks or even months. This condition is accompanied by general disturbances, such as fatigue, weakness, loss of appetite, impaired digestion, and a decrease in weight. Nevertheless, it is surprising to find the number of individuals who are able to carry on their daily work, even in the face of such obvious disability.

(3) Mild Type.—In the milder forms of relapse the onset is gradual, and the health status of the patient becomes only slightly impaired. The symptoms as a whole differ in degree, rather than in character, from those of the preceding types. The patient is seldom forced to bed, although there is usually a marked slackening in his daily activities. In addition to the intestinal upset, he experiences for the most part a loss of appetite, slight disturbances of digestion, and lassitude. The number of bowel movements rarely exceeds two or three for the entire day; the evacuations are soft and without form, but the true dysenteric elements are often lacking. Upon close inspection, small mucoid masses will be detected, intimately mixed with the fecal portions of the stool. Blood may not be present in every movement, although it has been the author's experience that, even in the mildest grades of entamebic dysentery, slight hemorrhages amounting to streaks of red

blood or blood-tinged mucus are rarely missing from the stools during the periods of acute or subacute exacerbation of symptoms.

Unless there has been a history of previous attacks of a more acute character, the entire train of symptoms may prove to be so slight that the true nature of the malady is overlooked. In such instances, the case is commonly treated as one of simple catarrhal colitis. The disease may progress in this manner for months or even years, pursuing an irregular course, which varies between temporary attacks of intestinal disturbance, mostly of a mild character, and periods in which there is an entire absence of all symptoms. The non-recognition of the infection, in such cases, may prove of serious consequence, since complications in the liver and other organs not infrequently arise as a result of failure to treat mild cases.

Chronic Entamebic Dysentery

Active or Relapsing Type.—This constitutes by far the most common clinical form of entamebic dysentery, met with both in tropical and in temperate countries. The outstanding feature of this type is the occurrence of acute or subacute relapses, as described above, with intervening periods of comparatively good health. Patients may go for months or years without experiencing an acute outbreak of symptoms. These quiescent periods often prove deceptive, leading to the belief that the infection has been entirely removed. However, apart from the occurrence of typical intestinal disturbances, certain definite clinical features are usually associated with a chronic state of infection induced by the *Entœmeba histolytica*. The patient, while not definitely ill, frequently notices some impairment of his bodily vigor. He becomes easily fatigued and depressed, even after ordinary exertion; his digestion becomes upset, and in addition there is usually a progressive loss in weight. In a small percentage of cases, these constitutional symptoms prove so outspoken as to incapacitate the patient for work, or for prolonged effort of any kind. The majority are able to continue their daily vocations, but upon a reduced scale of efficiency. These constitutional symptoms may be analyzed in further detail, as follows:

Gastro-intestinal Disturbances.—Digestive disturbances of many varieties are not uncommon during the quiescent stage of the disease, and become greatly accentuated, as a rule, during the periods of acute bowel derangement. In the intervals between attacks, the tongue may appear dry and coated, and the patient will complain at times either of loss of appetite or of a certain capriciousness in the desire for food. Gastric symptoms, when present, are practically always of functional origin, and have their source, for the most part, in the absorption of toxic products from the intestinal tract. The patients complain of eructation of food, with heaviness and fullness after eating, and often with nausea and vomiting. Special precautions must be taken with the diet; some patients drift gradually into a state of confirmed dyspepsia. In the meantime, the bowel disturbances may be so insignificant as to

scarcely attract attention. Moreover, in some cases, an obstinate constipation is present during the entire stage of quiescence. In fact, the physician may be consulted for the relief of a chronic constipation, and only casual reference be made in the history to the occurrence of intermittent attacks of looseness of the bowels, or dysentery. In this connection, it should be remembered that a diagnosis of entamebic infection of the bowel can be made, even in constipated individuals, by a routine search of the hardened feces for encysted forms of the organisms.

Loss in Weight.—Accompanying the general impairment of health, there is in most instances a perceptible loss in the body weight. In the 217 cases of chronic entamebic dysentery which the author carefully compiled, the average loss in weight was twelve pounds. The highest loss recorded was forty-two pounds, in the case of a patient whose history of infection dated back ten years. The smallest loss in weight in this series of cases was two pounds. None of the patients showed a gain in weight until the organisms had been removed from the tissues by a proper course of treatment.

Secondary Anemia.—A moderate degree of anemia is present in many of the chronic cases. Its source can be traced, in most instances, to a persistent oozing of the ulcerated areas in the intestinal tract. The blood may not be visible in the stools, but the constant loss of even small amounts over prolonged periods may produce a considerable degree of anemia. Very severe types are, however, rarely met with. During the quiescent stage of the disease, no increase in the white-cells is observed. The presence of a high leukocytosis always indicates a septic complication, such as the formation of an hepatic abscess. Eosinophilia, likewise, does not form a part of the blood picture of entamebic diseases, and the presence of this condition usually indicates infection with other intestinal parasites.

Abdominal Pain and Soreness.—Pain and soreness in the right iliac fossa constitute frequent symptoms during the course of chronic entamebic dysentery. Acute attacks of pain in this region may prove quite deceptive, resembling in many respects the clinical picture of acute appendicitis. Most patients complain of a diffuse abdominal tenderness, and palpation may reveal points of sensitiveness along the various segments of the bowel, corresponding to the site of the more advanced lesions. Some of these individuals experience an indefinite feeling of discomfort in the abdomen, which is made worse by pressure of any kind. A bearing-down sensation in the region of the rectum is likewise not uncommonly complained of, at times even after the bowel movements have become normal in character.

Latent Type.—That infection of the intestinal tract with the *Entameba histolytica* might exist for an indefinite period without producing clinical symptoms is now a fully recognized fact. The absence of symptoms in such cases indicates a low-grade infection with limited, circumscribed lesions, usually located within the cecum or ascending colon. Owing to the lack of clinical phenomena, it is difficult to

estimate the extent of time covered by such infections, although in most instances it is probably of a prolonged character. The organism enters into a complete cycle of development within the tissues, but rapid transformation from one form to another, which is characteristic of the relapsing type, is prevented by a definite measure of resistance on the part of the body cells. The great importance of a latent entamebic infection of the intestinal tract lies in the fact that the patient is constantly exposed to the danger of serious complications in other organs. It is well known among experienced clinicians, especially in the tropics, that in a great number of cases of hepatic abscess, a history of previous intestinal disturbances is not always obtainable. This is likewise true, although to a lesser extent, of complications arising in the brain, spleen or other organs. In a similar manner, latent intestinal ulcerations may give rise to sudden and unexpected local complications, such as hemorrnage or perforation of the bowel wall. Rogers has recently reported an instance of acute intestinal perforation followed by fatal peritonitis in a patient who had given no previous evidence of entamebic infection of the bowel.

Unsuspected, high grade pathological lesions of the disease are at times first noted at autopsy. In endemic regions, especially, this is by no means a rare condition. In some of these latent cases, in spite of the entire absence of intestinal symptoms, slight impairment of the general health is nevertheless observed at times, as described previously in connection with the chronic relapsing type of the disease.

Atypical Type.—The intestinal disturbances of entamebic dysentery do not always pursue a typical or classical course. The clinical picture may, in fact, prove to be so unusual that no suspicion is aroused as to the possible existence of an entamebic infection.

In some cases, for example, there is a complete absence of dysenteric features throughout the entire course of the disease. The author has on several occasions unexpectedly run across actively motile pathogenic entamebæ in examining specimens of stool from persons suffering from an apparently ordinary form of diarrhea. The bowel condition had previously proved to be of an intractable nature, and did not respond to ordinary methods of treatment. In a case of this type, observed recently, a history of intermittent attacks of diarrhea was obtained, extending over a period of fifteen years. At no time had blood appeared in the stools, and there was likewise an entire absence of other dysenteric symptoms. However, the stool specimen showed an unusually large number of *histolytica* organisms, containing ingested red blood-corpuscles. In another atypical case, which came under observation some years ago, the sole complaint proved to be a bearing-down sensation in the lower region of the abdomen. This patient was a male of middle age who had enjoyed previous good health. The abdominal pain had persisted for two years without relief. Involvement of the lower bowel had not been suspected in this case, although the patient had been conscientiously examined in other respects. The bowel movements were described as normal, although occasionally the stools were

soft, and contained small amounts of mucus. The proctoscope revealed, nevertheless, extensive ulceration of the lower bowel, and, upon examination of scrapings from these ulcers, great numbers of *Entameba histolytica* were discovered in their most active stage. Relief of the abdominal pain followed the destruction of the protozoal organisms.

In connection with atypical clinical types of entamebic dysentery, Sellards and Baetjer have raised an interesting point in regard to the possible variation in the strains of the *Entameba histolytica* as found in various regions of the world. In several cases of chronic diarrhea which these authors observed in Baltimore, entamebæ were discovered in the stools which presented morphological differences from the usual forms of pathogenic entameba. The nuclear structure conformed to that of the *tetragena* stage, but in other respects there was a close similarity in structure to the *Entameba coli*. In the course of this description, no claim was made for the establishment of a new species of intestinal entameba, but the authors were rather inclined to attribute the variation in the morphology of the organisms to the change in environment from a tropical to a temperate climate.

DIAGNOSIS

The diagnosis of entamebic dysentery must, in the final analysis, always rest upon the discovery of the specific protozoal organism in the stools. Reliance is not to be placed upon the clinical symptoms alone, no matter how suggestive they may prove to be. Fortunately, at the present day, the microscopical examination of the stools provides an easily available method for differential diagnosis, and one which should be resorted to without fail in all doubtful intestinal conditions.

Examination of Stools.—Methods of Obtaining Specimens of Stool for Examination.—Formerly, when the diagnosis of protozoal infections of the intestinal tract was thought to depend entirely upon the discovery of actively motile organisms in the stool, particular attention was directed to the matter of maintaining the freshly voided specimen at body temperature. This procedure, which is at best a rather cumbersome one, is no longer considered essential, since even in the absence of live motile parasites the diagnosis can be made from the resting or encysted forms. When a fresh specimen of stool is required, this is best obtained directly from the patient at the time of examination. The great majority of patients suffering from entamebic dysentery are of the ambulatory type, and are able to appear in person for office examination. At this time, a specimen may be easily procured by introducing a fenestrated rubber rectal tube into the rectum, or, better still, by resorting to proctoscopic examination. This latter plan is to be highly recommended, whenever applicable, since it affords opportunity, at the same time, for inspection of the lower bowel. By a gentle curetting of an open ulcer, the author has on numerous occasions been able to discover motile entamebæ which were not revealed by previous examinations of the whole stool. In the

examination of a specimen of stool from a dysenteric patient, it is important to examine both the fecal and the mucous parts. The vegetative organisms are most often detected in the slimy, bloody portions, while the cysts are usually found in greatest numbers in the more solid fecal particles.

Number of Stool Examinations Required.—More than one examination of the stool may be required in order to determine the presence of an entamebic infection. This has been conclusively demonstrated by routine examinations of the stools made in the case of large numbers of suspected individuals in endemic regions. Wenyon found, for example, that in one series of 92 cases examined by him, 12 *Entameba histolytica* infections were present, but of these, only 4 were detected at the first examination. As many as six examinations have been insisted upon by some authorities before a negative report may be rendered. Most observers agree, however, that three examinations are sufficient, as a rule, to eliminate all doubt as to the presence of the organisms. It must be remembered that the typical *tetragena* cysts are of as much importance in establishing a diagnosis of the disease as are the vegetative organisms.

Difficulties Involved in the Differentiation of the Entameba Histolytica from Other Protozoal Organisms Found in the Stools.—Attention has been called to the variations in morphology which characterize the different species of parasitic entameba. Emphasis was also placed upon the many difficulties which beset even the trained protozoölogist in differentiating the organisms one from the other, during the various phases in their life cycle. In the microscopical examination of the ordinary stool specimen, these difficulties are greatly accentuated. Most authorities are now thoroughly in accord with the view that a differentiation of the pathogenic entameba from the harmless varieties is, at times, impossible during the vegetative stage. As a rule, if the organism is seen to move by means of active explosive-like protrusions of the pseudopodia, and in addition possesses an indistinct type of nucleus with a clearly-defined refractile cytoplasm, it is most probably of the pathogenic variety. Size and color prove of little value in the differentiation. According to Wenyon, no ameba is to be considered as pathogenic which does not contain red blood-corpuscles within the endoplasm. This view has been universally accepted at the present time, and should serve as the main guide in distinguishing the disease-producing type of parasite from the harmless varieties. In stained preparations, the differences in nuclear structure become clearly defined, which fact renders differentiation much less difficult. The cysts of *Entameba histolytica* are distinguishable chiefly by their glassy, refractile appearance, their relatively small size, and their smooth cytoplasm. The nuclei are from one to four in number. This type of cyst resembles in size and number of nuclei that of the *Entameba nana*, but the latter is, as a rule, ovoid in shape rather than spherical, and possesses numerous vacuoles of comparatively large size. There is also a marked distinction in the nuclear structure of the two organisms, which may be observed especially

in stained preparations. The cysts of *Entameba coli* are considerably larger than those of *Entameba histolytica* or *Entameba nana*, and present from eight to sixteen nuclei, which are characterized by a relatively large central granule and irregularly massed chromatin at the periphery.

In searching for cysts, it is important to select the more solid particles of feces, to be diluted with normal saline solution to form a very thin smear. The nuclei of the cysts usually lie at different levels, so that careful focusing is necessary in order to distinguish their structure. A double strength Lugol solution is frequently of value in enabling one to count the nuclei with accuracy. The author has recently made use of the Donaldson iodin-eosin stain for this purpose. This stain is prepared as follows: A 5 per cent. potassium iodid solution is saturated with iodin. A saturated solution of eosin is prepared in another container. It is preferable to employ a physiological salt solution as a solvent, both for the potassium iodid and for the eosin. A combination of these stains is made in the following manner: Two parts of the eosin stain are added to one part of the iodin-potassium iodid solution diluted further with two parts of normal salt solution. These must be mixed fresh each morning. In the presence of this double stain, the cysts stand out as pale yellow or saffron-tinted bodies against a bright red background. The nuclei are stained a deep brown color, and become clearly defined from the rest of the cytoplasm. Yeast cells as well as other cellular elements in the stool take up the eosin stain. Dead cysts are likewise stained red, but in fairly fresh stool specimens this phenomenon is rarely observed.

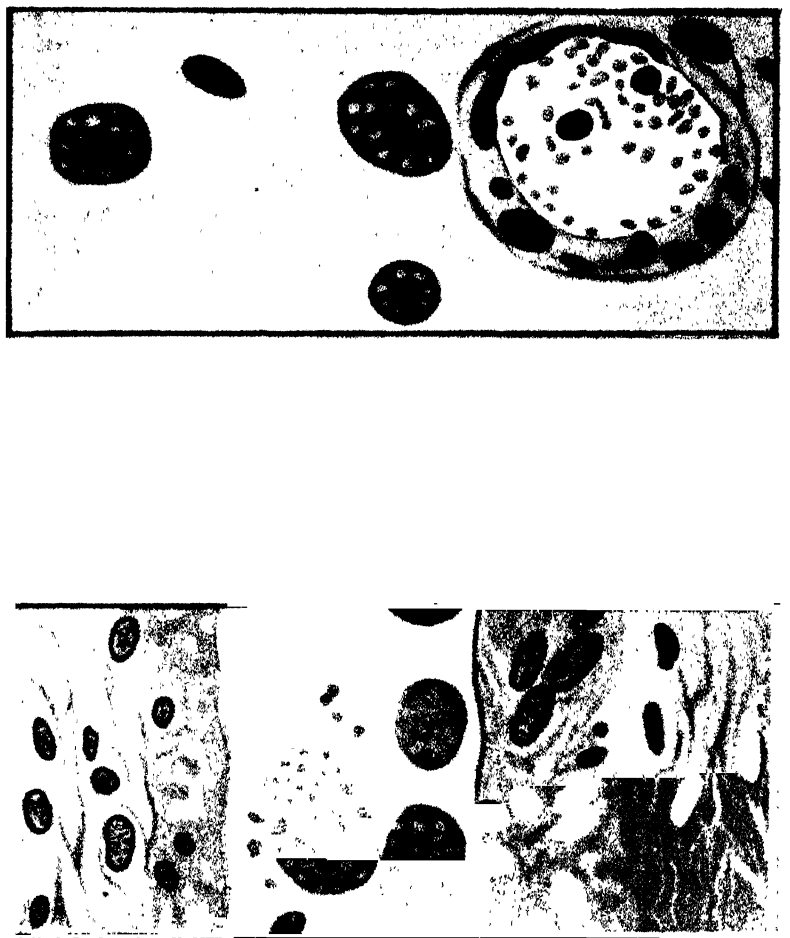
The vegetative forms of other intestinal protozoa, including the various types of the flagellates and ciliates, present such distinct differences from the species of entameba that little difficulty should be encountered in their differentiation. However, in the encysted forms the differences are not so marked and may require a degree of caution in their interpretation. The characteristics of the encysted forms of other protozoa will be found under another heading. The same methods apply for the staining of these organisms as have been described in detail above.

Staining of Fixed Preparations.—In order to bring out the finer details of structure of both the free organisms and the cysts, more elaborate staining methods are required. For the free forms, the following method, suggested by Rosenbusch, has been found to give satisfactory results:

Rapidly smear out with a toothpick a small particle of feces or other material containing protozoa and, while still moist, fix by Giemsa's method and, after getting rid of the mercury with iodin followed by 95 per cent. alcohol, treat the smears with a 3.5 per cent. solution of iron-alum in distilled water for one-half hour or over night; then wash thoroughly in distilled water.

Following this, stain from five to twenty minutes in a hematoxylin

PLATE I.



THE STAINING REACTIONS OF THE VEGETATIVE ENTAMEBA (1/6 Zeiss). (From G. B. Bartlett, "Pathology of Dysentery in the Mediterranean Expeditionary Force, 1915." Quarterly Journal of Medicine, 1916–1917, x, 185–244.)

A. Vegetative entamebæ in submucous tissues around a blood-vessel in a case of entamebic ulcerative colitis. Stained by Ehrlich's acid hematoxylin and counterstained by eosin. The cytoplasm of the vegetative entamebæ is markedly hematoxyphile and is vacuolated; the ring nuclei show very distinctly; they do not resemble the nuclei of any of the body cells. The vegetative entamebæ vary considerably in size. There is no cellular infiltration in the tissues around them.

B. Vegetative entameba in a blood-vessel of submucosa of the colon. Stained by Weigert's iron-hematoxylin and counterstained by Van Giessen's stain. The cytoplasm of the vegetative entamebæ is slate gray, and their nuclei show distinctly. Red

stain prepared as follows: (1) 1 per cent. solution of hematoxylin in 95 per cent. alcohol. It takes at least ten days to ripen. (2) A saturated solution of lithium carbonate. Add to 10 c.c. of the hematoxylin solution 5 to 6 drops of the lithium carbonate solution. Next wash well and differentiate with about 1 per cent. solution of iron-alum. Again wash in water, pass through alcohols to xylol and mount in balsam.

Moist fixation, as carried out in the above method, has proved on the whole to be more satisfactory than the dry fixation methods which have been recommended by some. The author has not found the various Romanowsky modifications suitable for the staining of the intestinal protozoa.

A special technic is required for the fixing and staining of cysts. The method devised by Daniels is probably the best one yet suggested, although it requires a considerable amount of time and patience to obtain proper results. The details of this method are given in full:

(1) Make a film on a cover-slip and do not let it dry.

(2) While still wet, drop it face downwards on to the fixing solution:

Saturated solution of sublimate	2 parts
Absolute alcohol	1 part

Leave it to fix for fifteen minutes.

(3) Take out of the fixing solution and place in 40 per cent. alcohol for ten minutes.

(4) Place in 70 per cent. alcohol to which a few drops of Gram's iodin solution have been added. Leave in this ten minutes.

(5) Place in methylated spirit for ten minutes.

(6) Place in 70 per cent. alcohol for five minutes.

(7) Place in 40 per cent. alcohol for five minutes.

(8) Place in water for an indefinite time.

(9) Place in iron-alum solution (2 1/2 per cent.) for from two to three hours.

(10) Rinse lightly in water.

(11) Stain for two or three hours in hematoxylin solution made as follows:

Hematoxylin crystals	1 gram
Absolute alcohol	10 c.c.
Distilled water	90 c.c.

This solution should be kept for a month to ripen. Then add another 100 c.c. of water.

(12) Wash well in water.

(13) Differentiate in iron-alum solution (25 per cent.). This is best done in a watch-glass with just enough solution to cover the under-surface of the film. The process can be watched under the microscope with a 1/6 objective.

(14) Dehydrate in spirit of gradually increasing strength; 40, 70, 90 per cent. and absolute.

(15) Pass through xylol and mount in Canada balsam.

For the staining of the organisms in the tissues, the reader is referred to special treatises on pathological technic.

Differentiation of Intestinal Entamebæ from Inflammatory Tissue-Cells Found in the Stools.—Under certain conditions, a great deal of difficulty may be experienced in differentiating the vegetative entamebæ from the larger types of tissue-cells which are often present in the stools as a result of inflammatory conditions. These tissue-cells are principally of two kinds:

(1) A large round mononuclear leukocyte.

(2) A more irregularly shaped and larger type of cell, generally known as a macrophage, which is most probably an hypertrophied endothelial cell, originating in the inner lining of the blood-vessels during inflammation.

Both types may become phagocytic for leukocytes and red blood-corpuscles, a fact which causes further confusion in differentiating them from pathogenic entamebæ. They are, however, non-motile even in freshly voided stools, and lack the distinctly ring-shaped nucleus which is characteristic of the protozoal organisms. The cytoplasm of these tissue-cells frequently contains numerous small vacuoles and refractile granules, which have been mistaken at times for the nuclei of protozoal parasites. In the cellular exudate of the acute dysenteric stool, these and other irregular types of degenerate tissue-cells are usually found to be present in large numbers. They may also be observed at times in the thin, glairy, mucous discharge from patients suffering from chronic mucous colitis. The inexperienced observer should take particular care not to confuse these degenerate tissue-cells with resting or encysted forms of intestinal protozoa.

Differentiation of Entamebic Dysentery from Other Intestinal Diseases.—Entamebic dysentery exhibits a marked similarity in its intestinal features with a number of other diseased conditions of the lower bowel, chief among which are the following: acute bacillary dysentery, chronic ulcerative colitis of bacillary origin, carcinoma of the rectum, intestinal tuberculosis, and diarrheas associated with other forms of tropical diseases.

Acute Bacillary Dysentery.—Many of the essential points in connection with the differential diagnosis of acute bacillary and acute entamebic dysentery have already been considered. Mixed infections are of common occurrence and the predominating type is often difficult to determine. In uncomplicated bacillary dysentery, the onset is usually sudden and the disease pursues a highly acute and toxic course, accompanied by general bodily depression, high temperature, severe abdominal pains, and a constant desire for stool. At first the passages are of a watery, fecal consistency, but within the space of a few hours they

generally become dysenteric in character. The acute phases of entamebic dysentery, on the other hand, ordinarily have a much milder clinical course. There may be an entire absence of the highly toxic features which characterize the acute bacillary types. Although the appearance of the stools in both conditions may be strikingly similar, in bacillary dysentery there is usually a larger content of cellular exudate as well as of mucus and blood. The clinical differences are, however, on the whole not very sharply defined. Examination of the stools for the specific microörganisms must serve, after all, as the chief determining factor in the diagnosis. In bacillary dysentery, the blood will often be found to agglutinate with pure cultures of the Shiga or Flexner-Harris bacilli. This fact frequently proves of considerable diagnostic value in the presence of doubtful or mixed infections.

Chronic Ulcerative Colitis of Bacillary Origin.—Extensive ulceration of the large bowel may result from chronic infection with various strains of intestinal bacteria. This condition frequently gives rise to a clinical picture strikingly similar to that of chronic entamebic colitis. The element of chronicity is present in both conditions, and little difference is to be noted in the clinical manifestations. There is a history of dysenteric attacks, alternating with periods of normal bowel evacuations or of constipation. In bacillary colitis, quiescent periods are, however, rarely of long duration, and are dependent to a great extent upon the use of astringents. Small, frequent stools, containing large amount of mucus, more or less streaked with blood, constitute a characteristic clinical feature in both diseases. An inspection of the lower bowel by means of the proctoscope often reveals similar ulcerative lesions, for the most part indistinguishable in their gross appearance. The ulcers of the bacillary type, however, appear to be more superficial and less ragged, although these are not to be taken as entirely trustworthy points in the differential diagnosis. It must also not be overlooked that the two types of infection may coëxist. The diagnosis must ultimately depend upon a careful search of the stools for pathogenic entamebæ. It is only when the presence of these organisms can be excluded with certainty that a diagnosis of ulcerative colitis of purely bacillary origin is rendered justifiable.

Carcinoma of the Rectum.—The clinical features of carcinoma of the rectum are, at times, difficult to distinguish from those of chronic entamebic dysentery. In advanced ulceration of the rectum due to malignancy, there is frequently a history of numerous daily evacuations, often containing blood and mucus. The evacuations are sometimes attended by considerable tenesmus. In such cases, even the loss in weight, and other evidences of malnutrition which characterize the clinical course of a malignant growth may fail to arouse suspicion at first of the real source of trouble, since chronic entamebic infections of the large bowel are known to give rise to a similar train of constitutional symptoms. A specific course of treatment for entamebic colitis is not infrequently resorted to, thereby robbing the patient of an opportunity for early surgical interference. The differential diagnosis is not difficult,

if the possibility of malignancy is kept in mind, especially in the case of individuals who have passed the fourth decade of life. In the presence of malignancy, palpation of the lower bowel will serve to clear up all doubt at once, if the growth is situated within reach of the finger. The proctoscope and sigmoidoscope are also of value in doubtful cases, and in addition, careful search of the stools should be made in each case for the presence of the *Entameba histolytica.*

Intestinal Tuberculosis.—This condition is by no means infrequent in tropical countries, and may therefore give rise to confusion in diagnosis, especially in centers of entamebic infection. Tuberculosis of the bowel is seldom confined to the large gut. The most common site of the lesions is in the terminal ileum and cecum, where the disease process often results in the formation of a tumor-like mass which may be palpated through the abdominal wall. Pain is likewise referred chiefly to this region. In the presence of a tuberculous infection of the large bowel, the symptoms are usually those of severe colic, an irregular type of fever, and diarrhea. The diarrhea may eventually merge into true dysentery, particularly when the ulcerative lesions extend as far as the descending colon and rectum. Under such circumstances, the clinical features of the disease may resemble those of chronic entamebic dysentery. A differentiation of the two conditions will then depend upon the discovery of the specific type of microörganism present in the evacuations.

Diarrhea Associated with Other Tropical Diseases.—Diarrhea is a common symptom of a number of tropical diseases, such as sprue, pellagra, malaria, cholera, typhoid fever, bilharziasis, balantidiasis and the various flagellate infections of the intestinal tract. The milder types of entamebic dysentery are therefore easily confused with other specific forms of diarrhea. Ulcerations of the rectum may likewise occur in connection with the more advanced stages of the above conditions, which fact renders the clinical differentiation from entamebic dysentery even more difficult at times. Again, the absence of pathogenic entamebæ from the stools after careful search should point at once to other etiological factors, as the basis of the intestinal disturbance.

COMPLICATIONS

Entamebic Appendicitis.—A special type of appendicitis due to the invasion of the walls of the appendix by the *Entameba histolytica* has been described by a number of observers. Strong claims to have met with this complication in 7 out of his 100 fatal cases. In 4 of these, death resulted from general peritonitis following perforation of the cecum or colon. Musgrave observed appendicular lesions in about 10 per cent. of the cases which came to autopsy. Gant believes that many of the clinical cases which fail to respond to treatment will be found to have ulcerative lesions in the appendix. He is also of the opinion that **irrigation** of the large bowel through an appendicular opening will succeed as a rule

in relieving this type of case when other measures prove inadequate. The morbid lesions in the appendix are similar to those found in other parts of the large bowel. It is not improbable that the presence of actively motile entamebæ in the walls of the appendix serves as a means for the introduction of intestinal microörganisms, thus leading more readily to the occurrence of an ordinary type of appendicitis. Clinically, the diagnosis of entamebic involvement of the appendix is rendered extremely difficult because of the close proximity of lesions in the cecum and ascending colon. Acute symptoms are rare unless bacterial infection has occurred secondarily.

Postcolic Abscess.—Rogers was among the first to call particular attention to the occurrence of this complication. The condition originates from perforation of the bowel wall, a previous formation of adhesions serving as a protection for the general peritoneal cavity. Secondary infection of this walled-off peritoneal pocket—usually situated behind the colon—constitutes the final stage in the process. The location of this lesion is most frequently in the cecal or right iliac region. Rogers himself never observed a postcolic abscess in any part of the transverse or descending colon. Clinically, the onset of symptoms occurs rather suddenly during the course of a chronic entamebic infection of the bowel, and is accompanied by a considerable degree of swelling and tenderness in the right iliac or lumbar region. High fever and a marked leukocytosis may be present in the acuter forms, and in such cases the disease proves rapidly fatal as a rule. In some instances, the abscess is of slow, insidious formation and is attended by few, if any, toxic features. Its existence is then made known solely by the presence of local signs such as swelling, tenderness, muscular rigidity, and in the later stages, by bulging. Simple drainage fails to effect a cure in an abscess-pocket of this nature, unless its entamebic nature is recognized, and specific medication is employed in conjunction with surgical procedures.

Peritonitis.—A localized peritonitis is probably more common in long-standing cases of intestinal entamebiasis than clinical records would show. Attention has already been called to the tendency shown by chronic ulcerations to progressively invade the muscular layer, eventually reaching the peritoneal coat. A localized patch of peritonitis will frequently develop under such a condition, and may give rise to symptoms of localized pain and tenderness over the abdominal wall. In contrast to the comparative harmlessness of this simple type of lesion is the gravity of acute general peritonitis, which results from the sudden perforation of a deep ulcer. The clinical features of this type of accident are in fact the same as those of sudden perforation of the bowel wall from any other cause. This serious complication occurs in entamebic dysentery under the following conditions:

(1) As a result of an extensive necrosis of the bowel wall during the progress of a highly acute or fulminating attack.

(2) As a sequel to the accidental rupture of a chronic ulcerative lesion which was not walled off previously by adhesions.

The latter type of perforative peritonitis was present in 19 of the 100 fatal cases observed by Strong in the Philippines. Fortunately, this complication is comparatively rare in clinical practice. Craig observed it in only 4 cases, while Strong found that it occurred in 1½ per cent. of the 200 clinical cases carefully studied by him. The author has encountered acute perforation only five times in his experience. The prognosis is of course always extremely grave. Immediate **surgical interference** is indicated.

Massive Intestinal Hemorrhage.—Small capillary hemorrhages from the ulcerative lesions situated along the bowel wall are exceedingly common, as has been stated previously. Massive bleeding, on the other hand, is but rarely observed and, when present, constitutes a distinct complication. In a few cases, death has been known to result from the profuse bleeding. One such case was reported by Councilman and Lafleur in which 125 c.c. of blood was passed before death. Similar cases have been observed by Strong, Hassler, Futcher and Freer. Strong believes that the presence of this complication is indicative of hepatic abscess. In most instances, a marked diminution in the coagulability of the blood is also found, which is probably brought about by sepsis. Profuse hemorrhage in prolonged chronic cases is prevented, for the most part, by the occurrence of thrombosis in the blood-vessels leading to the edges and bases of the ulcerative areas.

SEQUELÆ

Abscess of the Liver (Hepatic Entamebiasis)

This is by far the most important of the remote complications or sequelæ of the disease, occurring with especial frequency in tropical countries. On account of this, it is often referred to as "tropical abscess of the liver." This designation is, however, somewhat misleading, since the condition is by no means uncommon in temperate countries as well.

Association of Hepatic Abscess with Dysentery.—The close clinical relationship which exists between hepatic abscess and dysentery has been recognized among medical men since the time of Hippocrates. During later periods, frequent references are to be found in the literature to the association of the two conditions, notably in the writings of Pringle, Hunter, Budd and Sydenham. Koch, in 1883, was the first to discover the presence of amebæ in the pus from a liver abscess. This finding was confirmed by Kartulis, and in 1890, in America, by Osler. Councilman and Lafleur subsequently demonstrated a direct etiological relationship between amebæ found in the intestinal tract and focal centers of necrosis in the liver. This relationship is now universally acknowledged, as is also the view that the hepatic involvement is always secondary to that in the intestinal tract. The intimate connection of hepatic to intestinal entamebiasis is clearly shown in the following table of 63 fatal cases, compiled by Rogers:

Clinical and postmortem evidence of dysentery	35 cases	(55.6 per cent.)
No history, but postmortem evidence of dysentery	13 "	(20.6 per cent.)
History, but no postmortem evidence of dysentery	9 "	(14.3 per cent.)
No history or postmortem evidence of dysentery	6 "	(9.5 per cent.)

As showing the relative frequency of the two conditions in clinical practice, the following figures have been collected from observers in different countries:

McDill, for example, in a statistical review of over 100,000 cases of dysentery in the East, found approximately 4,000 cases of liver abscess. Rogers noted hepatic involvement in 20 per cent. of his large series of cases. Strong and Musgrave ran across 23 instances of liver abscess among 100 fatal cases of amebic dysentery in the Philippines. In a series of 78 fatal cases reported by Craig occurring mostly in this country, 33 per cent. showed liver abscess at autopsy. These figures indicate that hepatic abscess occurs in at least 20 per cent. of the fatal cases of entamebic dysentery. The incidence is less, however, in the general average of clinical cases, due to the fact that in many instances entamebic infection of the intestinal tract is overlooked entirely.

Etiology.—Predisposing Factors.—*Climate.*—Entamebic abscess of the liver is largely a disease of the tropics and subtropics, although scattered cases are not infrequently found in other regions. Many cases are discovered, in fact, among individuals who have never resided in tropical countries. In the United States the disease is by no means rare, especially in the South, where its prevalence has been, to a certain extent, overlooked. Elliott was able to collect 116 cases from two hospitals in New Orleans, covering a period of three years. The majority of these patients had never been outside of the country.

Race as a Predisposing Factor.—Europeans residing in the tropics are more susceptible to the disease than are natives. Manson places the relative frequency of hepatic involvement at 95.2 per cent. for Europeans, as contrasted with 4.8 per cent. for native residents. These figures are rather notable in view of the fact that entamebic dysentery is relatively more common among the native population. Stitt claims that abscess of the liver is more prevalent in those centers of amebic infection where foreigners possess little knowledge of the conditions necessary for the maintenance of health in the tropics. According to Musgrave, the Chinese are especially immune to hepatic complications of entamebiasis. This, he believes, is due to the simple quality and to the excellent manner of preparation of food common to the Chinese, and also to their habit of tea drinking.

Other Factors.—Persistent irritation of the liver with certain articles of *food*, as well as with *alcoholic stimulants*, is undoubtedly an important predisposing factor to the disease. An excess of animal foods and strong condiments is especially prone to bring about hyperemic states of the liver. Overindulgence in such foods, and especially in alcohol, probably furnishes an explanation of the greater susceptibility to the disease shown by the whites in the tropics. *Men* are likewise much *more*

frequently affected than *women*. The disease is exceedingly *rare in children*. The majority of cases occur between the ages of *twenty-one and forty*. *Occupation* would seem to play no special rôle in the etiology.

Symptomatology.—The clinical symptoms of entamebic hepatitis depend upon the duration of the disease, upon the size and location of suppurative lesions, when present, as well as upon the existence of secondary infections. Rogers has described two distinct clinical stages as follows:

(1) A presuppurative stage, representing the earlier period of hepatic involvement, before suppuration has set in.

(2) A suppurative stage, which is characterized by the formation of either single or multiple abscesses.

PRESUPPURATIVE STAGE.—This presents itself clinically as an ordinary acute hepatitis, accompanied by enlargement of the liver, pain and tenderness in the right costal region, and fever, which is usually of a remittent type. There is frequently a high leukocytic count present (15,000-30,000), even during the initial stages. In some cases, the onset may be more insidious and the clinical course less highly acute.

In tropical and subtropical countries in particular, the physician should be constantly on guard for the early recognition of hepatic complications. Rogers has submitted a convincing array of figures to prove that a great reduction in the death rate occurs in hepatic entamebiasis as a result of the prompt recognition and cure of the infection during the presuppurative stage. He claims that during four consecutive years, no case of hepatitis in the Calcutta European General Hospital went on to abscess formation, every potential case having been aborted by the prompt employment of emetin, while in a considerable number of cases in which suppuration was already established in the organ, a marked reduction in mortality was likewise noted as a result of the use of this drug.

SUPPURATIVE STAGE.—Unless treatment is instituted at an early period, suppuration practically always occurs and the case then becomes one of frank abscess of the liver. With the formation of pus, the clinical course becomes modified in many respects from that of the presuppurative stage. The septic element is increased and the local symptoms also become more pronounced. The chief clinical features of the abscess stage are as follows:

General Disturbances.—A characteristic picture is usually present, especially during the later stages of the disease. The facies presents an expression of intense lassitude with drawn features and sunken eyes. The complexion is sallow or muddy, the mucous surfaces show considerable pallor, and the conjunctiva often appears faintly jaundiced. The pulse is rapid and of low tension, and there is, as a rule, great muscular exhaustion, which finally forces the patient to go to bed. The whole picture is one of general constitutional depression due to profound toxemia. On the other hand, in the absence of the toxic element, even a large abscess may pass through successive stages of development without serious constitutional disturbanees.

Fever.—Fever constitutes one of the most constant and reliable of the clinical symptoms of hepatic abscess. The patient is not always aware of the presence of increased temperature, and it is frequently first discovered by the use of the thermometer. In the majority of cases, the fever is continuous, with only a slight rise during the afternoon hours. In other cases, the afternoon rise is more marked, reaching 104° F. (40° C.) at times, and there may be complete defervescence during the early part of the day. The latter intermittent type of temperature is most commonly observed during the earlier stages of the disease, before the abscess cavity has become walled off by fibrous tissue. When this process is complete, the fever curve assumes a lower range and may eventually become normal. Abriol noted 4 cases of normal temperature among 38 cases observed by him in the Philippines. The spontaneous rupture or drainage of an abscess is usually accompanied by a sudden and sharp rise in temperature, due to secondary infection with bacterial organisms.

Sweating.—Copious sweats are frequently present in connection with the increased temperature. When very profuse or drenching in character they tend to lower the fever temporarily, and may produce considerable depression. If the fever happens to be of the intermittent variety, with a high afternoon rise followed by a drenching sweat, the condition is often looked upon at first as one of malarial infection. The examination of the blood in conjunction with other signs should suffice, however, to clear up all doubt in regard to the diagnosis of the two conditions.

Local Symptoms.—The local symptoms vary greatly in each case. The symptom most frequently complained of is pain situated in the right hypochondrium. In most instances, the pain is of an aching or boring character and is apparently increased by any physical effort on the part of the patient. Even a turning movement from side to side may bring about increased signs of distress. The pain is rarely of a severe nature, but the constant nagging sensation in the region of the liver proves very depressing to the patient. Complaint is made at times of a peculiar sense of fullness and heaviness under the right costal arch, due to increased tension in Glisson's capsule. As the abscess encroaches more and more upon the peritoneal surface of the liver, the pain becomes sharper and more lancinating in character. This type of pain is, as a rule, a sure indication of the onset of a localized peritonitis. When the dome of the right lobe becomes involved, just beneath the diaphragm, the pain is often referred to the right shoulder, or may even radiate down the right arm to the finger tips. There is, however, nothing characteristic in this feature, since it is observed in other disease conditions affecting the right lobe of the liver.

Physical Signs.—An increase in the normal border of the liver dullness is brought about by enlargement of that organ. This, therefore, constitutes a common physical sign in abscess of the liver. The character of the enlargement is necessarily determined by the size and location of the abscess. When the right lobe is affected, the enlargement is usually directed upward towards the diaphragm, resulting in en-

croachment upon the normal borders of the right lung. The upper edge of liver dullness, in this case, is often irregular in contour with the highest convexity in the axillary line. When the abscess occupies a posterior position, much difficulty may be experienced in differentiating the condition from pleural effusions. A similarity of clinical symptoms may create further confusion. Abscesses in the left lobe are also a special source of diagnostic difficulty which often requires considerable time and skill to solve. This condition usually presents itself as an indefinite enlargement or bulging in the epigastrium, with ill-defined borders of dullness and considerable tenderness and rigidity of the abdominal wall. Bulging is likewise observed in advanced abscesses situated in the right lobe. With the onset of a localized peritonitis, friction sounds may be heard occasionally in the region of the right lobe. This may be either of peritoneal or of pleuritic origin. The normal free excursion of the diaphragm to the right may be entirely absent (Litten's sign). This signifies inflammatory fixing of the diaphragm and may serve as an indication of impending rupture into the pleura. In the presence of a large abscess, shortly before rupture, the thoracic walls become especially sensitive to touch and deep pressure over the liver region will frequently produce excruciating pain.

Cough.—When rupture takes place into the pleural cavity or into one of the larger bronchi, cough becomes a prominent symptom. However, even in the absence of this complication, a dry, hacking, rasping cough is frequently present from the onset. This latter type of cough is caused by irritation of the diaphragm or pleura. Expectoration is profuse in the case of rupture into the lung, and the sputum has a characteristic chocolate color or the appearance of anchovy sauce.

Blood Changes.—A leukocytosis, when present, is a valuable diagnostic sign both in the suppurative and the presuppurative stages. It should be remembered that a high leukocytosis is frequently present, even before suppuration has set in. Rogers records a count of 28,500 in one case, which subsided completely without abscess formation. In only 2 of this author's series of 63 well studied cases did the count exceed 35,000, even when extensive suppuration had developed. Leukocytosis is, however, found entirely lacking in some cases. In 8 of Abriol's 38 cases, for example, the leukocytic count was practically normal, varying between 6,000 and 10,000. Rogers believes that a low leukocytic count is always associated with a marked degree of anemia, so that the decrease is relative rather than real. The differential count is probably more important diagnostically than the total count of white-cells. In entamebic hepatitis, whether suppurative or non-suppurative, the polymorphic neutrophils do not register the proportionate increase which appears in other septic conditions, rarely exceeding 70 per cent. of the whole. The presence of this low polynuclear count, in conjunction with a high total count, should always prove suggestive of entamebic complication in the liver. In advanced abscess cases, a mild degree of secondary anemia is very rarely absent.

Diagnosis.—The clinical symptoms of the disease are subject to

many variations and, in fact, the entire course may be so insidious that the first indication of the serious nature of the malady is revealed by the sudden perforation of the abscess into some neighboring organ. In tropical practice, the uncertain manifestations of the disease are well recognized and the diagnosis is not overlooked as often as is the case in regions where the infection appears only sporadically. The following admirable set of rules, formulated by Manson, may be made to apply in all regions:

"Golden rules in tropical practice are to think of hepatic abscess in all cases of progressive deterioration of health, and to suspect liver abscess in all obscure abdominal cases associated with evening rise of temperature, and this particularly if there be enlargement of, or pain in, the liver, leukocytosis and a history of dysentery—not necessarily recent dysentery. If doubt exists, there should be no hesitation in having early recourse to the aspirator to clear up the diagnosis."

Almost every type of enlarged liver has been mistaken at times for entamebic abscess. Special confusion exists in inflammatory swellings where a high leukocytic count is present. The relatively low polynuclear count in entamebic hepatitis may prove of value under such circumstances. Cases which show marked daily remissions or intermissions of temperature are often treated for malariai fever before the true nature of the trouble is revealed. The difficulty in diagnosis is further increased by the presence of an enlarged liver, in many cases of chronic malarial infection, although examination of the blood should serve to remove all doubts. The various forms of tuberculosis, and particularly tuberculous pleurisy with its irregular hectic type of temperature and increased thoracic dullness, have likewise been frequently mistaken for abscess of the liver. Here the definite aspect of an enlargement of the liver with a previous history of dysentery should prove of assistance in the diagnosis.

The *x*-ray has been employed in recent years as an aid in the diagnosis of liver abscess. Under the fluoroscope, the diaphragm will often appear fixed and immovable over the dome of the liver. The shadow of the organ as a whole may show great enlargement and, in some instances, definite bulging and pointing of the abscess can be made out with clearness. Pathological conditions in the lungs can also be promptly differentiated in this manner from those which have their origin in the liver.

In all doubtful cases, the exploratory needle or aspirator should be used, as previously mentioned by Manson. If more use were made of this comparatively simple procedure, the author is firmly convinced that a great amount of unnecessary suffering on the part of the patient as well as of embarrassment to the physician might be avoided.

Complications.—Aside from the uncertain effects of the toxins upon the various organs of the body, the chief complication encountered in the course of the disease is the spontaneous rupture of the abscess into contiguous areas surrounding the liver. The most frequent route of rupture is through the right pleural cavity or lung. Craig has arranged

the following table, based upon statistics obtained from different observers, which furnishes a guide to the relative frequency of rupture involving the neighboring regions of the liver:

Observers	Cases of Liver Abscess	Cases of Rupture	Pericardium	Pleura	Lung	Colon	Stomach	Bile ducts	Vena cava	Kidney	Lumbar Region
Waring....	300	68	14	28	15	2	1	1	3	2	2
Dutroulau.	66	25	2	10	7	1	1	..	..	..	4
Rouis.....	162	54	11	17	14	3	6	2			
Haspel....	25	6	4	2							
Camboy...	10	3	...	2							
Howard...	6	5	5								
Craig.....	24	7	2	5							

The average percentage of rupture in this series of 593 cases is 28 per cent. With modern methods of treatment, the probability of rupture into other organs has been reduced to a degree considerably below this figure. The clinical manifestations of a spontaneous rupture depend almost entirely upon its location. When rupture takes place into the lung, expectoration of typical liver abscess pus follows, as described above. Rupture into the pericardium is, as a rule, promptly fatal. On the other hand, the spilling of the abscess contents into the peritoneal cavity may not prove fatal, if secondary infection with bacteria is absent at the time of rupture. In those cases in which drainage is established through the skin, a local infection with the specific organism is sometimes set up. A particularly intractable type of phagedenic ulcer has been found to occur over the skin surface, and scrapings from the ulcers, as a rule, show characteristic forms of *Entameba histolytica*.

Treatment.—Treatment is largely of a **surgical** nature. A number of medical aspects are also presented, however, which require brief discussion. According to Rogers, suppuration might be prevented, in many instances, by the prompt use of **hypodermatic injections of emetin** during the presuppurative stage. Great reduction in the incidence of hepatic abscess, as a whole, has been claimed by this author, since the introduction of **emetin as a routine method of treatment.** As a result of his vast experience with the disease in India, Rogers believes that the following conclusions are justified: "It is not too much to say that the vast majority of early cases of amebic hepatitis should be rapidly cured and the formation of tropical liver abscess should become a very exceptional occurrence, and one which ought to cause serious questionings in the mind of the medical man under whose care it has been allowed to develop." This view is gradually gaining acceptance in all quarters.

After the formation of the abscess, **open drainage** unquestionably constitutes the best method of treatment. Small single abscesses may

occasionally be cured without drainage by **aspiration** in conjunction with **subcutaneous injections of emetin.** After drainage has been established in the larger abscesses, the abscess cavity itself may be **washed** out with various anti-amebic solutions. **Solutions of quinin** have been extensively used for this purpose. Mebane suggests the treatment of the abscess walls with solutions of fluid **extract of ipecac** in a strength of one-half ounce to a quart of saline. **Aqueous solutions of emetin** (1-50,000) have also been recommended for the same purpose. Most authorities agree that great assistance is rendered during the post-operative treatment by the employment of **systematic daily doses of emetin hypodermatically.** If recurrences are threatened, further progress of the morbid lesions is often checked by the prompt use of this drug.

Prognosis.—The chances of recovery in entamebic involvement of the liver depend upon several factors, as follows:

(1) *The stage of the disease:* The outlook is considerably more favorable in those cases which do not suppurate, or where the suppurative process is quickly checked by proper medical treatment.

(2) *The number of abscesses present:* This is of decided importance in the prognosis. Multiple scattered abscesses present a serious condition because of the difficulty involved in drainage and of the greater degree of toxic absorption which ensues. Fortunately, this type of the disease is rare.

(3) *The site of the abscess:* Abscesses of the right lobe yield a higher mortality than those situated in the left lobe. This is probably due to the greater size which abscesses of the right lobe attain before their presence is discovered.

(4) *Size:* Since the size of an abscess is largely determined by length of time it has existed, chronicity plays an important part in the prognosis. However, recovery has been found to follow in some instances where the abscess cavity has occupied as much as one-half of the entire right lobe.

Upon the whole, the prognosis is always to be looked upon as grave. The following table, compiled from various sources, furnishes an insight into the grave consequences of the disease:

Observers	Cases	Country	Mortality (per cent)
Rouis	203	Algiers	80
Castro	125	Egypt	72.5
Rogers	64	India	53
Megaw	292	India	60.1
Rogers	52	India	73
Futcher	27	United States	70

Pathology.—A series of progressive changes take place in the liver as a result of the invasion of that organ by the *Entameba histolytica.*

The initial step in the pathology of the disease is the occurrence of a simple hepatitis, which results from a diffuse spreading of the active vegetative organisms through the small radicals of the portal veins. This corresponds clinically with the presuppurative stage, described by Rogers. The factors which eventually determine the formation of pus are not altogether clearly defined. Thrombosis is set up in some of the smaller vessels as a result of a cytolytic toxin, so that the organisms themselves become entangled, and further passage through the vessels is stopped. Here further toxins are evolved which eventually bring about a more active proliferation of the tissue-cells. Enlargement of the particular lobe involved is a natural sequence to this diffuse regenerative process. In some cases, the pathological process never passes beyond this stage. Rogers believes that the formation of pus is due to the escape of the pathogenic organism through the vessel walls. This phenomenon is observed only when thrombosis has developed, cutting off a further supply of blood to the parts. In the necrotic center thus produced, the protozoal parasites are enabled to migrate from the vessels into the liver-cells, thus setting up proteolytic changes. A coalition of several such small foci results in the formation of the larger type of abscess, commonly found in the disease. The size of the abscess cavity becomes limited by a dense fibrous capsule which is produced by a defensive reaction on the part of the liver-cells. In chronic protracted cases, which have not drained, this limiting membrane gradually increases in thickness and eventually becomes a source for the constant secretion of purulent material (pyogenic membrane). In this manner, the abscess cavity continues to enlarge and reaches a size out of all proportion to the amount of liver substance involved. Some authorities have reported the finding of as much as 2,000 c.c. of purulent material in the aspiration of a single abscess. The number of abscesses vary within wide limits. In over 70 per cent. of the cases, the morbid process is limited to a solitary abscess, which usually reaches large proportions before its presence is discovered. Rogers believes that multiple abscesses are always the result of a mixed infection with staphylococci. Pus aspirated directly from the abscess cavity is almost always found to be sterile. The pus itself is of a characteristic thick viscid consistency and possesses no odor. Under the microscope, a large number of disintegrated liver-cells appear, in conjunction with red blood-corpuscles, leukocytes, fat globules, cholesterin and Charcot-Leyden crystals. Entamebæ are rarely found in the aspirated pus, but may appear in large numbers when fresh scrapings are made from the abscess walls.

Abscess of the Brain (Cerebral Entamebiasis)

In nearly every instance, this condition occurs as a sequela to abscess of the liver. It is, on the whole, a rare complication. Forty-eight cases in all have been reported in the literature to date. An excellent review of the bibliography, including a detailed analysis of all previously reported cases, is to be found in an article by Armitage in the *Journal*

of Tropical Medicine and Hygiene (April 15, 1919). The first recorded case was described by Morehead in 1838. The infection reaches the brain from the liver by way of the arterial circulation. The smaller vessels, just as in the case of entamebic hepatitis, act as a barrier to the passage of the pathogenic organisms. The obliteration of the vessels serves as the starting-point for the formation of a necrotic infarct. From these foci, the organisms set up further changes, eventually forming large abscesses, varying in size from that of a nut to that of an apple. The abscesses may be single or multiple. Practically all parts of the brain may be affected, including the cerebellum. Both vegetative and encysted entamebæ can usually be obtained from the pus or abscess wall. The clinical symptoms depend largely upon the location of the abscess and do not differ markedly from those found in other forms of cerebral abscess. When the silent areas of the brain are involved, local symptoms are, as a rule, missing. Indeed, the condition may be detected only at autopsy, as in a case recently reported by Stout and Fenwick.

In larger abscesses, the course is usually rapid and fatal. A small abscess, according to Brown, may encyst and give rise to no further trouble. Cerebral abscess is always to be suspected when severe toxic symptoms persist after the drainage of a liver abscess. In some cases, the condition only appears after the hepatic lesions have subsided.

The treatment is principally surgical.

Abscess of the Spleen (Splenic Entamebiasis)

This complication is even less frequent than that of cerebral abscess. The route of infection is usually through the portal vessels, although direct invasion of the organ is possible by contact with ulcerative lesions situated in the splenic flexure of the colon. Abscess of the spleen supervenes, as a general rule, during or following hepatic abscess. The clinical symptoms are those of splenic tumor, accompanied by evidences of general toxemia.

The prognosis is not favorable on account of the rapid progress of suppurative lesions in the spleen.

Urinary Entamebiasis

Infection of the genito-urinary tract with parasitic amebæ was first recorded by Baelz, in 1883. He found large motile amebæ in the bloody urine and in the vaginal secretion of a patient in Japan. The organisms measured from 23 to 50 microns in diameter, and possessed short blunt pseudopodia. Baelz's observation was made many years before the present basis for the differentiation of the entameba was established, so that the exact character of this particular organism cannot be accurately determined. Cases very similar in character were subsequently reported at different intervals by Jurgens, Posner, Kartulis, Wijnoff and Jefries. In all of these cases, the symptoms were those of an infected bladder in conjunction with a purulent and san-

guineous urine. In 1911, Craig made a complete study of the organism associated with this condition, which up to this time had been considered as entitled to specific rank, under the name "Entameba urogenitalis." Craig came to the conclusion that this organism did not represent a distinct species, but was to be looked upon as identical with *Entameba histolytica.* The parasite appears in the genito-urinary tract, solely as a result of an accidental migration from its original habitat in the intestine. This view has been generally accepted by recent writers. Fischer, Lynn, Walton, Chalmers, O'Farrell and Macfie, have each recorded cases of genito-urinary entamebiasis as a sequela to intestinal entamebiasis. The mode of entrance of the organism into the urinary tract varies in each instance. At autopsy in one of Craig's cases, a small fistulous opening was discovered between the large bowel and the bladder. Walton believes that the infection in his case, that of an East Indian, was brought about by the transference of the organism from the rectum to the genitalia, through ablution of the parts. It is probable that the organisms reach the bladder, in most instances, by direct migration from the anus when cleanliness of the parts is not carefully observed.

TREATMENT

General Prophylaxis

Entamebic dysentery, like other infectious conditions of the intestinal tract, nearly always arises from the swallowing of contaminated food or drink. The chief infectious agent is now generally recognized to be the encysted form of the organism rather than the trophozoites, since the latter are readily destroyed by the action of the gastric juice in the new host, and, in addition, cannot withstand destructive influences outside of the body. The cysts, on the other hand, are highly resistant to external conditions, and remain viable for an indefinite period after they are discharged from the body, if afforded protection against sunlight and dryness. Wenyon states that the cysts of *Entameba histolytica* are killed instantaneously when deprived of a sufficient amount of moisture; the cysts of other intestinal protozoa are affected in a similar manner. Thompson and Thompson found from their experiments that the entamebic cysts remained unchanged in water for as long a period as one year and the same proved true for feces, if a proper degree of moisture was provided. The moist soil and humid atmosphere of tropical countries thus affords a suitable environment for the continued life of the cyst after it leaves the body. From the soil, the cysts are distributed by various means to supplies of drinking water and to foodstuffs.

Flies and other insects serve as the chief disseminators of the infection. As a result of an elaborate series of experiments carried on principally with flies, Wenyon and O'Connor concluded that:

(1) Flies allowed to feed on infected feces are enabled to take up encysted and other forms of protozoa readily into the intestines.

(2) The cysts do not degenerate to any extent in the gut of the fly, and are passed on unaltered in their droppings.

(3) Flies can thus deposit in their droppings material which they have ingested only five minutes before.

(4) Flies becoming infected in this way will naturally deposit material on any kind of food on which they feed, and it seems that the wide distribution of human protozoal infections in warm countries can best be explained in this way.

(5) The fly is much more dangerous on account of material passed through the intestine directly, than on account of material which it may regurgitate, or which has become attached to its legs or body, as the latter quickly dries, and is in most instances quickly destroyed.

The observations of these authors, which have now been confirmed by practically all other workers in this field, demonstrate the great importance of directing stringent sanitary measures toward **destroying the breeding-places of flies** and **limiting** the uncontrolled **distribution** of these and other insects in the homes and eating-places of human beings.

The part played by moisture in keeping the cysts alive after they have been discharged from the human body, or after their deposit from the intestinal tract of flies, has been insisted upon by Woodcock. This factor must likewise not be overlooked in considering the epidemiology of the disease.

In general, the measures to be employed in the prophylaxis of entamebic diseases, may be summarized under the following headings:

(1) The destruction of the organisms within the human body, by means of specific medication, before opportunity has been allowed for encystment.

(2) The destruction of the organisms, and especially the encysted forms, following their evacuation from the body.

(3) Measures directed toward the prevention of contamination of the soil by the cysts.

(4) The safeguarding of all potential sources of infection from contact with flies and other insects.

As regards the destruction of the organisms within the body prior to encystment, it may be said that a solution of this problem would in time serve to eradicate the disease completely. This is, however, to a great extent impracticable, especially where large numbers of individuals are involved.

Two types of disease carriers are recognized:

(1) The convalescent carrier, who has experienced previous clinical manifestations from his infection.

(2) The contact carrier, who has remained entirely free from symptoms, but who is none the less a free distributor of the infection.

In both instances, the disease is transmitted to other individuals through cysts passed in the stools. The active motile entamebæ succumb quickly outside of their ordinary intestinal environment. Encystment

takes place only within the body, and it is probable that the cysts are never destroyed by the administration of therapeutic agents.

Bass has approached the prophylaxis of malaria by attempting, on a large scale, within certain districts in the State of Mississippi, the destruction of the malarial cysts in the human carrier.

The constant killing off of the vegetative forms of these organisms in the blood stream, by means of sufficient doses of quinin, has rendered it possible to prevent the further spread of the disease to other individuals, by eliminating the carriage of cysts in the bodies of mosquitoes. A somewhat similar procedure is possible in the case of entamebic infections, within definite localities, but its success would necessarily depend upon a broad scope of operation. Lacking this, prophylaxis must be confined to **controlling the spread of the cysts outside of the body.** The measures to be adopted to this end should include:

(1) The disinfection and sanitary disposal of feces in infected localities.

(2) The safeguarding of the water supply from infection, as well as the boiling of drinking water and milk, when the possibility of infection is present.

(3) The avoidance of raw fruits and raw vegetables, grown in infected soils.

(4) The general destruction of flies and other insects as well as the screening of homes against their free and unlimited access.

General Medicinal Treatment

Ipecacuanha.—In the treatment of entamebic dysentery, only one drug is to be seriously considered, and that is **ipecacuanha,** administered in some one of its many forms. Fortunately, we possess in this drug a true specific for the malady, and one which will prove successful in the vast majority of cases, if properly administered.

The use of ipecac in connection with dysenteries dates back, in point of fact, to a very early period in medical history. The drug was first introduced into Europe in 1682 by a traveler, who had heard its virtues extolled during a brief sojourn in Brazil. For many decades prior to this time, the natives of the latter country had made empirical use of the drug as a remedy against the many types of enteric disturbances which abound in that region. A large quantity was subsequently procured by Helvetius, a Dutch physician then residing in Paris, who proceded to dispense it liberally in all forms of dysentery, without revealing its nature. Great prominence was finally attained in the case of the Dauphin, son of Louis XIV, who had suffered from dysentery for many years. The favorable outcome in this case so impressed the French government, that the closely guarded secrets of the wonderful formula were purchased outright from Helvetius. In course of time, ipecac came into general use in all forms of bowel derangements, without regard to the cause and with only varying degrees of success. Before the discovery was made that dysentery was not in itself a clinical entity, but

denoted merely a group of clinical symptoms arising from widely different causes, it was but natural that diversity of opinion should have existed in regard to the therapeutic value of the drug. It is in fact only within the past half century that its distinctive value in entamebic infections has become definitely established. Nevertheless, it is interesting to note that even in quite recent years the specific effect of ipecac in entamebic infections has not always been clearly seen or acknowledged. This was exemplified by a number of our army officers in the Philippines, following the close of the Spanish American War, who seemed to be particularly opposed to the use of the drug.

In discussing the treatment of entamebic dysentery at that time, Strong claimed that he had employed ipecac in many cases which came under his observation in the Philippines, and did not consider this agent in any sense curative; he attributed the subsidence of acute symptoms to the effects of the opium which was used in conjunction with this drug. Jackson appeared even more outspoken in his opposition, stating that he had seen the drug tried out thoroughly, and was convinced of its utter uselessness, and also of its harmfulness. Sandwith was also frank in acknowledging his lack of faith in the remedy at an earlier period of his career in the British colonial service, but subsequently became convinced of his error. He explained his reason for this change of opinion in the following words:

"I think it is now obvious that my failures, which were also experienced by many good clinicians in India and other tropical countries, were chiefly due to two facts:

"(1) We knew but little of the various types of dysentery, and when we met with no success or with very partial success, we blamed the ipecacuanha, instead of discovering that we were very often aiming at bacilli with a weapon which we know now is only warranted to kill amebæ.

"(2) We were taught to administer ipecacuanha in single doses, repeating it, though it was vomited by the patient, and occasionally giving a third dose if necessary, but it was not the fashion to prolong the use of the drug. It hardly occurred to us to imagine that if slight temporary benefit occurred after one nauseous bolus, a permanent cure might be attained by continuing the remedy."

This frank acknowledgment of previous failure and ultimate success with ipecac may be taken to heart with profit by many conscientious physicians at the present day. The real credit for preserving faith in the specific action of the drug in entamebic diseases must be accorded to Sir Patrick Manson, whose allegiance to this particular remedy never seemed to waver, even in the face of skepticism expressed on all sides. Largely as a result of Sir Patrick Manson's enthusiasm, the writer himself, in 1908, after experiencing many failures with other measures, ventured to make use of the ipecac root in the treatment of a number of chronic entamebic infections of the intestinal tract. The marked success which attended the trial of the drug in these cases was made

the basis for a report published during the following year. A short time previous, Dock had reported similar favorable results from the same field.

The publication of these two papers, almost simultaneously, caused a general revival of interest in this old-time remedy, especially in this country and in its newly acquired tropical possessions. It had been found that the nauseous effect of the drug in pill form might be overcome, to a considerable extent, by a proper enteric coating of **salol**, in accordance with a suggestion previously made by Rogers.

INTRODUCTION OF EMETIN.—Nevertheless, many bedside disadvantages still clung to this plan of treatment and, in the course of time, demand was made for a more simple and less disagreeable method of administering the drug. This demand was met in 1912 by the introduction of **emetin**, one of the active alkaloidal derivatives of the ipecac root. Two years previous, Vedder had made the discovery that the ipecac alkaloids were effective in destroying *ameba limax* in culture, in dilutions as high as 1 to 100,000. Credit is due chiefly to Rogers for making clinical application of this finding in the treatment of entamebic diseases in man.

As early as 1817, Peletier, a French chemist, had made a study of the constituents of the ipecac root. The name emetin was given by Peletier to the single alkaloid, which he believed that he had extracted from the plant. In 1894, Paul and Cownley proved conclusively that the substance known as emetin was, in fact, a mixture of three alkaloids, which were entitled in turn: *emetin*, *cephalin*, and *psychotrin*. Each of these alkaloids was found to possess distinctive pharmacological properties. According to these authors, the emetic action of ipecac was produced for the most part by cephalin, and did not reside, as was formerly believed, in emetin alone. A further analysis of the alkaloids was undertaken by Wild in 1895, who carried on an extensive series of experiments in man and in the lower animals. Not only was Paul and Cownley's work confirmed, but Wild also became convinced that the medicinal effect of ipecac was due to cephalin and emetin respectively to about equal degrees. Psychotrin was shown to be devoid of all therapeutic action.

Following the publication of Rogers' successful clinical results with emetin, the drug gained wide and extensive usage in the treatment of entamebic dysentery and its allied conditions. In the midst of the general acclaim over the virtues of this newly discovered therapeutic agent, the previously established value of the parent drug was almost entirely overlooked. In the eyes of many careful observers, the fact soon became apparent, however, that while emetin did undoubtedly exercise marked control over the acute and subacute manifestations of entamebic dysentery, in the majority of instances, the effect was merely temporary, the organisms being checked in their activity without suffering complete destruction. This latter effect had formed an important claim made in behalf of ipecac by those who had previously become fully conversant with its effect in chronic cases. In large numbers of cases treated

with full doses of emetin, relapses were found to occur with considerable frequency. No question could be raised concerning the selective action of the drug on the pathogenic entamebæ, but this action appeared to be confined to the large trophozoites, and did not materially affect the smaller and more resistant vegetative forms.

Since the clinical symptoms of entamebic dysentery are dependent in great measure upon the activity of the *histolytica* organism, it is easy to understand the marked effect produced by emetin upon the acute manifestations of the disease. None the less, the author is firmly of the opinion that apart from this clinical phase, the **entire ipecac root** must needs be relied upon to achieve complete sterilization of the intestinal tract in the presence of a firmly intrenched infection.

Method of Administering Emetin.—Emetin is commonly administered in the form of the hydrochlorid or hydrobromid salt. Both have proven to be equally effective, but the hydrochlorid combination, on account of its greater solubility, is more applicable for general use. The oral administration of the drug is accompanied by little, if any, discomfort to the patient, in marked contrast to the nauseous effect produced by ipecac, when given by mouth. The amebicidal action of the alkaloid is very feeble, however, when taken directly into the digestive tract. For this reason, the subcutaneous method is to be preferred. When injected under the skin, the drug is rapidly absorbed and reaches the blood stream in a more concentrated form than by the oral route. In highly acute and fulminating cases, requiring immediate and urgent treatment, intravenous injections may be resorted to without danger to the patient. The dose for the intravenous injection should not exceed ½ grain (0.0324 gram). For hypodermic medication, as much as 1 to 1½ grains (0.065 to 0.097 gram) may be employed every twenty-four hours, with perfect safety in most instances. Any amount above this, however, is liable to be followed by toxic symptoms, especially if repeated for several days without intermission. In chronic cases, the plan usually followed is to administer daily doses of from ½ to 1 grain (0.0324 to 0.065 gram) by needle, covering a period of ten days. In obstinate infections, some authors have recommended the repetition of this dosage in several courses, or until the organisms have entirely disappeared from the stools. Some danger is connected with the continued use of emetin in this manner, so that precaution is necessary when the prolonged use of the drug is undertaken.

Toxicology of Emetin.—Within a short period following the introduction of emetin, instances of its toxic effects on the human organism were recorded from numerous sources. As early as 1895, Wild had made an exhaustive study of the toxic properties of emetin and cephalin, both in man and in the lower animals. At that period, the subject had possessed a purely academic interest, but it achieved great prominence subsequently when to the pharmacological aspect a clinical aspect was added. In more recent times, further contributions have been made to the subject, so that fairly accurate knowledge is now available in regard to the toxicology of these agents. Of these contributions, the

most notable perhaps has been the extensive series of experiments, conducted by Pellini and Wallace in 1916, regarding the toxic action of emetin upon the various organs of the body. These authors employed cats for the most part in their experiments, and as a result of their findings they were able to formulate the following conclusions:

(1) Emetin depresses, and may eventually paralyze, the heart.

(2) It is a powerful gastro-intestinal irritant, whether given by mouth or by subcutaneous injection.

(3) It causes a definite derangement of metabolism characterized by an increase in nitrogen loss and an acidosis.

(4) While in normal individuals, if the drug is given in moderate doses, these actions may not be of importance in pathologic states of the circulation, intestinal tract or metabolism, there may be a very definite source of danger.

In clinical practice, markedly poisonous effects are rarely observed in connection with the comparatively small doses of emetin ordinarily employed, although mild attacks of toxemia are by no means uncommon. In the writer's opinion, the harmful features of the drug have been on the whole overemphasized. In a large series of cases in which moderate doses were employed over a limited period, complications were encountered in but relatively few instances. Any dosage in excess of 1 grain (0.065 gram) per day, without control over the duration of the treatment, will increase the probability of toxic effects to a considerable extent. Under such conditions, the various organs of the body may be affected in the following manner:

Gastro-intestinal Tract.—In most instances where hypodermic injections of emetin are found to produce vomiting, contamination of the drug with cephalin is to be suspected. The author is led to this belief by the fact that when a pure product has been obtained, vomiting has rarely, if ever, occurred. As stated previously, cephalin constitutes the true emetic principle of the ipecac root, acting directly upon the vomiting center in the medulla. In many instances in which emetin is used in excessive doses, and especially over long periods, a particularly obstinate type of diarrhea develops. This condition does not always clear up readily, according to the author's experience, even with the discontinuance of the drug. Considerable importance is attached to this so-called emetin diarrhea, since often a vicious circle is produced by persisting in the use of the drug for an indefinite time, long after its amebicidal action has been completely expended.

Circulatory System.—In the experience of most observers, emetin may at times produce a depressing action on the heart and blood-vessels. Even sudden death has been attributed in rare instances to an over-use of the drug. In the lower animals, large doses of the drug have been shown to exert an especially deleterious effect upon the heart functions. This was noted by Dale in a series of observations made upon dogs, and more recently by Pellegrini and Wallace in the case of cats. In man, Wenyon observed signs of disturbances of the heart's action in only 2 cases in

his entire series of bedside observations with emetin. In both cases, irregularity of the heart-beat and shortness of breath were the predominating symptoms. In one of the author's own cases, marked cardiac arhythmia followed the use of comparatively small doses. A fatal issue was reported by Rowntree in the case of 2 individuals, where only moderate doses of the drug had been employed. These cases claimed considerable attention because of the fatal outcome, but in neither instance was it definitely proven that the emetin alone had served as the cause of death. Rowntree himself attributed the result to the presence of certain impurities in the drug itself, although he was not able to ascertain their exact nature. Nevertheless, experiments on the lower animals have clearly indicated that a certain degree of caution is necessary in the administration of emetin, in the case of individuals who are suffering from myocardial and circulatory diseases. Patients of this type should be kept in bed and under constant observation for approaching signs of cardiac depression.

Nervous System.—Undoubtedly, the most frequent complication met with in the routine administration of emetin is a mild form of peripheral neuritis. The lower extremities are affected in the majority of cases. As a result of this complication, the patient experiences a feeling of soreness and stiffness in the muscles, which becomes especially noticeable when he walks. In some instances, he is compelled to remain in bed until the more acute manifestations have subsided. Permanent impairment of function is, however, very rarely observed. The muscular discomfort will usually be found to clear up within a short period, seldom exceeding two or, at most, three weeks in duration. There is a certain degree of susceptibility on the part of the nervous system in the case of some individuals, which explains the unexpected occurrence of peripheral neuritis at times, even when only comparatively small doses have been employed.

Local Irritation.—When the powdered ipecac root is brought into contact with the skin and mucous surfaces of the body, it produces marked irritation. For this reason, individuals who are compelled to handle the drug in large quantities for commercial purposes sometimes suffer much inconvenience. The subcutaneous injection of emetin is occasionally followed by a marked local reaction. The majority of patients, however, suffer few disagreeable effects from their injections. In introducing the drug under the skin, care should be taken to avoid the finer nerve-trunks and blood-vessels. It is also inadvisable to inject the drug into the muscles, since this is almost invariably followed by a sensation of soreness which may persist for many days. With these precautions in mind, the entire course of hypodermic medication with emetin can be accomplished with comparatively little annoyance to the patient.

ADMINISTRATION OF CEPHALIN.—While the investigations made in regard to the toxicology of **cephalin** have not been carried out upon as extensive a scale as has been the case with emetin, a close similarity in the action of the two alkaloids has nevertheless been revealed. Cephalin

not only possesses greater emetic properties, but is to a considerable degree more irritating to the skin, when given hypodermatically, than is emetin. As amebicidal agents, both are probably equally effective. This was strongly indicated in the course of some clinical experiments which the author was enabled to make some few years back upon a limited number of adult subjects who were suffering from an active type of entamebic dysentery. The following conclusions were drawn from these observations:

(1) Cephalin would seem to possess an amebicidal action upon the free-living entameba to a degree at least equal to that of emetin in the same dosage.

(2) The destructive effect of cephalin upon the more resistant strains of the organism would appear to afford more promise of success than that induced by emetin. One of the author's cases has remained free from relapse for a period of five months. Repeated examinations revealed no reappearance of the cysts in the stool during that time.

(3) The administration of cephalin by the subcutaneous route produces considerably more irritation and pain at the site of puncture than does emetin.

(4) Evidences of gastric disturbances accompanied by nausea and vomiting are encountered with more frequency and to a greater degree with the use of cephalin than with emetin.

(5) There is less tendency to diarrhea in the course of the cephalin therapy than follows the use of emetin.

(6) The employment of a combination of the two alkaloids by hypodermic injection would seem to promise a greater amebicidal effect than is obtained with emetin alone.

(7) No evidence of toxemia was observed following the employment of the comparatively small doses of cephalin.

These conclusions were not altogether in accordance with those of Rogers, who had also experimented with the drug on a limited scale, but without meeting with especially favorable results. Rogers concluded that cephalin had little effect upon the pathogenic entamebæ.

The local irritation produced by cephalin when used hypodermically is sufficient to bar it from general use.

Synthetic Combinations of the Ipecac Alkaloids.—In view of the relative ineffectiveness of the ipecac alkaloids in chronic entamebic infections, and likewise in consideration of the toxic properties which have been shown to be inherent in these agents, attempts have been made within recent years to devise higher synthetic combinations in the hope that the various objectionable features of the simpler products might thereby be overcome. Of these compounds, perhaps the two most widely employed have been **emetin-mercuric iodid** and **emetin-bismuthous iodid** prepared in accordance with definite formulas devised by Du Mez in 1915. The insolubility of these preparations renders them unsuitable for hypodermic administration. They rarely produce nausea or vomiting if they are taken by mouth immediately after a heavy meal. The

usual dosage is 1 grain (0.065 gram) per day, in an undivided dose, to be given for a period of twelve days. Greater preference has been shown for the bismuth preparation, which has proven less toxic than the mercurial combination. Many claims have been made as to the curative effect of the double iodid of bismuth and emetin in the more intractable forms of entamebic dysentery. This is particularly true for British observers, who in recent years have reported especially brilliant results with this drug in the clearing of cysts from the intestinal tract. This latter phase of treatment will be discussed in more detail when consideration of the carrier state is reached.

Mention might also be made of other synthetic combinations of emetin and of cephalin, for which extravagant claims have been made from time to time. The soluble compound, **methyl-emetin sulphate** was employed in a number of cases by Wenyon and Low with apparently favorable results. According to these authors, this drug might be given hypodermatically in daily doses as large as 2 grains (0.138 gram), which are less toxic in their effect than are the smaller doses of emetin ordinarily employed.

Walters and Koch were likewise impressed with the results obtained in the use of several synthetic combinations of cephalin, citing with particular favor that of **cephalin-iso-amyl-ether-hydro-iodid**. This is an insoluble preparation, which can be given orally in doses as high as 1 grain (0.065 gram) three times a day without toxic results. According to the author's experience, the amebicidal action of this synthetic compound is rather uncertain and cannot be depended upon in the treatment of chronic infections.

A similar opinion may be expressed in respect to **alcresta**, a trade name applied to an absorption compound of the ipecac alkaloids with hydrated aluminum salicylate (fuller's earth). This preparation, although widely advertised as a cure for entamebic dysentery, is not to be recommended in chronic cases. During periods of relapse, an amelioration of symptoms can often be noted following its use, but this proves to be merely temporary and rarely, if ever, curative.

Cause of Failure of Emetin Treatment in Chronic Cases.—Based on analogy with other therapeutic agents, the active principles of the ipecac root should, in these cases, possess a value at least equal to that of the parent substance. Nevertheless, there can no longer be any doubt concerning the superior merit of ipecac over its constituent alkaloids in actual clinical practice. The cause of this apparent therapeutic anomaly has not been made altogether clear. In the author's opinion, the most plausible explanation lies in the measure of concentration attained by the respective drugs in the blood stream after absorption. In the case of emetin, although absorption is rapid, yet considerable dilution is obtained in the circulating fluids in the body, so that by the time the drug reaches the disease-producing organisms within the large bowel, its amebicidal strength has become more or less dissipated. Ipecac, on the other hand, when administered in the form of enteric coated pills, escapes absorption until the large bowel is reached. During the process

of absorption in this region, the drug is brought into intimate contact with the pathogenic organisms, lying buried for the most part within the tissues of the bowel wall. More complete destruction of the infectious organisms is thus brought about than is possible through the indirect route afforded by the blood stream. Various other theories have been advanced from time to time to explain the apparent discrepancy in the results of treatment obtained with the two drugs. It has been held by some that the particular difficulty experienced in the treatment of chronic cases with emetin arises from the fact that, although this drug circulates freely in the blood, it fails to reach the infectious organisms, due to a fibrous state of the tissues surrounding the older ulcerations. It has likewise been urged that a thrombosed condition of the vessels leading to the site of the lesions might possibly interfere with the free circulation of the drug in the disease-bearing areas. A further suggestion has been made that in some cases strains of amebæ may be present which are able to resist the destructive effect of emetin. This resistance on the part of the organisms, it is thought, might be produced by small and inadequate doses, especially if administered over a prolonged period.

Treatment of Acute and Subacute Entamebic Dysentery

The treatment of the acute stage of entamebic dysentery conforms in many respects to the general line of treatment employed in acute bacillary dysentery. The patient should be **placed in bed**, preferably under the care of a competent nurse. The **diet** in the beginning is to be restricted solely to **liquids**, such as broths or strained soups, tea, whey and albumin water. Even milk is contra-indicated during the earlier stages, since its high protein content tends toward further disturbance of the intestinal functions. All substances are best administered **hot** and in **small quantities**.

A **saline purge** is usually needed in the beginning, in order to rid the upper intestinal tract of retained masses of feces. This may be repeated in small doses from time to time, so as to insure a continual drainage of the intestinal contents from above downward. Some form of **opiate** is indicated as a rule, and should be given in sufficient quantity to control pain and afford mental relaxation to the patient. Too large a dosage, on the other hand tends to paralyze the bowel musculature, and otherwise produces a harmful effect by checking the secretions of the body. **Morphin** is to be preferred to other opiates, and should always be given hypodermatically in small and frequently repeated doses, until the desired effect is obtained. Considerable relief is also afforded by the use of **hot, moist compresses** to the abdominal wall. As soon as the presence of the pathogenic entamebæ has been confirmed by stool examination, no time should be lost in administering **emetin hydrochlorid** subcutaneously. In very acute cases, the drug can be injected directly into the vein, in doses not exceeding ½ grain (0.0324 gram) at a time. This may be repeated within six hours, should the urgency of the case

demand. In less severe cases, the subcutaneous method will suffice, the dose ranging from 1 to 1½ grains (0.065 to 0.097 gram) over a period of from twelve to twenty-four hours. Any dosage in excess of this is rarely justifiable. The prompt response to emetin exhibited by practically all acute cases of entamebic dysentery affords a striking example of the specific quality of the drug. In probably no other disease are the symptoms controlled with such marked rapidity and effectiveness. Within a space of from one to two hours or, at most, from three to four hours, a prompt subsidence of the more acute manifestations is noted, as a rule, affecting not only the frequency and character of the evacuations, but the tenesmus and other abdominal disturbances as well. The relief of distressful symptoms should not be taken as an indication for the discontinuance of the drug, since it is now recognized that relapses are apt to occur at a very early date, unless full doses are employed, covering a period of at least a week or ten days. During convalescence, careful search of the stools should be made for vegetative, as well as for encysted organisms. No case should be considered as cured until repeated examinations of the feces have failed to reveal the presence of the infectious organisms. In most instances cysts will be found in the stools after recovery, and the patient then becomes a convalescent carrier with the probability of a recurrence of acute symptoms at a subsequent period.

Treatment of Chronic Entamebic Dysentery

In the treatment of entamebic dysentery, a clear distinction must be made between the relief of clinical symptoms and the complete removal of the infection from the tissues. The lull which follows in the wake of the stormy period of an acute or subacute relapse, in nearly every instance, signifies the conversion of the pathogenic organisms from the *histolytica* stage to the less active *tetragena* or *minuta* stage. While emetin proves to be of great value in the acute or subacute relapses of the disease, it is not to be depended upon for clearing the intestinal tract of a persistent infection. For this purpose, recourse must be had to the **powdered ipecac root,** administered in full dosage and at regularly repeated intervals. The old objection to the employment of ipecac, on account of its nauseous qualities, has unfortunately still not been entirely disposed of. Nevertheless, these slight bedside disadvantages are more than counterbalanced by the highly specific value of the crude drug.

Method of Administering the Powdered Ipecac Root in the Form of Enteric Coated Pills.—The carrying out of this method of treatment on a successful basis depends to a great extent upon a strict observance of details. A general outline of the proposed plan of treatment should, first of all, be conveyed to the patient in order to secure his full coöperation and acquiescence. Complete **rest in bed** is essential throughout the entire course of treatment, which rarely covers a period of over two weeks. The patient should not even be allowed to visit the toilet, a bed-pan or commode being provided for his convenience. At the

outset, it is customary to administer a simple *laxative*, preferably one ounce of *castor oil*, in order to rid the intestinal tract of accumulated food débris. During the first week of treatment, the **diet** should be restricted entirely to **liquid** substances, such as broths, strained soups, tea, coffee, albumin water and nutrient alcoholic preparations. Milk may be added to this list after five or six days. No solid food substances should be allowed during the entire period of the administration of the pills. The main object of these stringent dietary restrictions is the exclusion of all impediments to the ready passage of the pills into the large bowel.

In the compounding of the pills, special care is necessary, and the process should not be entrusted entirely to the uncertain knowledge or skill of the pharmacist. A good quality of ipecac should be provided, containing, if possible, full alkaloidal strength in accordance with the requirements of the U. S. P. Since the **Rio ipecac** possesses the highest assay of alkaloids, it is considered preferable to the Carthagena variety. The pills are dispensed in 5 grain (0.324 gram) quantities, after which they are immersed in a bath of melted salol. Skill is required in obtaining a coating of proper thickness for each pill, which, under ordinary circumstances, should not exceed one-eighth of an inch. In order to prevent caking and cracking of the salol coating, it is recommended that the pills be freshly prepared for each case, in lots not exceeding one hundred at a time.

It has been found best to administer the pills at night when the patient is about ready for sleep. Under no circumstances should the dose be divided into smaller lots for use at different intervals of the day, as has been recommended in some quarters. This defeats one of the main essentials in the treatment, which aims at a concentration of the full effects of the drug at one stated period within each twenty-four hours. For this purpose, at least 10 pills must be employed as a dose, although this may be increased to 15, according to the individual requirements of the case. It is advisable to discontinue all nourishment two or three hours before the administration of the pills, and the patient should be urged to fall asleep as promptly as possible after their ingestion.

A slight attack of nausea and vomiting may occur during the early morning hours, but is readily overcome by the application of **ice cloths** to the neck, and by other simple measures. In the case of some individuals, the drug produces considerable emesis. This may be caused by a lack of sufficient coating of the pills, a deficiency which can be easily corrected; or there may be a definite idiosyncrasy on the part of the patient to the drug. The latter condition is a difficult one to deal with, and recourse must be finally had, in some cases, to other plans of treatment, although fortunately this is rarely necessary. **Opium** will be found to be a valuable adjunct to the treatment when severe vomiting is present. From 10 to 20 drops of the tincture of opium may be given one-half hour prior to the administration of the pills, or **morphin** may be employed hypodermatically in from ⅛ to ¼ grain (0.008 to 0.016

gram) doses, which is equally as effective. Phillips recommends the incorporation of **tannic acid** in the pill mass—from ½ to 1 grain (0.0324 to 0.065 gram) to each pill—as a useful measure to control nausea and vomiting. The author has found this plan to be an admirable one in a number of instances.

The full course of treatment includes the retention of at least 100 pills, equivalent to 500 grains (32.5 grams) of the powdered root. Since in some cases a number of pills are passed undissolved in the stools, a chart should be kept, indicating the exact amount of ipecac retained during each day of the treatment. The following style of chart has been found useful for this purpose:

Date	Pills Administered Each Day	Total Pills Taken	Pills Passed Each Day	Total Pills Passed	Total Pills Retained	Clinical Notes
Oct. 1.....	10	10	0	0	10	
Oct. 2.....	14	24	1	1	23	Slight emesis in early morning hours
Oct. 3.....	14	38	5	6	32	Considerable discomfort during night from nausea
Oct. 4.....	15	53	4	10	43	Several salol shells noted in the stool
Oct. 5.....	15	68	2	12	56	
Oct. 6.....	15	83	5.	17	66	Three salol shells passed
Oct. 7.....	13	96	8	25	71	
Oct. 8.....	15	111	0	25	86	Pills punctured
Oct. 9.....	15	126	3	28	98	Pills punctured Considerable emesis
Oct. 10.....	10	136	0	28	108	

The presence of 2 or 3 pills in the passages during each twenty-four-hour period may be disregarded. Should a larger number than this escape without dissolving, the success of the treatment becomes impaired, since, as stated previously, the efficacy of the drug is measured almost entirely by the concentration of its full strength within the large bowel. The enteric coating affords protection against the absorption of the

ipecac in the stomach and small intestine. The pills readily traverse this portion of the digestive tract, which has previously been rendered free of bulky fecal matter, and reach the large bowel approximately within six hours after their ingestion. It is then that the enteric layer is entirely dissolved away, preparatory to the solution of the ipecac mass itself, which finally brings the drug into intimate contact with the disease-bearing areas in the bowel. At least 50 grains (3.25 grams) of the drug should thus be brought into play at one definite period during the twenty-four hours, so as to insure the needed measure of concentration for the destruction of the organisms.

Several plans have been considered in connection with the passage of excessive numbers of the pills from day to day. While a reduction in the amount of the salol coating will prove sufficient, in some cases, to overcome this difficulty, the piercing of the outer coating with a sharp-pointed surgical needle has proved, in the author's experience, to be the most effective measure. By this means the alkaline intestinal secretions are enabled to penetrate beneath the salol shell, thus bringing about more certain disintegration of the pill mass.

A further difficulty met with in the course of treatment arises from a disinclination on the part of some patients to swallow large numbers of pills at one period. In such instances, a trial may be made of the **duodenal intubation method** as suggested by Beck. The tube may be introduced at night at the hour usually employed for the administration of the pills, after which the drug may be instilled directly into the duodenum, either in the form of the fluid extract—from 1 to 2 ounces (30 to 59.2 c.c.)—or as a suspension of the powdered root in water, in amounts as high as from 30 to 60 grains (1.95 to 3.9 grams). Both procedures are commonly followed by a considerable amount of retching, and therefore the plan is not to be recommended unless strong persuasion has failed to overcome the patient's aversion to pills.

Other Methods of Treatment

In a disease having such a widespread distribution and occurrence as has entamebic dysentery, and especially one which presents such protean clinical manifestations, complete accord in respect to treatment is hardly to be expected. In some quarters, the specific action of ipecac upon the course of the disease is still questioned, and other methods of treatment have been substituted, for which equal and even superior results have been claimed. A brief discussion of some of these measures will be undertaken, although no attempt will be made to enter into a full description of their respective merits or deficiencies.

Irrigations of the Large Bowel.—Flushing of the large bowel with various antiseptic preparations has always occupied a prominent place in the minds of clinicians as a cure for all forms of dysentery. In an entamebic infection of the bowel, the main purpose sought is the destruction of the pathogenic organisms. This, some believe, may be accomplished by bringing various chemical agents, held in solution, in contact with the organisms within the lumen of the bowel. Among the

many substances which have been employed in this manner, the following stand out most prominently; **quinin sulphate**; **formalin**; **copper sulphate**; **potassium permanganate**; **silver nitrate**; **hydrogen peroxid**; **thymol**; **coal oil** and others. Even **ice water irrigations** were recommended at one time by Tuttle, who believed that the *Entameba histolytica* could be readily destroyed within the bowel by immersion in ice cold solutions.

The chief virtue of intestinal irrigations lies in the cleansing of the lower bowel of retained mucus and inflammatory débris, which might otherwise interfere with healing. The major lesions of entamebic dysentery are buried beneath the mucosa, and the specific organisms are mostly out of reach of antiseptic solutions, regardless of the potency of these substances outside the body. This procedure is therefore largely palliative and should in no sense be considered curative. It is best to avoid the use of medicated solutions in the lower bowel during the period of treatment with ipecac, since this may interfere to a considerable extent with the solution and absorption of the drug. When once complete destruction of the organisms has been achieved by a course of specific medication, irrigations of the lower bowel with mild astringent solutions may be useful in assisting in the healing of the inflamed mucosa.

Bismuth Subnitrate.—The introduction of this drug as a specific remedy in the treatment of entamebic dysentery is to be credited to Deeks. While insoluble preparations of bismuth have been used since an early period in clinical medicine to control diarrheal conditions, Deeks was the first to claim a special virtue for this drug in entamebic infections of the intestinal tract. The *rationale* of its use has not been made altogether clear. It was thought at first that the bismuth acted upon the pathogenic entamebæ as a direct poison. This was disproved, however, by Darling, who claimed that he was able to raise cultures of the free-living ameba on media, heavily impregnated with insoluble bismuth salts. Mix has offered the suggestion that the destruction of the entameba may be due to the fact that bismuth subnitrate in large doses takes up sulphur as fast as it is formed in the intestinal tract. This causes a decrease in the amount of nascent hydrogen sulphid, which experiments have indicated to be essential to the life of the organisms.

While doubt may be cast upon these various hypotheses, no question exists, according to James, as to the destruction of the entameba, which is accomplished by the free use of bismuth subnitrate. In order to obtain the full effects, the drug must be administered in very large doses. A heaping teaspoonful is to be given every three or four hours during the day, and this dosage is maintained over a period of from one to two weeks, or until the stools become thoroughly formed.

James claims that with this dosage the organisms are rarely found in the stools after the second day of treatment. This therapeutic measure may commend itself in those rare instances in which ipecac is not tolerated by the patient, but in the author's opinion it should not be depended upon for the routine treatment of entamebic dysentery.

Chapparo Amargoso.—The first mention made of this drug for the

treatment of dysentery was by Putegnat, of Brownsville, Texas, in 1883. A few years later, J. W. Nixon, of Gonzales, Texas, published an article advocating the use of the drug, especially in cases of entamebic infection of the bowel. Subsequently, a number of other observers, including H. A. West, W. J. Crittenden and P. I. Nixon, reported excellent clinical results following the administration of this therapeutic agent in many cases of entamebic dysentery.

In recent times, attempts have been made to demonstrate the amebicidal action of Chapparo amargoso in an experimental way. The results obtained did not, however, prove very convincing. According to P. I. Nixon, the drug is not indicated in ordinary diarrhea, and is probably without action in other parasitic intestinal infections.

Chapparo amargoso is a small, thorny bush, which grows without cultivation on dry, rocky soils. Its distribution is limited for the most part to the hilly sections of southwest Texas and northern Mexico. The medicinal properties are obtained from all parts of the plant. All efforts to extract an active principle have, up to the present, failed. Nixon believes that the therapeutic action depends upon either an alkaloid or a glucosid, and has carried on experiments to prove that the large amount of tannin contained in the plant constitutes a negligible element.

The drug may be employed either in the form of an infusion or as a fluid extract. The latter preparation has been marketed, and is the one most generally employed. Both preparations are intensely bitter, but no untoward symptoms, such as nausea and vomiting, follow the oral administration. Even large doses are without detrimental effect upon the human organism.

The infusion is administered in doses of from 6 to 8 ounces (178 to 236 c.c.) three times a day, preferably before meals. This is continued over an indefinite period or until the patient has been relieved of all symptoms. Since the drug has a tendency to produce constipation, it has been found best to administer **salines** at periods of from three to four days. Rectal injections of the infusion are also recommended in conjunction with the administration of the drug by mouth. The fluid extract may be employed in doses of 1 or 2 teaspoonfuls, likewise before meals, three times a day.

The use of the drug has been confined, for the most part, to certain regions of Texas, where entamebic dysentery prevails extensively. Isolated references are, however, found in the literature from other sources.

Shepherd and Lillie treated 81 *Entameba histolytica* carriers in England with Chapparo amargoso, and reported 34 as successfully cured by its use. Sellards and McIver, in this country, have likewise reported success with an aqueous preparation of the dry plant, in a number of cases. These authors found that headache and malaise sometimes follow the use of the drug in large doses.

Salvarsan and Neosalvarsan.—In recent years, success has been reported by several observers with the use of salvarsan and neosalvarsan in the treatment of obstinate cases of entamebic dysentery. O. J. Mink,

for example, records a case occurring in his experience in Nicaragua, which had resisted all forms of treatment, including even the flushing of the bowel, through an appendicostomy opening. This patient received 1 grain (0.065 gram) of salvarsan intravenously, and within ten days complete recovery from the entamebic infection was confirmed by stool examination. Revaut and Krolunitzky have reported similar favorable results with this drug. These authors recommended intravenous injections of 5 grains (0.3 gram), to be repeated every third day until 10 injections in all have been given. Mention is also made of the success which attended the treatment of chronic cases with salvarsan administered orally in capsules, each containing ¾ grain (0.05 gram) of the drug. Rectal injections of both salvarsan and neosalvarsan have also been administered by Calame and others with satisfactory results. In discussing the incidence of intestinal spirochetes in the Philippines, Crowell and Haughwaut have called attention to the association of these organisms with the *Entameba histolytica,* in certain cases of entamebic dysentery. The difficulty experienced at times in bringing about a cure in entamebic infections is thought by these authors to be due to a possible cross infection with spirochetal organisms. The success of the salvarsan treatment may be explained on this basis. The author has had no personal experience with these drugs in the treatment of entamebic infections.

Adrenalin.—According to Bayma, the use of adrenalin is indicated in all cases of entamebic dysentery, whether acute or chronic. The drug may be administered either orally, or by way of the rectum. From 10 to 20 drops of a 1 to 1,000 solution may be given by mouth every two hours without harmful effect. Bayma finds that prompt relief of clinical symptoms follows the use of the drug in this manner, and that within a few days the stools are freed of vegetative and encysted organisms. Daily enemas of the drug were also successful (two liters of normal saline in 1 to 1,000,000 or 1 to 1,500,000 strength). This treatment has likewise been strongly recommended by Von Groeer. In connection with the success claimed for this method of treatment, Remlinger and Dumas call attention to the presence of the suprarenal syndrome in many cases of chronic, prolonged dysentery. This syndrome is attended by sunken eyes, a pinched nose, bluish discoloration of the skin, emaciation, frequent thready pulse, dry tongue, extreme thirst, nausea and vomiting, along with abundant and liquid stools. These symptoms can all be traced to a deficiency of the adrenal secretion, which in itself is the result of chronic changes in the glandular structure incidental to a prolonged infection. In cases showing marked improvement following the administration of adrenalin, cross infection with organisms of the *Bacillus dysenteriæ* group is to be assumed, since the *Entameba histolytica* is not known to produce such high-grade morbid changes in the suprarenal tissues.

Treatment of the Carrier State

Attempts have been made in more recent times to place the treatment of cyst carriers in a separate category from that of the chronic infections with the vegetative organisms. This classification is a purely hypothetical one, since the carrier condition, after all, merely represents a quiescent stage of the disease without involving any difference in the character of the infection. As Wenyon correctly intimates, "acute cases differ from the carrier cases only in degree, for between the attacks of dysentery, the acute cases are actually in the carrier condition, passing amebæ and cysts, which are indistinguishable from those passed by the carriers who have, perhaps, never had an attack of dysentery." The carriers, as has been stated previously, exhibit some ulceration of the intestine, although it is of a low-grade type and insufficient to produce symptoms. The vegetative entamebæ are therefore present in the intestinal wall and constitute the source from which the cysts are derived. The cysts occupy a position similar to that of the ova present in the stools as a result of infection with intestinal worms. There would be as much justification for attempting to destroy the ova in such infections, as there is for employing a special mode of treatment for the cysts in entamebic infections. This explanation is necessary, since in the minds of some the treatment of the cyst-bearers of protozoal diseases demands a special plan. Interest in this subject has been stimulated in recent years on account of the return of numerous carriers to England and to other European countries from the various theaters of war situated within the tropics. Emetin has been found to be of little value in clearing the stools of cysts. Many of the British observers have reported great success in the treatment of the carrier state with the **double iodid of bismuth** and **emetin.** It is not probable that this remedy possesses any special virtue in entamebic infections, entitling it to the fulsome praise which it has recently received.

The same methods should be used in the treatment of the carrier as have proved successful in the treatment of all chronic infections with the organism. This includes the administration of **ipecac** in massive doses, according to the detailed plan outlined above.

PROGNOSIS

The prognosis is upon the whole exceedingly favorable, especially in the absence of complications. In a former day, before the institution of specific treatment in the disease, the outlook proved to be considerably less hopeful. Among 78 cases collected by Harris, for example, in the early nineties, as many as 30 deaths were recorded. Again, in the Johns Hopkins series of cases mentioned by Strong, the mortality was 28 out of 119 cases, or approximately 23 per cent. Contrasted with this, Strong himself observed only 12 deaths among 200 carefully treated

cases, and later, Tuttle met with only 3 fatal cases out of 73 handled by him.

The fatality of the disease depends to a great extent upon the period at which the patients come under observation and the thoroughness with which specific treatment is carried out. Since the reintroduction of ipecacuanha, a great reduction in the mortality has unquestionably been achieved. In the acute stages, the use of emetin by subcutaneous injection, or intravenously, has proved of the greatest value in saving lives that otherwise would have been lost.

The chances of recovery are lessened by the presence of complications such as hepatic or cerebral abscess. The prognosis of these conditions has already been considered.

In the tropics, the natives suffer more severely from the disease than do foreign residents, because of unsanitary conditions usually present in the quarters occupied by the natives. The death rate is likewise higher in heavily infected regions, where the virulency of the organism is undoubtedly increased by the rapid passage from host to host.

Such a condition is met with, for example, in India, where Rogers found the mortality rate as high as 43.3 per cent. among 30 cases, even in the absence of complications in other organs.

The age and physical condition of the patient at the time of infection are to some extent determining factors in the outcome. Weak, debilitated subjects, and especially those suffering from advanced arterial or cardiac lesions, are particularly prone to succumb, unless treatment is undertaken at an early stage.

PATHOLOGY

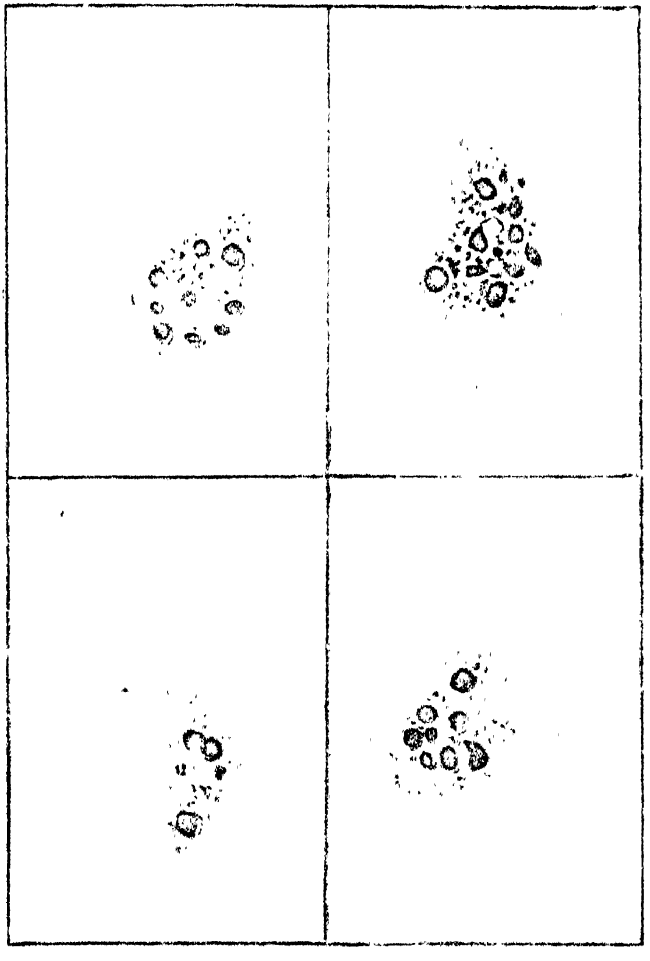
Tissue-invasive Power of the Pathogenic Entameba.—The basis for the development of the pathological lesions of entamebic dysentery depends upon the tissue-invasive power of the *Entameba histolytica.* This organism, by means of its dense and sharp-pointed pseudopodia, is able to force a passageway through the intercellular spaces of the bowel wall, with comparative ease. In contrast to this, the relatively blunt and inactive pseudopodia of the *Entameba coli* and *Entameba nana* render it impossible for these organisms to penetrate the tissues. The original mode of entrance of the pathogenic entameba into the tissues occurs through mechanical means rather than by the aid of a special cytolysin. It is probable that some slight trauma to the surface epithelium forms the basis for the initial entrance of the organisms into the tissues. Once having gained admittance, the plastic nature of the cytoplasm permits the organism to wedge its way further into the deeper layers of the bowel wall. Whether the necrosis that follows is the result of a special cytolitic ferment or merely represents a reaction on the part of the body cells to the normal catabolic processes of the parasite constitutes a problem as yet unsolved. Haughwout believes that too much attention has been paid in the past to the action of the protozoal

parasite upon its host, and that the importance of the cellular reaction of the host to the presence of the organism has been entirely overlooked. Until cultivation of the *Entameba histolytica* has been successfully accomplished, the occurrence of specific toxins and ferments, as a result of the activity of the organism, must stand upon purely speculative grounds.

The Fundamental Histopathology of Entamebic Dysentery.—In the absence of definite experimental proof, it may be assumed that the presence of the *Entameba histolytica* within the tissues gives rise to some low-grade cytolitic toxin. This serves to stimulate the growth of the submucosal endothelial cells. This endothelial proliferation represents the essential host reaction to the organism and constitutes the fundamental and primary pathological lesion of the disease. The dense aggregation of these cells within a given focus cuts off nutrition, thus causing eventual necrosis of tissue. An exudation of leukocytes follows in the wake of the necrotic process and produces a further degree of compression of the involved areas. The disintegration of these exudative cells liberates a proteolitic ferment, which, in turn, brings about liquefaction. At this stage, a confluence of the microscopic lesions results in the formation of minute nodules which eventually become visible on the inner surface of the bowel. The smaller nodules gradually merge into larger forms, some of which reach the size of an English walnut. Microscopic section through these nodular swellings shows massed infiltration with endothelial cells, lymphocytes and neutrophilic leukocytes. These cells are all undergoing degenerative changes and are surrounded by a serous exudate, which not infrequently contains red blood-cells.

Vegetative and encysted forms of entamebæ will often be found along the outer borders of the nodules. As liquefaction proceeds, the nodule becomes capped with a characteristic yellow gelatinous material. The margins remain highly injected and red. Further necrosis of tissue results in the formation of open ulcers which may eventually retract, producing distinct umbilication. The irregular elevations on the inner surface of the bowel with yellow sloughs and incrustations give the appearance of foreign bodies which are referred to at times as "boutons de chemise." The break in the continuity of the mucosa overlying the lesions permits the entrance of numerous bacteria normally present in the intestinal flora. It is to be doubted whether bacteria enter into the pathology of the disease up to the time when abrasion of the mucous surface occurs. The comparatively small number of bacteria which might follow directly in the train of the invading organism are most probably promptly killed off by the tissue-cells. When once cross infection takes place, the intestinal bacteria undoubtedly play a most important rôle in the subsequent pathology of the malady. The true lesions of entamebiasis are regenerative rather than inflammatory. When an inflammatory factor is added to the pathological process, greater hyperplasia of connective-tissue cells results, with consequent thickening of the bowel wall, and particularly of its inner tunics. Further and more extensive ulceration likewise occurs as a result of bacterial invasion.

PLATE II.



VEGETATIVE FORMS OF ENTAMEBA HISTOLYTICA (THE TYPICAL HISTOLYTICA STAGE).

Showing finger-tipped pseudopodia, ingested red blood-cells and granules. The nucleus cannot be seen. Note the clear demarkation between the ectoplasm and endoplasm. (After Bass and Johns, from drawings made direct from the unstained specimen.)

The soft gelatinous material of the original entamebic lesion, it should be remembered, is not to be considered as pus. The conversion of this substance into purulent material is the result solely of secondary infection with bacterial organisms.

Gross Pathology.—In advanced, chronic cases of entamebic dysentery which come to autopsy, the large bowel presents an unusually diversified appearance. All steps in the pathological process of the disease are represented, as a rule, from the initial minute nodular lesions situated in the submucosa and mucosa, through various stages to the development finally of large patches of deep-seated ulcerations and sloughing, which are characteristic of the later periods. The affected portions of the gut appear for the most part to be thickened and nodulated, and section through these areas discloses a great increase in the reparatory connective-tissue, along with inflammatory edema. The earliest gross change which becomes visible to the naked eye is a small circumscribed elevation, usually along the folds of the mucosa. As necrosis proceeds, the summit of these small elevations becomes capped with a yellowish crater. Umbilication eventually occurs, and finally complete disintegration with the formation of an open ulcer. The small ulcer of the original lesion gradually enlarges by an undermining and sloughing of the edges and center. Exposing the entire inner surface of the bowel wall, ulcers in various stages of development are brought into view, along with numerous bulbous swellings. These swellings appear as hemispherical elevations on the mucosa and are often covered with an unabraded yellow gelatinous substance. Upon section, deeply buried nests of necrotic tissue are found undergoing disintegration, especially at the center.

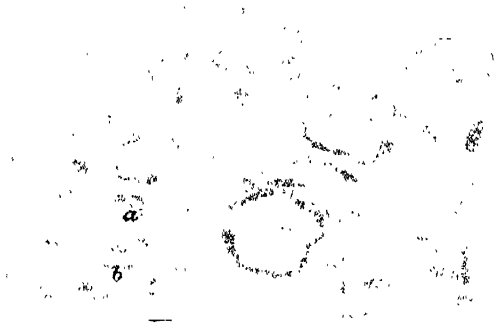
The ulcerations vary considerably, both in size and in form. Some of the earlier ulcers are no larger than a pin-head, and represent mere surface denudations. These are, however, not as characteristic of the disease process as are the smaller ulcers, which dip down into the submucosa and serve as fistulous openings for the discharge of accumulated collections of pus and débris. The larger ulcers, likewise, often communicate freely through irregular channels in the submucosa, with similar lesions separated by a considerable distance. Although the intervening mucous membrane often remains completely intact, section through it reveals an extensive degree of tunneling within the submucosa. These spans of mucosal bridges, so to speak, hiding from view major pathological lesions beneath the mucous surface, constitute the most characteristic feature of the morbid anatomy of the disease. Entamebic ulcerations are typically irregular in form. As a result of the disproportionate excavations of the submucosa, the ulcers present ragged, overhanging and depressed margins. In the earlier lesions, the edges may, however, be raised above the surface of the mucous membrane. The base of the ulcers is undermined and is covered, as a rule, with a tenacious mucoid material. During a subsequent period, the sloughs are thrown off, producing a punched-out appearance with clean, smooth, fibrous edges and bases.

FIG. 9.—PORTIONS OF COLON SHOWING ENTAMEBIC ULCERATION. (From G. B. Bartlett, "Pathology of Dysentery in the Mediterranean Expeditionary Force, 1915," Quarterly Journal of Medicine, 1916-1917, x, 185-244.)

A. Portion of colon showing thick-set acute entamebic ulcers and confluent acute entamebic ulceration (W. T. Shiells). From a portion of descending colon. The drawing shows numerous small ulcers; these show as pits with a raised margin. The letter "a" is placed beneath a typical "bouton de chemise" ulcer. By the confluence of these small lesions an ulcer of the type above letter "b" is produced. The whole of this ulcer stands out from the level of the mucous membrane of the gut, and in the ulcer is a ragged, yellow débris, which frequently has a pitted or honeycombed appearance. Some of the ulcers tend to spread transversely. Vegetative entamebæ were readily found in all these ulcers.

B. Portion of colon showing isolated group of entamebic ulcers, from the descending colon. The drawing shows that the mucous membrane of the colon, apart from the group of amebic lesions, is intact. The group of ulcers is prominent; it appears to stand up from the level of the mucous membrane. The ulcers contain the typical yellow, necrotic débris which indicates that entamebæ are present. There is a small slit-shaped ulcer on the summit of one of the rugæ.

C. Portion of colon showing confluent entamebic ulceration, from descending colon. The drawing shows deep, clean-based ulcers alternating with islands and bridges of mucous membranes. Tags of mucous membrane are left hanging into the lumen of the gut. There is a great deal of undermining of the mucous membrane, and a bristle has been passed beneath one bridge of mucous membrane. The general direction of the ulcers is transverse, and the muscle coat can be seen in the bases of the ulcers. Entamebæ were not found in these advanced lesions, but they were present in the smaller lesions of this intestine.



A



B



C

FIG. 9.

Location of the Lesions.—The initial site of infection in the large bowel varies considerably, but the most common location is undoubtedly at the flexures or more narrowed segments of the gut. Slight trauma to the mucosa probably plays some part in determining the location of the earlier lesions. When once the organisms have penetrated the tissues, extension of the morbid processes takes place more readily in the direction of the peristaltic movements of the bowel. The comparatively sluggish entamebæ travel willy-nilly astride the fecal current, but cannot swim against it. This probably explains the extreme rarity of lesions in the small intestine, even in the segment immediately distal to the ileocecal valve. The fact that the terminal ileum escapes infection in nearly all instances is all the more notable in view of the frequent proximity of the most advanced types of lesion in the cecum. Primary involvement of the small bowel has never been known to occur. For reasons not altogether clear, the liberation of the young ameba from the cyst in the intestinal tract of the new host is unattended with harm until the confines of the large gut are reached.

According to the records of most observers, the entire length of the large bowel is affected in over 50 per cent. of cases that come to autopsy. Rogers found, in the course of his twelve years' experience with the disease in Calcutta, that the most advanced lesions appeared in the cecum and ascending colon. Harris believes, on the other hand, that the most intense localization is usually to be found in the descending colon and sigmoid. Strong is probably correct when he states that no segment of the large intestine is predisposed to the invasion of the organisms, and likewise that the lesions are distributed on an average equally over all parts of the large gut. In cats and other lower animals the morbid disturbances are confined almost entirely to the rectum and sigmoid.

Healing.—The initial stage in the healing of the entamebic ulceration of the bowel is attended by the formation of minute granulations which appear first at the base of the ulcer and extend gradually to the mucosal edges. The organization of the granulation tissue proceeds slowly, as a rule, but eventually brings about complete reparation of the destroyed areas. During the reparatory process, the ulcers lose their sloughs and, at a later stage, present a smooth-floored, clean appearance. Healing is seldom uniform in the ulcerated areas, and as a consequence, patches of completely restored tissue are found to alternate with segments of the bowel wall which are still undergoing disintegration. The permanency of the new granulation tissue depends upon the destruction of the tissue-invading organisms. When a cure of the infection is obtained, healing proceeds rapidly, as a rule, along the entire bowel. Puckering may be noted at times in the scar tissue of extensively ulcerated patches. Actual fibrosis or stricture is, however, rare in the case of entamebic ulcers. Pigmentation is not uncommonly observed in healed and cicatrized areas, and especially in the neighborhood of the older and more advanced lesions.

Pathological Aspect of Perforation.—Perforation of the bowel

wall in entamebic dysentery is always the result of an extension of the ulcerative process into and beyond the muscular tunic. In fulminating cases, even though a tendency to gangrene exists, the bowel wall often becomes softened to a dangerous degree, but rarely perforates. This phenomenon is confined almost exclusively to chronic cases with slowly progressing ulceration extending into the deeper layers of the gut wall. Fortunately, in most cases in which perforation occurs, a previous walling off of the threatened areas by peritoneal exudation serves to prevent involvement of the general peritoneal cavity. When perforation takes place into a walled-off pocket within the abdomen, secondary infection occurs, due to the spilling of intestinal contents, resulting in the formation of an abscess. Such an abscess is usually located behind the colon (postcolic abscess). The misleading clinical features of this condition have been considered in a previous chapter.

In rare instances, a chronic and insidious form of peritonitis develops as a result of prolonged entamebic infection of the bowel wall. Rogers relates an unusual case of this type occurring within his experience, which subsequently produced fatal strangulation of the small intestine.

Postmortem Findings in Other Organs.—Apart from the characteristic lesions in the bowel wall, little uniformity is shown in other organs, in those cases which come to autopsy. When the abdomen is opened, a slight excess of peritoneal fluid is found, as a rule, along with a conspicuous dilatation of the subserous and mesenteric veins, leading from the disease areas in the colon. Enlarged mesentery glands are also commonly present. Smears of blood taken from the dilated veins and hypertrophied glands along the colon not infrequently show examples of typical regenerative *Entameba histolytica*. The visceral organs exhibit a general tendency to toxic degeneration with diffuse capillary hemorrhage. This is particularly marked in the kidneys and adrenals. The heart-muscle is, in most instances, atrophied with a moderate degree of fatty degeneration. The commonest change noted in the liver is a cloudy swelling or fatty degeneration of the parenchymatous cells of the central zone. In some cases, a well-defined hepatitis with round-cell infiltration of the portal vessels appears. This is, of course, entirely apart from the typical pathological lesions, produced by the direct invasion of the liver by the pathogenic organisms themselves. Moreover, it is to be doubted whether the toxins elaborated by the pathogenic entamebæ can alone give rise to degenerative changes in remote organs. These changes are probably effected by bacterial poisons which result from cross infections with numerous strains of intestinal microörganisms.

HISTORICAL SUMMARY

Dysentery has been known since the most remote period of time as an independent malady of widespread and almost universal distribution. In the very earliest writings on medicine, references may be found to the disease, and the part it has played through the ages, especially in connection with the fatalities of army life, has left an impress on the historical records of practically every nation. It is only within modern times, however, that steps have been taken to classify the disease under a definite etiology. The differentiation of the old-time bloody flux, with its confused clinical picture and indefinite causation, into the two clearly defined types identified today under the names of entamebic and bacillary dysentery, has been the result of investigations entered upon only within the past three-quarters of a century.

Lambl, in 1859, was in fact the first to offer the suggestion of a possible specific cause for dysentery. In the course of a routine examination of the intestinal mucus removed from a child who had died of enteritis, he ran across an ameboid body, probably a flagellate, which impressed him as a possible factor in the inflammatory process. This observation did not create much comment at the time, and further investigations in this direction were lacking until 1870, when Lewis and Cunningham independently noted the presence of amebæ in the dejecta of cholera patients in India. The detailed recording of a case by Loesch in 1875 attracted the first universal attention to the possible relationship of amebæ to dysentery. The case reported by Loesch was that of a Russian, aged twenty-four, who came to Petrograd from the Province of Archangel in Russia, suffering from typical symptoms of acute dysentery. In the mucus and bloody evacuations of this patient, Loesch discovered amebæ in large numbers. The description which he gave of these organisms corresponded almost in full to the morphology of the *Entameba histolytica* as it is known today. The patient died within four months of an intercurrent pneumonia. At autopsy, extensive ulcerations of the large bowel were found. Scrapings from the ulcers were inoculated into four dogs, both by mouth and by rectum. One of the dogs became parasitized within eight days and died on the eighteenth day following inoculation. The rectum of the animal was found to be inflamed and ulcerated in three localities, and numerous amebæ were recovered from the depths of the ulcers. Because of the fact that three of the dogs remained uninfected after inoculation, Loesch did not believe that the ameba itself was the direct cause of the disease, but that it was present merely as a secondary invader. The publication of this case, so rich in detail, stimulated widespread interest in the possibility of the ameba as a causative factor in dysentery. In 1879, Grassi discovered ameba cysts in the stools of healthy individuals, as well as of those suffering from dysentery, and therefore did not consider the organisms as pathogenic. In 1883, the dysenteries of Egypt were closely investigated in conjunction with the study of cholera, by a commission ap-

pointed by the German Government under the supervision of Robert Koch. Amebæ were found in sections from the bases of choleric ulcers in 5 cases which came to autopsy. Kartulis, impressed by these findings, subsequently made a study of over 500 cases of dysentery in the Nile Valley. Amebæ were found in a large proportion of these cases, and Kartulis became convinced of the pathogenicity of the organism. This author likewise succeeded in reproducing the disease in kittens by inoculating them with intestinal contents and with pus obtained from liver abscesses. These experiments were later confirmed by Hlava at Prague (1887) in a series of observations on cats and dogs.

In this country, the amebæ were first discovered by Osler, in 1890. Shortly afterward confirmation came from various sources. Within one year, Stengel found 3 cases of amebic dysentery in Philadelphia, and Musser, 4 from the same city, while Dock was able to report 12 cases of the acute and chronic types from Galveston, the first to be recorded from the far South.

At this time, considerable confusion existed in respect to the nomenclature of the organism. The original designation, *Ameba coli* (Loesch), was changed by Councilman and Lafleur in 1891 to that of *Ameba dysenteriæ* on purely clinical grounds. The former term was retained for the species of non-pathogenic organisms, which these authors believed were present at times in the intestinal tract of man and the lower animals.

Quincke and Ross interested themselves principally in the question of the pathogenicity of the ameba, using cats as a basis for their experiments. The conclusions which they arrived at were substantially the same as those of Councilman and Lafleur. The whole subject of the classification of the organisms remained in a somewhat chaotic state until 1903, when Schaudinn presented his series of highly important observations on the morphology of pathogenic and non-pathogenic intestinal amebæ. Schaudinn accepted the special genus, *Entameba,* which had been previously established by Cassigrandi and Barbagallo as a basis for the classification of the parasitic amebæ of man. The tissue-invading or pathogenic organism was designated *Entameba histolytica,* while to the non-pathogenic species, frequently found in the intestinal contents, the name *Entameba coli* was applied.

The fundamental principles of this classification were promptly accepted by practically all workers in this field. Some of Schaudinn's conclusions, however, have since been found to be erroneous. The descriptions he gave of the *Entameba histolytica* showed that he had not succeeded in working out the complete life cycle of this organism. The incompleteness of his work was in fact the cause of much subsequent confusion.

In 1906, Hartmann and Viereck described a third species of entameba under the name: *Entameba tetragena.* Walker, in 1912, and afterwards, Darling, James, Craig and others were able to prove definitely that the *Entameba tetragena* was not a separate species, but represented merely one phase in the life cycle of *Entameba histolytica.* In the same

manner, *Entameba minuta*, first described by Elmaissian as a new pathogenic species, was found to be a part of the life history of the *histolytica* organism. In 1916, however, Wenyon discovered another distinct type of parasitic entameba, *Entameba nana*, which he found in the intestinal contents of many individuals in Egypt. This organism was first looked upon as a form of *Ameba limax*, but was subsequently identified as a true species of entameba, of non-pathogenic properties.

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CHAPTER XXXII

BALANTIDIAL DYSENTERY

By Sidney K. Simon, A. B., M. D.

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Definition.—A disease of the large bowel caused by infection with the *Balantidium coli*, a protozoal organism, belonging to the order *heterotricha*, of the *Infusoria*. The clinical course is slow and insidious and is characterized chiefly by alternating attacks of diarrhea and constipation. Ulceration of the colon extending into the submucosal layer constitutes the chief feature of the pathological process. The first case of infection in a human subject was recorded by Malmsten, in 1857.

Etiology.—Predisposing Causes.—The disease is of comparatively rare occurrence, not over two hundred cases in all having been reported in the literature. It is observed most frequently in cold climates, though, as indicated below, under Geographical Distribution, numbers of cases have likewise been reported from tropical and subtropical regions.

Exciting Cause: Description of the Organism.—(*a*) *Morphology.*—The free forms as they appear in the stools present a striking and characteristic appearance, and cannot well be mistaken for other protozoal organisms. In size, they are by far the largest of the parasitic protozoa of the intestinal tract, measuring from 70 to 200 microns in diameter. Some of the larger parasites may thus be detected with the naked eye. Under the microscope, they appear as slightly oval cells, the entire circumference being covered with a delicate layer of wave-like cilia. The ectoplasm and endoplasm are clearly distinguishable. The latter contains coarsely granular material, consisting of bacteria, fat globules and other food particles, and occasionally also red and white blood-corpuscles. Two contractile vacuoles are usually present, and an anus or cytopyge may be observed at the posterior extremity during the moment of expulsion of undigested food particles. The organism possesses two nuclei of different size and shape. The first or larger nucleus, also known as the macronucleus, is bean-shaped, and is mainly concerned in reproduction; while the smaller, rounded nucleus, or micronucleus, exercises control over nutrition. A funnel-shaped peristome is situated at the anterior end, and serves as a mouth organ for the ingestion of food. The contractile vacuoles act as digestive organs. The cilia are arranged in longitudinal rows which cover the entire sur-



FIG. 1.—BALANTIDIUM COLI. (After Wenyon.)

1. Free ciliate as it lives in human gut. *m*, macronucleus; *n*, micronucleus; *c*, contractile vacuoles; *p*, peristome; *f*, food particles.

2. Encysted form containing two ciliates. Note the double contour of cyst wall with absence of contractile vacuoles and food particles.

3. Red blood-corpuscle, to show relative size.

face of the cell. Their wave-like movements not only create food currents in the direction of the peristome, but produce a certain degree of locomotion. The motility of the organism is, however, for the most part, sluggish. Reproduction occurs during the vegetative state by binary fissure, resulting in two fully matured daughter-cells. Under unfavorable environmental conditions, the organism encysts. The cysts bear a striking resemblance to the free forms and, on account of their size and peculiar structure, are easily differentiated from other intestinal protozoa.

(*b*) *Modes of Conveyance.*—The infection is transmitted to man almost entirely through food or drink, which have become contaminated with the encysted forms of the organism. The balantidia are normal inhabitants of the intestinal tract of pigs and swineherds, farm hands, and butchers, who are brought into close contact with these animals, are mostly subject to the disease. Among the 117 cases collected by Musgrave, in 25 per cent. the source of infection could be traced directly to these animals. It is not probable that the vegetative forms serve at any time as infectious agents in the new host, since they are readily destroyed by the gastric secretion. The cysts, on the other hand, are better able to withstand destructive influences, and remain viable until the confines of the large bowel are reached. Many believe that catarrh of the mucous membrane of the intestine brought on by other causes always precedes the actual invasion of the bowel wall by the organisms.

Experimental Balantidiasis.—Transmission of the infection to lower animals has been attempted by a number of observers, in most instances with negative results. Cassigrandi and Barbagallo carried on a series of experiments in healthy young cats, by injecting the feces of human subjects as well as of pigs, containing free and encysted balantidia, into their rectums. The organisms were also introduced *per os*, but in no instance did actual colonization occur. These authors believe that the parasites might be made to live in the intestine of cats if a catarrhal condition were produced as an initial step. Brumpt achieved a greater degree of success in experiments carried on by him with monkeys and with young suckling pigs. Infected material in this case was obtained from monkeys, who are known to suffer at times with a spontaneous infection with the *Balantidium coli*. Parasitation was obtained in the case of six healthy monkeys, the incubation period varying from two to seventeen days. Not one of these animals subsequently developed diarrhea, and no lesions in the large bowel were discerned at autopsy, though numbers of balantidia were found in the feces. Brumpt's subsequent success in bringing about actual infection in young pigs is all the more notable since it is recognized that the balantidium of the pig rarely proves harmful to its host. The morphology of the organisms present in the intestinal tract of the lower animals does not differ from that in man, and it is therefore probable that but one species of balantidium exists.* The pathogenicity, on the other hand, may vary with

* A second species, *Balantidium minuteum*, was described by Schaudinn in 1899 in a case in Berlin. One other case of this infection has been reported by Schultz, also from Berlin. In both instances a mild form of diarrhea was present.

different strains. In 1913, Walker undertook a number of experiments on healthy monkeys, who had previously been found free of intestinal infection with protozoa. The infected material was introduced into the monkeys either by mouth or by rectal injection, both free and encysted forms being employed. Twenty-two monkeys were experimented upon. A number of the animals became parasitized, but only a small proportion suffered actual infection of the bowel wall. A most important finding in these observations was that the parasites appeared in the stools intermittently and at irregular intervals. Walker believes that each individual parasitized with *Balantidium coli* is liable sooner or later to develop balantidial dysentery.

Symptomatology.—The clinical manifestations of balantidial dysentery are insidious in their onset, and the disease usually pursues a prolonged chronic course. The earlier symptoms are mild and suggest, as a rule, some simple type of diarrhea. As ulcerative lesions develop, the intestinal symptoms assume a more distinctly dysenteric character. At this stage, the evacuations usually contain large amounts of mucus with varying quantities of intermingled blood. A considerable degree of tenesmus may also be present, and in other respects the condition is indistinguishable clinically from other types of dysentery. Just as in entamebic infections of the lower bowel, alternating periods of diarrhea and constipation may occur. During the quiescent periods, only the encysted forms can be found in the hard dry feces. In prolonged infections, the intervals between the diarrheal attacks are shortened and the intestinal disturbances become more pronounced; the stools often assume an offensive odor, and the amount of blood may become greatly increased. Constitutional symptoms are not uncommon at this time, the patient complaining of anorexia, loss of weight, and digestive disturbances of many kinds. Anemia is also a common symptom during the later stages, and some observers have noted occasionally edema of the feet and ankles. Physical signs are distended abdomen with marked tenderness along the colon, especially along the sigmoid. Leukocytosis is rarely present, but a relative degree of eosinophilia is not uncommon.

Diagnosis.—From the above, it will be seen that balantidial dysentery does not differ clinically to any marked extent from other forms of chronic dysentery. The diagnosis can only be made with certainty by discovering the typical vegetative forms or cysts of the organism in the stools. On proctoscopic examination, numbers of ulcerations may often be seen on the rectal mucosa. Scrapings from these ulcers usually contain the parasites in large numbers. Cysts are found most frequently in the solid fecal particles.

Treatment.—Prophylaxis.—Prophylactic measures include, in the main, the **confining of pigs to their proper quarters** in infected localities. These animals should not be permitted to roam at large as they do in many rural districts, and, in particular, should be kept out of dwellings. **Swineherds and farm laborers should be advised to wash their hands before eating.**

Curative Treatment.—Various drugs have been employed, but the

treatment on the whole has proved unsatisfactory. As in entamebic dysentery, a subsidence of symptoms is often interpreted as a cure of the infection. Up to the present time, no specific remedy has been discovered. Phillips recommends highly large daily doses of **thymol.** Behrenroth also became impressed with the value of this remedy. Barlow succeeded in relieving one case entirely with the internal use of **methylene blue. Ipecac** and **emetin** have been advocated by some, though **most observers report highly disappointing results** with the use of these drugs.

Dutcher, after failure in one case with emetin, switched to **intravenous injections of salvarsan,** 0.06 gram (1 grain) which succeeded in removing all traces of the infection from the stools.

In some quarters, rectal irrigations with various antiseptic solutions, such as **quinin** (1:1000), **silver nitrate** (1:3000), **iodin** (1:5000) and **argyrol,** have been accorded a trial with more or less ineffective results.

Rest in bed and **restricted diet** are undoubtedly valuable aids in any plan of treatment.

Prognosis.—The prognosis of the disease is generally unfavorable. This is due in great measure to the lack of specific medication. When treatment is instituted at an early stage, before ulcerative lesions have set in, the chances of recovery are greatly increased. The mortality has been estimated at about 30 per cent., which is considerably higher than that of either bacillary or entamebic dysentery.

Pathology.—According to Gant, 35 autopsies in all had been held up to 1915 upon cases of balantidial colitis. The morbid processes varied in these cases from a simple catarrhal congestion of the mucosa to extensive ulcerative lesions involving the mucous and submucous layers.

The balantidia penetrate the tissues of the intestinal wall by mechanically pushing aside the cells, and reach the submucosa, where colonization is finally effected. As a result of their presence, congestion of the blood-vessels arises, with subsequent tissue infiltration in which round cells and eosinophils predominate. The secretion of a proteolytic ferment eventually brings about necrosis and, finally, open ulcerations on the mucous surface. This is followed by a secondary invasion of intestinal bacteria, which produces changes of a more distinctly inflammatory character. *Balantidia coli* are, however, able to produce abscesses and ulcerations of the intestinal wall without the aid of bacteria. This effect was observed by Walker in a case of human balantidiosis that came to autopsy. Closed abscesses were found in the thickened submucosa, entirely surrounded by sound tissue. Upon section, the "pus" was found to contain only mononuclear cells, in addition to the specific protozoal organisms.

The character of the gross lesions depends largely upon the stage of the infection. In advanced cases, the pathological processes are not greatly dissimilar to those found in chronic entamebic dysentery. Bowman, who observed three cases at autopsy, concluded that there were no means of distinguishing late entamebic ulcerations from those caused by *Balantidium coli,* though fresh entamebic ulcers appeared to be somewhat

more punctate in character. Not infrequently in the later stages, the organism will be found to have penetrated into the blood-vessels and lymph spaces of the mesentery, extending even at times into the larger lymphatic glands. Invasion of the liver has never been distinctly confirmed.

Geographical Distribution.—The distribution of the infection is rather widespread, having been recorded in Russia, Scandinavia, Finland, Germany, Italy, Serbia, the Cochin Provinces of China, and other parts of Asia, the Philippines Islands, Nicaragua, Porto Rico and Cuba. Only a few scattered cases have been reported in the United States. These cases with their respective locations and observers are as follows: New Jersey, one case by Gant; Arkansas, three cases by Grey, and one by Deaderick; Louisiana, one case by Bel and Couret; Minnesota, one case by Sistrunk. The Rockefeller Sanitary Commission in addition has reported two cases in North Carolina, and one in Mississippi.

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CHAPTER XXXIII

THE FLAGELLATE DIARRHEAS

By Sidney K. Simon, A. B., M. D.

Classification of flagellates, p. 359—Diarrhea caused by Lamblia (Giardia) intestinalis, p. 360—Diarrhea caused by Cercomonas intestinalis, p. 362—Diarrhea caused by Trichomonas intestinalis, p. 363—Diarrhea caused by Tetramitus (Chilomastix) mesnili, p. 366—Infection with Waskia intestinalis, p. 368—Bibliography, p. 369.

Classification of Flagellates.—The flagellates comprise a group of protozoal organisms belonging to the class *Mastigophora,* which possess as their chief characteristic one or more flagella or whip-like processes of the cytoplasm. These appendages serve both for locomotion and for the capture of food. The *Flagellata* include a large number of species, most of which are free living. They inhabit both fresh and salt water, and are especially prevalent in the moist soil and stagnant pools of tropical countries. Only a few of the species are capable of a parasitic life within the human organism. Included in this class, besides the intestinal flagellates, are the *Trypanosoma* (flagellate parasites of the blood stream, which cause the fatal African sleeping sickness) and the *Leishmania donovani* and *Leishmania tropicum,* flagellate organisms of the blood-vessels and skin, which produce kala-azar and oriental sore, respectively.

Doubt is still expressed in some quarters regarding the essential pathogenicity of the intestinal flagellates. Most authorities are now agreed, however, that when present in large numbers, these organisms are capable of inflicting injury to the intestinal mucosa, and may thus become responsible at times for an intractable type of diarrhea. Enough has been shown from recent investigations, according to Haughwout, to despoil the flagellates of the reputation for harmlessness to man they have previously had. On the other hand, the fact should not be overlooked that flagellates are frequently present in the gut without producing symptoms of any kind. Wenyon believes that just as there is a normal bacterial flora, there may likewise be a normal protozoal fauna, which can live in the intestine without inflicting harm upon the host. Actual penetration of the tissues by flagellate organisms has never been demonstrated, so that their harmful effects must result either from mechanical insults inflicted upon the epithelial surface of the bowel, or from the secretion of specific toxic bodies. The following represent the chief types of flagellates that occur in the human intestine:

Lamblia (Giardia) intestinalis (Lambl, 1859).
Cercomonas intestinalis (Davaine, 1854).
Trichomonas intestinalis (Leuchart, 1879).
Tetramitus (Chilomastix) mesnili (Wenyon, 1910).
Waskia intestinalis (Wenyon, 1916).

Diarrhea Caused by Lamblia (Giardia) Intestinalis.—This organism has a wide distribution in tropical countries. In some localities it has been found to be the predominant type of intestinal protozoa. Noc claims, for example, that in Tonkin, 50 per cent. of the population harbor lamblia in their stools. In recent years, numerous scattered cases have been reported from temperate countries, many of which have proved to be of indigenous origin. Judging from the collection of published cases, the organism is, however, seldom encountered in the United States. Stiles has noted an isolated instance of its occurrence in Baltimore, and Logan and Sanford found this form of protozoa present in only 66 out of a total of 6,000 stool examinations, made upon individuals from all sections of the country. In the author's experience, *Lamblia intestinalis* is rarely met with in the Gulf region of the Southern States.

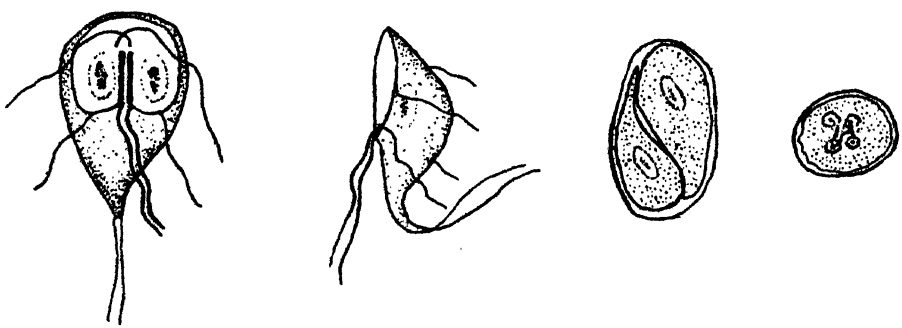


FIG. 1.—LAMBLIA INTESTINALIS. (After Wenyon.)

1. Surface view showing the two sucking disks, the nuclei, and the eight flagella.
2. Side view of same organism.
3. Encysted form containing two flagellates.
4. Appearance of cyst when viewed on end.

ETIOLOGY.—*Description of the Organism.*—In its free state, the organism possesses a striking and characteristic appearance, which renders differentiation from other intestinal organisms a matter of little difficulty. The contour of the body is of pear shape, and the various structures are arranged in bilateral symmetry. Stained specimens produce a particularly grotesque appearance, suggesting a spectacled countenance. Two sucking disks, each with raised convex edges, are present on the ventral surface. These disks possess contractile properties, which enable the organisms to attach themselves by a kind of suctorial action to the epithelial cells of the mucosa. Two rod-like ridges lie upon each

side of the center axis, extending in length from the sucking disks to the tapering end of the organism, and terminate finally in two long flagella. In addition, three other pairs of flagella are present, which project from the anterior and posterior aspects of the sucking disks. A small kinetic granule is found to form the base of each individual flagellum. Of the 8 flagella, the median pair are by far the most active. Two nuclei are present, situated symmetrically on each side of the rods at the anterior extremity. In structure, the nuclei are similar, each possessing a distinct karyosome. Because of the number of flagella, the organism is exceedingly active, and swims about in the fecal current with a peculiar swaying movement. In size *Lamblia intestinalis* varies from 10 to 21 microns in length and from 5 to 12 microns in breadth. Reproduction in the unencysted state has been observed by Wenyon to take place by a process of longitudinal division. The vegetative forms live, for the most part, in the small intestine, and are seldom found in the fecal contents, unless active peristalsis is present. The cysts, on the other hand, appear in abundant quantity, as a rule, in the stools of infected individuals. Their appearance is not constant, however, long intervals elapsing at times, when even a careful search may fail to reveal their presence. The cysts are oval, and measure from 10 to 14 microns in diameter. During reproduction within the cyst, a number of complicated changes take place, the process terminating in the formation of one or two completely developed organisms. When stained, the cysts are found to contain from two to four symmetrically arranged nuclei, situated at the extreme upper pole. Four curved axostyles are seen to project in a longitudinal direction from the region of the nuclei, while a number of comma-like parabasal bodies complete the highly characteristic picture. Lamblia cysts are apparently able to maintain their infectivity for a long time after their discharge from the body. Rats and mice are the main reservoirs for human infections, the cysts being taken into the body, as a rule, through cereals contaminated by the vermin of these animals.

PATHOGENESIS.—According to Wenyon, of all the flagellates of the human intestine, *Lamblia intestinalis* has the best claim to pathogenicity. This is obvious when one considers the great activity of these organisms and the manner they have of attaching themselves intimately to the intestinal epithelium. Most authorities now recognize a distinctive form of diarrhea which is associated with the presence of these parasites in the intestinal tract.

Fantham and Porter report, for example, 187 cases of pure lambliasis among 1,305 British soldiers invalided home from Gallipoli and from the western front, during the recent World conflict. These authors conducted experiments with the organism on lower animals and were able to bring about parasitization in 13 out of 17 kittens and mice fed with material containing the cysts. The chief symptoms in these animals proved to be an intractable form of diarrhea with emaciation. They likewise found erosion and distortion of the intestinal epithelial cells in human subjects, and believe the lamblia are able to produce distinct

pathological effects because of their suctorial action on the surface epithelium.

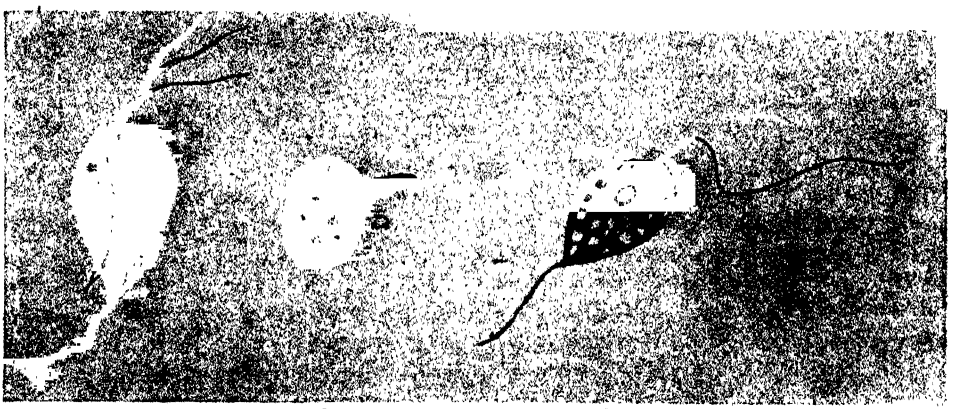
Kennedy and Rosewarne observed 12 cases of lamblia diarrhea out of 136 consecutive cases of bowel disorders in Gallipoli. Some of these cases presented features of a true dysentery. At intervals, blood and mucus were present in the dejecta, and tenesmus was likewise not uncommon. *Lamblia intestinalis* were the only organisms found in the stools. Logan and Sanford, in their cases, noted a history of diarrhea without blood or mucus. The movements occurred for the most part, during the early morning hours, and were accompanied by considerable rumbling and rolling in the intestine, and an indefinite type of abdominal pain, which was referred mostly to the right side. In many of these patients, functional disturbances of digestion were also present. Stitt believes that lamblial dysentery is second only to amebic dysentery in the frequency of its occurrence in the tropics. Cases which develop in the tropics show a tendency to spontaneous improvement upon a change to cooler climates. Rapid improvement has been noted on a number of occasions by British observers, among soldiers returning to England from tropical countries, only the encysted forms remaining in the stools as evidence of previous infection.

TREATMENT.—No satisfactory plan of treatment has as yet been offered for lamblial infections. Some observers have noted *an inhibitory effect upon the vegetative organisms* with the use of **emetin,** but this action is not to be considered in any sense a curative one for the infection itself. Dobell and Low, in conjunction with other careful British observers, have found that emetin is without permanent effect upon the organisms. **Thymol** has been highly recommended by Logan and Sanford. Other drugs for which success has been claimed from time to time are **beta-naphthol, bismuth salicylate, methylene-blue** and **male fern.** Escomel treated his cases with a **prolonged milk diet** and doses of **calomel followed by castor-oil.** The diarrhea tends to remit spontaneously in most instances, which will account for the marked success reported from time to time following the use of different medicinal agents.

Diarrheas Caused by Cercomonas and Trichomonas Intestinalis.—These are by far the most frequently encountered of all the intestinal flagellates, possessing a wide distribution throughout tropical and subtropical countries, as well as in many temperate regions. Considerable confusion has always existed in respect to the identity and differentiation of these two species.

A. Cercomonas Intestinalis.—*Cercomonas intestinalis* was first described by Davaine in 1854, but its existence as a distinct species has been denied by most observers. Wenyon takes the position that the term cercomonas has been employed very loosely in medical literature in the past, it having become a habit with some to call any actively moving flagellate seen in the feces a cercomonas, quite regardless of its structure. He concludes that while *Cercomonas intestinalis* is undoubtedly a separate species, it is of exceedingly rare occurrence.

-Description of the Organism.—The organism as originally described by Davaine, possesses a pyriform shape, and measures from 10 to 12 microns in length. But one real flagellum is present, which projects from the anterior or blunt surface. The fine tapering tip or posterior stem, however, constitutes in effect a second flagellum. It is this actively motile tip which is commonly observed in fresh, unstained specimens. The true flagellum only becomes visible, as a rule, in stained specimens. The organism is exceedingly active in movement. Reproduction takes place by simple division of the vegetative cell. It is probable that in most instances where cercomonas infections have been described, the organism has been mistaken for *Trichomonas*



1 2 3

FIG. 2.—TRICHOMONAS AND CERCOMONAS INTESTINALIS. (After Wenyon.)

1. Vegetative form of *Trichomonas intestinalis*, showing the flagella twisted around one another. Note also the undulating membrane, axostyle and nucleus.

2. Ameboid form of same organism, throwing out finger-like pseudopodia which rapidly pass down the side of the body, as outlined in dotted position.

3. *Cercomonas intestinalis*. The backward directed flagellum is adherent to the body.

intestinalis or *Tetramitus mesnili*. A careful staining of the specimen should serve to remove all doubt as to the nature of the organism present.

B. Trichomonas Intestinalis.—*Trichomonas intestinalis* is distinguished from *Cercomonas intestinalis* chiefly by the number of flagella present. Three varieties are recognized:

1. *Trichomonas*, which possesses three closely related anterior flagella.
2. *Tetratrichomonas*, in which an additional posterior directed flagellum is present.
3. *Pentatrichomonas*, presenting in all, five flagella.

The most common clinical variety is the tetratrichomonas.

ETIOLOGY.—*Description of the Organism.*—(*a*) *Morphology.*—*Trichomonas intestinalis*, when viewed in the fresh stool specimen, is pear-

shaped, and is extremely active in its movements. It measures from 10 to 20 microns in length and from 3 to 4 microns in breadth. When the organism approaches its resting stage, an undulating membrane can usually be made out, traveling from the anterior to the posterior ends of the organism. After fixing and staining, the parasite exhibits the following structure: A supporting rod or axostyle traverses the center portion of the cell from the nucleus in the anterior portion to the posterior tip. A definitely formed undulating membrane can be made out, which coils in spiral fashion around the axostyle. The nucleus occupies an eccentric position near the anterior extremity. A subsidiary nucleus, known as the blepharoplast, is also to be observed in close juxtaposition to the larger nucleus. The anterior flagella arise from a basal or chromatin granule on the rounded end of the cell body and project in a forward direction. These are, as a rule, three in number. When a fourth flagellum is present, it extends backward along the edge of the undulating membrane and projects beyond the tip of the posterior end. This flagellum is usually highly active in its movements. Reproduction takes place by longitudinal division mitosis occurring in the nucleus as a primary step in the process. Prior to division, complete reduplication of the various structures of the organism takes place, so that each daughter cell represents a completely matured form. An encysted stage has never been observed in this species. The organism commonly known as *Blastocystis hominis,* which was formerly thought to be the encysted state of *Trichomonas intestinalis,* is now recognized as of purely vegetable origin, frequently appearing in the stools in connection with protozoal infections. When the environmental conditions become unfavorable, the trichomonads cease moving entirely, and assume spherical shape. These forms are particularly resistant and most probably serve in the place of cysts in bringing about infection in the new host.

Distribution in the Body.—In the human intestinal tract, the trichomonas finds a suitable habitat for its life processes in the alkaline contents of both the small and large bowel. The fluid stool offers more favorable opportunities for growth and reproduction than does the dried out and hardened feces. The organism carries on a purely saprophytic existence in the intestinal tract, and no evidence is at hand to confirm the idea that it ever invades the tissues. Nevertheless, a certain measure of pathogenicity is to be ascribed to these flagellates because of the highly active whip-like movements of their flagella. It is to be doubted whether trichomonads themselves are able to initiate a diarrheal condition, but it is the author's belief that their presence in large numbers in the fluid stool undoubtedly produces a highly irritating effect upon the intestinal mucosa. When the fecal contents become less fluid, a gradual diminution in the number of parasites is noted, ending in their complete disappearance from formed stools. At this stage, the infection is often considered to have terminated, but the administration of a saline purge will, in most instances, produce a prompt reappearance of the organisms in the stools.

Some authors assign primary pathogenic properties to *Trichomonas*

intestinalis. Escomel, for example, collected 152 cases of dysentery in Peru, which he believed was caused solely by this organism. Rhamy and Metts claim that "during their seventeen years of laboratory experience, they had never found flagellate protozoa except in cases with existing or recent acute or chronic diarrhea, and are convinced that these parasites are of more importance as etiological factors in diarrhea than has been given them." They observed 7 cases of pure trichomonas infection with the following symptoms: Diarrhea with watery or slightly blood-stained stools, colicky pains, dyspnea, emaciation and anemia. On examination, the large bowel showed superficial ulcers. There was an eosinophilia (6 to 12 per cent.) present in each case.

Castellani states that trichomonad and cercomonad flagellates occur in the stools of about 25 per cent. of healthy persons in the tropics, as may be determined after administering a saline purge. This author believes that the organism is only pathogenic if present in enormous numbers.

Smithies found trichomonads present in the gastric contents of 2 cases that came under his observation. They were discovered in each instance in the residue of a test-meal and were present in large numbers. Both patients had been in the habit of drinking unfiltered surface water in the localities in which they lived.

Lynch is impressed with the fact that trichomonads found in the vaginal secretion, urethra, mouth and lungs are identical with the intestinal trichomonas. This author succeeded in infecting rabbits with feces obtained from human subjects. He likewise speaks of an encysted stage of the organism and claims to have cultivated the parasites in bouillon acidified with .05 per cent. acetic acid in a temperature of 30° C. Rabbits, as well as other lower animals, harbor trichomonads normally, and their presence in these animals is rarely attended by pathological states.

TREATMENT.—The treatment of cercomonas and trichomonas infections of the intestinal tract *rarely produces satisfactory results.* Some authors have reported success with the use of **ipecac** and **emetin.** It should be remembered that the organisms appear irregularly in the stools, and their disappearance should not be taken necessarily as an indication of the cure of the infection. The writer has noticed the frequent presence of trichomonads in the stools of individuals suffering with entamebic dysentery, though he has never observed any effect on these organisms from the large doses of ipecac or emetin employed. **Methylene blue** has been recommended by Rhamy and Metts and by Castellani. Care must be taken that this product is not contaminated by the presence of zinc chlorid. Two to three grains (0.130 to 0.195 gram) are administered by mouth in capsules three times a day and, in addition, the lower bowel is irrigated with a 1 : 5000 to 1 : 2000 aqueous solution of the drug. The treatment is discontinued from time to time in order to prevent the formation of methylene-blue concretions in the intestinal tract. The author has made use of this plan on several occasions, but has never succeeded in removing the infection by this procedure. In

one case, transduodenal lavage with a methylene blue solution was employed without success.

Smithies recommends repeated purgation with **calomel** and **salines**. Escomel has been impressed by the success which he has achieved in the treatment of trichomoniasis with the use of **turpentine** by mouth in conjunction with **rectal irrigations of iodin** (1 : 1000). The iodin enemata are employed for three consecutive days after the patient has been placed upon a strictly farinaceous diet. Should the organisms still appear in the stools after the fourth day of this treatment, the use of turpentine by mouth is indicated. The following mixture is recommended by Escomel for this purpose:

℞

Emulsion de Franck

Infusi cinchonæ (1:50, not acid)	72 c.c.	(2½ fluid ounces)
Extracti cinchonæ	11 "	(3 fluid drams)
Tincturæ cinnamomi	20 "	(5½ " ")
Syrupi Opii (0.5 Ext. in 1000)	14 "	(3¾ " ")
Tincturæ camphoræ compositæ	5 "	(1⅓ " ")
Olei terebinthinæ	3 "	(50 minims)

Julep gommeux

Mucilagonis acaciæ	2 "	(32 minims)
Aquæ florum aurantiorum	2 "	(32 ")
Aquæ destillatæ	20 "	(5½ fluid drams)
Syrupi	6 "	(1⅝ " ")

M. Ft. (Formula transcribed into the British Pharmacopeia by Marsden.)

A tablespoonful of this mixture is to be administered every two hours for the first three days, gradually decreasing in frequency until the organisms disappear entirely from the stools. As a substitute, Wenyon suggests the ordinary **Mistura terebinthina** in 10 minim doses, administered three times a day.

Diarrhea Caused by Tetramitus (Chilomastix) Mesnili.—ETIOLOGY. —*Description of the Organism.*—This organism was first described by Wenyon, in 1910, who ran across it accidentally in the course of a routine examination of the feces of a man from the Bahamas, who was under treatment in a London hospital at the time for some chest disorder. Its occurrence has subsequently been noted in many quarters, and it is now considered by careful observers to be of world-wide distribution. Kofoid claims that the cysts of *Tetramitus mesnili* are, next to those of the Lamblia, the most abundant type of flagellates found in the human stools. The free forms have undoubtedly been mistaken in the past for *Trichomonas intestinalis*. These organisms differ, however, in many of their structural details. Tetramitus is devoid of both axostyle and undulating membrane, but possesses instead a large cytostome, which extends almost the entire distance from the anterior to the posterior ends of the cell. The lips of this large longitudinal opening are curved inward, and

are frequently observed to overlap one another. A small flagellum emerges from the anterior extremity of the cytostome but, as is the case with the other flagella, takes its real origin from a basal granule in the blunt end. The posterior tip tapers out into different lengths, equalling at times that of the cell-body itself. When particularly elongated, this posterior flagellum takes on a spiral form, producing a characteristic twisted appearance. The cytoplasm contains an unusually large number of vacuoles. Reproduction in the unencysted stage has never been observed. The cysts vary in size from 7 to 10 microns. On account of their small size and the lack of internal structure in unstained preparations, the cysts are frequently mistaken for yeast cells. Some of the larger races of cysts are pear shaped, and contain a few

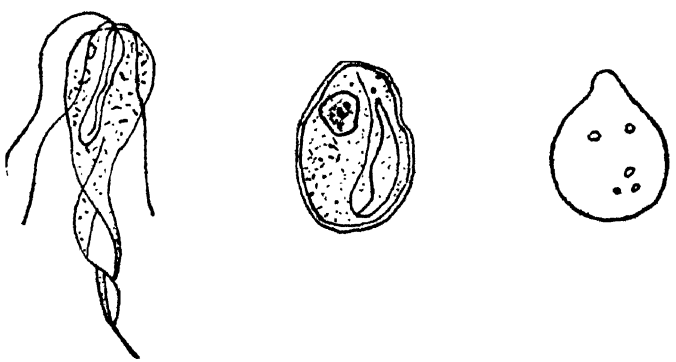


FIG. 3.—TETRAMITUS MESNILI. (After Wenyon and O'Connor.)

1. Free forms, showing twisting of the body. Note the cytostome at anterior extremity.
2. Encysted form, stained.
3. Encysted form, with refractile granules, as seen in fresh preparations.

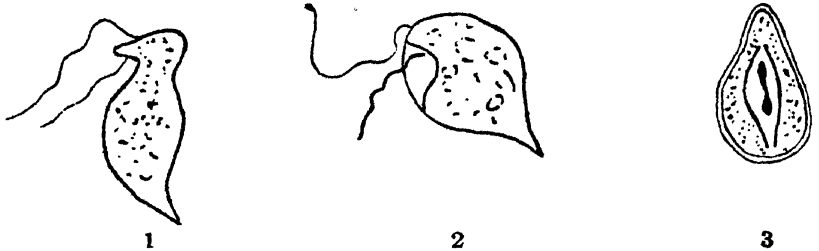
minute, pale green refractile granules. When stained with iron hematoxylin, many of the cysts show a distinct nucleus along with a typical elongated loop, forming the developmental stage of the cystostomal structure. In common with other flagellate cysts delicate flagellar filaments can also usually be made out.

Distribution in the Body.—Clinically, infection with *Tetramitus mesnili* has been observed occasionally in connection with persistent attacks of diarrhea. Gäbel has reported a case of tetramitus diarrhea in which the organisms persisted in the stools for as long a period as twelve years. Other instances of infection with the organism, which were associated with diarrhea, have been noted by Brumpt in France and by Nattan-Larrier from the Ivory Coast. Marques da Cunha and Torres have recorded 5 cases of chronic diarrhea, affecting Brazilian children, which they found to be due to the presence of the tetramitus in the intestinal tract. In infected individuals, the cysts often appear intermittently in

TREATMENT.—The treatment is similar to that of other flagellate infections.

Infection with Waskia Intestinalis.—The discovery of this new type of flagellate organism is also to be credited to Wenyon, who noted it in the course of routine stool examinations in the case of two carriers of *Entameba histolytica.* The organism was named after the Orwa-el-Waska section of the Nineteenth General Hospital in Alexandria, Egypt, where the infection was first discovered.

ETIOLOGY.—*Description of the Organism.*—The free forms possess two flagella which enable the organism to swim about in the feces in a highly active manner. Under the cover-glass, the movements appear to be jerky and the organism frequently assumes a lateral position, in



1 2 3

FIG. 4.—WASKIA INTESTINALIS. (After Wenyon and O'Connor.)

1 and 2. Flagellates as seen in fresh preparations. Note the characteristic bird-like appearance in 1.

3. Encysted form, with dumb-bell nucleus, after staining.

which the movements of the flagella can be carefully watched. The contour, under these circumstances, often suggests that of a bird. In addition to the nucleus, the cytoplasm contains many vacuoles. A cytostome is likewise present in the anterior extremity through which the shorter and less active flagellum passes. The posterior stem tapers in a direction opposite to that of the cytostome. The length of the organism varies from 4 to 9 microns. The cysts are pear-shaped bodies, from 4 to 6 microns in length, and are devoid of internal structure in the native preparation. They resemble closely the smaller races of tetramitus cysts, but lack the refractile granules which distinguish these latter organisms. When stained, the cysts appear as small pyriform bodies, containing an elongated nucleus with dumb-bell-shaped karyosome.

Distribution in the Body.—Waskia intestinalis does not appear to be a common type of flagellate, but few cases having been reported since the announcement of its discovery. Kofoid and Sweezy found an occasional instance of this infection in their records of stool examinations made on American troops who had returned from France. As far as is known, no pathogenic significance has as yet become attached to the presence of these parasites in the stool, though, from analogy with other flagellates, their presence in the intestinal tract in large numbers might not prove to be altogether without clinical importance.

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CHAPTER XXXIV

COCCIDIOSIS

By Sidney K. Simon, M. D.

Definition, p. 371—Description of the organism, p. 371—Distribution, p. 371—Morphology, p. 371—Coccidiosis in lower animals, p. 373—Human coccidiosis, p. 374—Treatment, p. 374.

Definition.—A common and frequently fatal disease in some of the lower animals, but comparatively rare in man, caused by infection with *coccidia,* minute protozoal organisms belonging to the class of *sporozoa.*

Description of the Organism.—Sporozoa are distinguished from other forms of protozoa by their great power of reproduction, coupled with their capacity for forming especially resistant spores. This group is the most widely distributed and highly differentiated of all protozoa, carrying on at least a part of their life cycle directly within the tissue cells of the host. As a result of their activity, the invaded tissue cells undergo hypertrophy and degeneration, and are eventually completely destroyed.

Distribution.—The coccidia exhibit a strong predilection for the epithelial cells of the body, and especially those situated along the intestinal tract and in the liver. In a few instances, the epithelium of the kidney is attacked, though this rarely occurs in human individuals.

Morphology.—As is the case with nearly all the parasitic protozoa, two distinct phases appear during the life cycle of the organism: (1) vegetative, and (2) encysted. In the vegetative stage, the size of the coccidium is extremely variable, limited largely by the capacity for growth within the epithelial cells. The cytoplasm is finely granular as a rule, and no differentiation exists between the octoplasm and the endoplasm. In form, the coccidium is rounded or slightly elliptical. A vesicular type of nucleus is present in all species containing generally one large karyosome.

Reproduction takes place by schizogony with the production of a varying number of merozoites. The liberation of the young schizonts is usually followed by the penetration of new tissue cells, which explains the rapid extension of the disease process in the affected organ. Schizogony continues in this manner for several generations, until a stage is finally reached when further segmentation becomes impossible without sexual conjugation. This latter process takes place in the following manner: The merozoites assume sexual attributes. The female form, or macrogamete, enlarges in size and becomes especially rich in granular material. The male organism, or microgamete, on the other hand, is of delicate structure, consisting mainly of nuclear substance and carries two flagella. Fertilization takes place usually within the tissue cells, and

the new formed sporoblast, though originally naked, within a short time secretes a particularly resistant membranous capsule. Segmentation of the fused nucleus then proceeds, resulting in the development of the matured sporocyst, or oöcyst.

The coccidia are subdivided into different genera, depending upon the number of spores in each oöcyst and likewise upon the number of

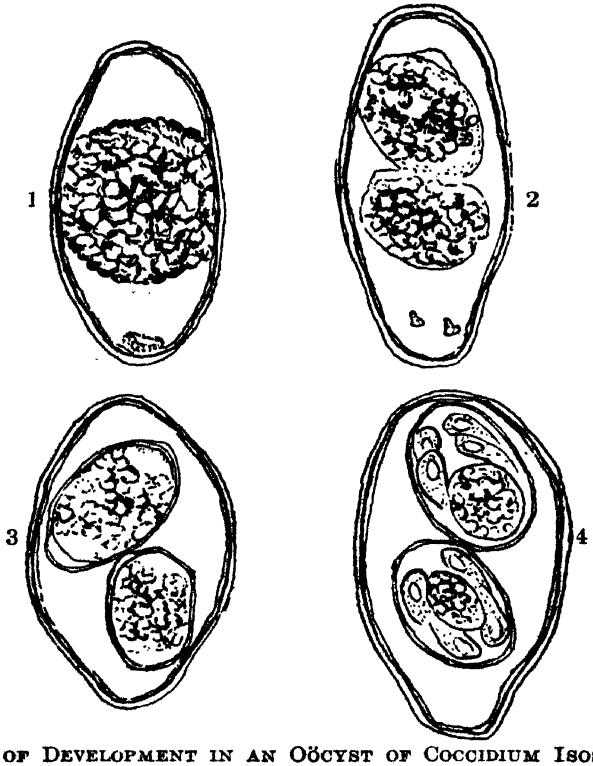


FIG. 1.—STAGES OF DEVELOPMENT IN AN OÖCYST OF COCCIDIUM ISOSPORA AS FOUND BY WENYON IN AN INFECTED INDIVIDUAL FROM GALLIPOLI.

(1) First stage, showing retraction of the protoplasm so that it does not completely fill the cyst. (2) The same, revealing formation of two sporoblasts by division of the single mass. (3) Further development into sporocysts. (4) Final stage, wherein each sporocyst produces four sporozoites, along with a residual mass of cytoplasm.

sporozoites, which develop from each spore. The genus *Eimeria* (Aime Schneider, 1875) is made up of organisms which produce oöcysts with four spores, each of which in turn contains two sporozoites. Two species are recognized, namely, *Eimeria avium* and *Eimeria stiedæ,* both of which are of great economic importance. The genus *Isospora* (Aime Schneider, 1881) comprises forms in which but two spores develop in the oöcyst, which further subdivide into four sporozoites. The species *Isospora bigemina* (Stiles, 1891) belonging to this genus is the form of coccidium usually encountered in human coccidiosis. *Eimeria avium* is a common coccidial parasite in poultry and wild birds, while *Eimeria*

stiedæ causes a fatal type of enteric infection in rabbits, cattle and other mammalia.

Coccidiosis in Lower Animals.—In lower animals, coccidial infections are of considerable importance. Coccidiosis is a particularly fatal disease among poultry and takes the form of a violent enteritis with diarrhea. The infection spreads rapidly from one animal to another, and great havoc is wrought when large numbers are collected together. The oöcysts of the infectious organism, the *Eimeria avium,* are readily conveyed in drinking water and food. After being swallowed, the sporo-

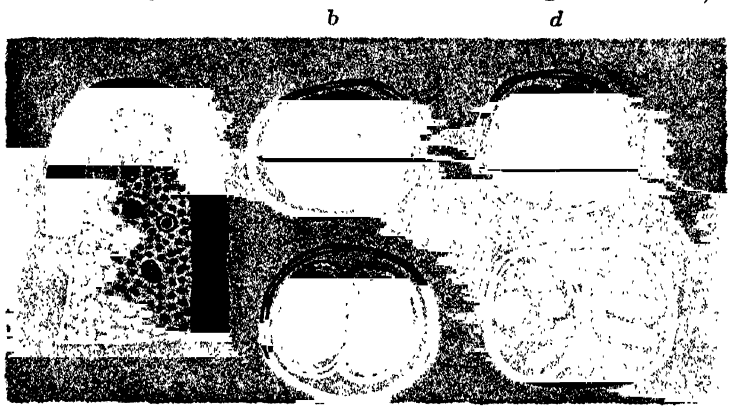


FIG. 2.—ISOSPORA BIGEMINA (STILES) FROM THE INTESTINES OF A DOG.

(*a*) Piece of an intestinal villus beset with Isospora—slightly enlarged. (*b*) Isospora bigemina (15 microns in diameter), shortly before division. (*c*) Divided. (*d*) Each portion encysted, forming two spores. (*e*) Four sporozoites in each part. On the left, a residual body is present—highly magnified. (After Stiles.)

zoites issue forth from the cyst wall, under the influence of the digestive juices and set up a destructive infectious process in the epithelial cells of the intestine. In rabbits and cattle, the *Eimeria stiedæ* produces similar disturbances. From the gut of the rabbit, the organisms spread at times to the liver, where the parasites continue to multiply, resulting in the formation of whitish nodules visible to the naked eye. These nodules upon section are found to contain both free and encysted organisms. Fantham and Porter believe that the eating of the livers of rabbits suffering with coccidiosis has resulted at times in the transference of the infection to human beings.

Human Coccidiosis.—Human coccidiosis presents itself almost entirely in the form of an intestinal infection, though involvement of the liver has been recorded in a few instances. While the total number of cases of human infection has upon the whole been small, there is strong probability that the disease has been mistaken in the past for other types of intestinal parasitism. Infection in man takes place by way of the mouth through the ingestion of food or water that has become contaminated with the sporocysts. Rapid destruction of the epithelial cells of the intestinal tract, which characterizes the disease process in lower animals, is practically never encountered in the human individual.

A mild type of diarrhea is sometimes noted in connection with the presence of coccidia in the human feces, though it is not clear whether these organisms constitute the direct cause. Savage and Young discovered 6 cases of infection with *Coccidium isospora*, complicating entamebic dysentery. Wenyon and O'Connor mention a number of instances of human infection with isospora which occurred under their observation in Egypt. Wenyon likewise observed 3 cases in a London hospital. Fantham found 4 instances of the same infection in a series of stool examinations among 1,305 British soldiers who had been invalided home from Gallipoli and Flanders. None of these latter cases had developed intestinal symptoms as a result of their infection, the diagnosis resting entirely upon the discovery of the typical oöcysts in the stools. Castallani, on the other hand, mentions 2 cases of diarrhea which he believed was caused entirely by coccidial infection. These cases occurred in connection with a group of 20 cases reported by himself and Richards from the Balkan States and Macedonia.

Coccidial cysts appearing in the stools are, as a rule, oval in shape and measure from 27 to 30 microns in length and from 12 to 15 microns in breadth. Each cyst contains two spores which have become further subdivided into four sporozoites. The cyst wall is thick and resistant and besides the spores, the cyst body is made up of granular protoplasm. This type of cyst belongs to the genus isospora as described above. Occasionally, eimeria cysts are found in the human feces which are of somewhat larger size than the preceding type. Considerable interest is attached to the presence of these cysts in the stools, since they may be easily confused with the eggs of various helminths and particularly those of the hookworm and of trematodes. Coccidial cysts are smaller as a rule than the ova of intestinal worms, but there may be considerable difficulty in the differentiation, especially to the unpracticed eye. When doubt exists, the stool should be set aside in a moist chamber for a few days when further developments may be observed.

TREATMENT.—Savage and Young believe that the coccidial infection in their cases was removed by rectal injection of *silver nitrate*. Castallani, on the other hand, found that intestinal disinfectants proved ineffectual in his series of cases, which were subsequently cured by means of **methylene blue. Ipecac and emetin** were both tried out thoroughly by several observers, but with unsatisfactory results.

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CHAPTER XXXV

BACILLARY DYSENTERY

By Frederick F. Russell, M.D.

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Synonyms.—Diarrhea (acute and chronic) enteritis, cholera nostras, winter cholera, intestinal grip, intestinal influenza, gastric fever, intestinal disorder, summer complaint; German, *Baccillenruhr;* French, *dysentérie bacillaire;* Italian, *dissenteria bacterica.*

Definition.—It is an infectious disease of the intestinal tract, caused by one of the bacilli of the dysentery group, occurring in both acute and chronic forms, sporadically and in small epidemics. It is characterized by frequent stools containing blood and mucus and accompanied by pain. It attacks all ages and in its severe forms has a high mortality.

Etiology.—Causative Factors.—The disease occurs in all countries and in all climates, but is commoner in the tropics and in the warmer parts of the temperate zones than in colder regions; it is more frequent in the hot weather of summer than at other seasons. Both sexes and all ages are attacked. There does not seem to be any racial immunity; nor does one attack apparently give much, if any, immunity against a second attack, although we have no exact studies on this point, in which the causative organism in two successive attacks is known. It is quite possible that second attacks are relapses of latent infections rather than new infections.

In well-developed communities where there is good water, adequate sewage system and efficient sanitary inspection of food and drink, particularly of the milk, the disease tends to disappear; where these safeguards do not exist, as among troops in campaign, in contractors' camps, in unsanitary settlements unprovided with sewer systems, pure water and milk, and in the tropics, it is still a serious problem, causing a high morbidity and mortality.

It also occurs not infrequently in institutions, particularly those for mental cases, where the personal hygiene of the patients is difficult to

control, and where a common kitchen, in which the patients perform part of the work, is in use. In such institutions it is easy to understand how a patient with an acute attack, in the earliest stage of the disease, or a chronic carrier, who is perhaps temporarily on duty in the kitchen or dining room, may infect many in the institution. In addition it is quite possible that the patients themselves may be more easily infected than normal healthy individuals.

Cross-infections among children and infants entering hospital wards for other diseases have been reported by Reed,[1] and it is therefore necessary to surround these patients with the same precautions used in typhoid fever wards; and in any event the stools, the bed and body linen must be disinfected and separate nurses and utensils must be furnished.

The disease is not infrequently a terminal infection in the case of cachectic patients and of those suffering from chronic disease.

The part played by flies in the distribution of the infectious material is probably quite important, as in some localities the dysentery season runs nearly parallel with the fly season. Under such circumstances both in hospitals and at home, even breast-fed children may develop the disease, although in such an event the infection may be mild in character.

Water-borne epidemics, more especially in the smaller communities where the water supply system is not continually under good supervision, are not infrequent.

C. J. Hunt[2] studied nine epidemics of dysentery occurring in cities and towns of Pennsylvania. Out of a total population of 152,000 involved 55,000 cases, representing about 36 per cent. of the population, were reported. In each case the disease might have been prevented by proper supervision of the water supply, as it was found that the infectious material had been distributed through that channel. In five out of the nine epidemics studied, a second outbreak, this time due to the typhoid bacillus, followed the dysentery in from ten to twenty days.

Bacillary dysentery is the cause of an enormous morbidity and mortality in the tropics and subtropical regions. Both natives and foreigners suffer from it; the foreigners, because of the better conditions under which they live, being perhaps less subject than the natives. Expeditions from northern countries to the tropics have always suffered severely and will no doubt continue to suffer, as it is hardly to be expected that there will be proper and adequate sanitary conditions in tropical ports for many years to come. The great prevalence of the disease among natives requires further study and differentiation into its various types. It is evident that a large part of the population fails to become immune, thereby rendering it essential, from the standpoint of protection, to learn the reason for the continued susceptibility of such a large percentage of people. Whether it is due to failure of one attack to give protection against another, or whether second and subsequent attacks are due each to a different causative organism, or are relapses, is, of course, a matter of prime importance.

That there is a considerable amount of latent dysentery in the southern and tropical regions has long been known, and J. Cunningham[3] has found that under proper and suitable conditions a survey of a community will give a total enteric index (of course, including all forms) comparable to the malarial index arrived at by spleen and blood examinations. Cunningham's studies were made in a jail in India, in a locality where dysentery was endemic. The macroscopic examination of the stools of the prisoners for mucus, and for blood and mucus, showed latent dysentery in prisoners who were, to all intents and purposes, in good health. The writer concluded that a series of ten successive examinations is sufficient to reveal all latent dysenteries in a given population. From Cunningham's data, MacKendrick found that 23 per cent. of the population were abnormal in this respect, and that the chance of detecting an abnormal person at one examination was about one in three; that with five examinations one could expect to detect about 90 per cent.; and with eight examinations about 97 per cent. The importance of latent dysentery with reference to the spread of the disease is obvious. Individuals in this condition are ordinarily classed as healthy carriers.

Acute and chronic carriers play the same rôle as in typhoid fever. The dividing line between the two classes is arbitrarily drawn at the expiration of three months from the time of the first symptoms. Healthy acute carriers are almost unknown. Healthy chronic carriers are not uncommon; a good example of this condition is described by Fletcher and Mackinnon.[4] The patient was a convalescent from rheumatism. He remembered having a slight attack of diarrhea soon after he first entered the hospital. Although his stools were formed and never contained mucus or blood, the Flexner bacilli were isolated "thirty-one times in forty-one examinations, frequently constituting from 50 to 80 per cent. of all the colonies present on the plates." He was still a carrier eighteen months after the first symptoms appeared.

The ordinary chronic carrier, however, gives a good history of an acute attack and usually of remissions and exacerbations of his disease. With suitable employment and careful diet the carrier of the Flexner-"Y" bacillus remains free from symptoms and is able to work the greater part of the time. The Shiga carrier, however, is rare, as he seldom recovers sufficiently to be considered healthy, even for a time, and is therefore more properly considered a chronic case.

The excretion of the bacilli is intermittent, as with typhoid carriers, and none may be found for weeks or months together; they return in gradually increasing numbers until more dysentery colonies may be found on the plates than colon bacilli. No satisfactory explanation for this phenomenon has been given, although several authors have pointed out the antagonism which exists between the colon and the dysenteric bacilli, and have suggested that the colon bacillus is probably able to kill off the dysentery organisms before the stool is passed.

A more attractive explanation is offered by Nichols,[5] who notes the fact that blood cultures are occasionally positive in dysentery, and

that bacilli of the dysentery group have at times been recovered from the gall-bladder at autopsy.[6]

Reasoning from analogy with carriers of typhoid, paratyphoid and cholera organisms, Nichols believes that further work will show gall-bladder infections in chronic dysentery carriers and suggests the necessity for further examination of cases, with this point in view. Cultures should be made at autopsy from the gall-bladder and other viscera because of the possibility of a portal system septicemia, and during life the bile should be examined by means of Einhorn's duodenal tube, a method which has given excellent results in the study of typhoid and paratyphoid carriers.[7]

The duration of the carrier state in the apparently healthy is unknown, although instances are given in which it has lasted over two years without any indication of change in the future. Fletcher and Mackinnon found that all of their 13 Shiga carriers were persistent carriers, whereas only 13 out of 61 of the Flexner-"Y" group were persistent.

House and family epidemics constitute one of the characteristic features of the disease, and in rural communities, the greater number of a household have been known to die in the course of a few weeks. Of course, proper hygiene and good sanitation would prevent such catastrophes, but we know that the knowledge of good personal hygiene penetrates slowly among the masses of the people. As in secondary cases of typhoid fever, the history not infrequently shows that the mother of the household acts as nurse for the patient and as cook for the well, and sooner or later in some manner or other contaminates the food.

The great importance of the disease has been well summarized by Barker,[8] who states that in the tropics it destroys more lives than cholera and has been more fatal to armies than powder and shot, and that it has been responsible for a greater amount of invalidism and deaths than has any other single disease.

Bacteriology.—The *Bacillus dysenteriæ* was first described by Shiga,[9] who isolated it during a severe epidemic which occurred in Japan in 1898. The method which he employed had often been used before, but rarely with success. It consisted in agglutinating a large series of organisms isolated in pure culture from the stools of dysenterics with the serum from convalescents. In this way, he found an organism which reacted positively with convalescent serum. On the basis of his early experiments, he also believed the bacillus to be motile. On the culture media in use at that period he was unable to differentiate it from the typhoid bacillus, except by its slight motility and by the agglutination reaction.

Subsequent studies by Kruse,[10] Flexner,[11] Lentz,[12] and Hiss and Russell [13] made it clear that the organism was non-motile and that it could be differentiated from typhoid by that character alone; this, together with the very clear-cut serological differences, established the identity of the dysentery bacillus.

The same series of studies showed that there were differences among

the dysentery bacilli themselves, and Kruse, by means of agglutination reactions, divided them into two classes, true and pseudodysenteries. In the first class he placed the organism discovered by Shiga in Japan and by himself in Germany, and in the second, or pseudodysentery class, the bacillus of Flexner and the organisms which he had isolated from cases of asylum dysentery in Germany. The term pseudo-dysentery was soon dropped, and it became customary in America to speak of the non-acid or non-mannite fermenting strain of bacilli (Shiga, which does not form acid from mannite), and of the acid or mannite fermenting strains ("Y," which ferments mannite only; Flexner, which ferments mannite, sucrose, dextrin and maltose; and Strong,[14] which ferments mannite and sucrose).

With this division into two principal classes and into three varieties of the second class, the subject rested until the outbreak of the World War, when the return of patients to England from the Eastern Mediterranean revived interest in the subject in English-speaking countries. Since the cessation of the war, which has permitted the transmission through the mails of the medical journals from the Central Powers, it has been learned that they also had many cases of dysentery, and that their investigations followed much the same lines as those of the British.

The failures of early investigators to find a single causative organism upon which they could agree led them to accept the hypothesis that the disease was caused by the commoner and well known bacteria of the intestine, which in some way had acquired great virulence. French and Italian authors reported the presence of a colon bacillus, called by them *Bacillus coli dysenterica*, which was pathogenic for cats and dogs, producing dysenteric lesions in the colon, including ulcers. (Magiori, Levaran, Armand, Celli, Fioca [1895] and Escherich.)

In Japan, Ogata[15] described a Gram-positive bacillus with liquefied gelatin and produced dysenteric lesions in laboratory animals. It has never been reported since except by Vivaldi, in a small epidemic in Italy.

Calmette isolated the *Bacillus pyocyaneus* from a form of dysentery common in Cochin China, where it is known as endemic enterocolitis; Lartigan in New York, Adami in Canada, and Barker in Baltimore, found the same organism in small epidemics, but no further references are found to this organism in the literature in recent years.

Many observers have noted the frequency with which streptococci (*Streptococcus intestinalis*) and other cocci are found in the stools in dysentery, and in the summer diarrheas of children, and have particularly observed their presence in enormous numbers in green stools. No one has recently attributed any pathological importance to them, however. (Zancard, Silvestri, Bertrand, Bauscher and Ascher.)

In 1906 Morgan,[16] working in London, published a study of the bacteriology of the summer diarrheas of children. He noted that the clinical picture of the disease in England was somewhat different from that reported in America; for example, he found blood in the stools to be quite exceptional there, whereas in America it is not infrequent.

He found none of the usual dysentery bacilli, but did isolate a series of organisms from stools and autopsy material. His method was as follows: The stools were plated on MacConkey's bile-salt, neutral red, lactose agar and all colonies unable to ferment lactose were transferred to lactose broth fermentation tubes. After three days' incubation all the lactose fermenters were discarded and transfers then made to gelatin; after three weeks' incubation all liquidifying cultures were discarded and the remainder retained for study. Morgan examined 304 cultures and found an organism since known as *Morgan's bacillus No. 1,* which is a Gram-negative, motile bacillus, producing acid and gas in dextrose, but not fermenting mannite, dulcite, lactose or sucrose. It turns litmus milk alkaline and produces indol. It caused death preceded by diarrhea in young laboratory animals, and was regularly isolated from the animal's spleen after death. Filtrates from young broth cultures were found to be quite toxic for rabbits. The stools of healthy children were repeatedly examined, but with uniformly negative results. Morgan's results from agglutination tests, using the patient's culture and serum, were disappointing, as only one serum out of forty examined showed agglutinins for the bacillus from the corresponding patient.

Kligler[17] has shown that while culturally these organisms appear to represent a single, definite species, serologically they are quite diversified. Among seventeen cultures examined, six different groups were found. In view of these wide antigenic differences it seems improbable that the organisms can be specifically related to any of these disease processes or to each other.

Up to the time of the publication of the papers of Kruse, 1901, and of Lentz, 1902, and of Hiss and Russell, 1903, and of Park and Dunham, 1902,[18] the various dysentery organisms had not been differentiated. These studies showed, however, that the Shiga bacillus fermented glucose only, and that the bacillus brought from Manila by Flexner in 1900 could be differentiated from the Shiga by its power of fermenting mannite, an alcohol which had not been used before that time by bacteriologists. Hiss and Russell showed, furthermore, that a third variety, which they called the "Y" bacillus, could be differentiated from the Shiga by reason of its power to ferment glucose and mannite only, whereas the Flexner cultures also fermented maltose, sucrose and dextrin.

In 1903, during a small epidemic near New York, Park and Carry[19] isolated another form which was like the Shiga in the fermentation reactions, but differed from it in possessing the power to produce indol and in not being agglutinated in either Flexner or Shiga serum. It is possible, therefore, that they anticipated the discovery of what is now known as *Bacillus ambiguus* or Schmitz's bacillus.

Thus it is seen that during the first years after the discovery of the organism much work was done, particularly in Germany and the United States, which resulted in showing the widespread distribution of the bacilli of dysentery; of late years, however, until the outbreak of

the World War, very little more was contributed to our knowledge of the bacteriology of the disease. The reason for this becomes evident when one considers the nature of the investigations upon intestinal organisms during the period. Drigalski and Conradi,[20] and soon after, Endo[21] and MacConkey, described new plating media for the isolation of typhoid bacilli from the stools and urine, making use of dyes as indicators. In the course of time these media, particularly the Endo, came to be used as a routine measure for the examination of stools in laboratories all over the world. Although these media are highly successful for the typhoid and paratyphoid bacilli, they are quite unsuitable for the examination of dysenteric stools, because of the inhibitory effect of the dyes and of the unfavorable reaction of most of the media. Only recently has the difficulty been recognized and steps been taken to correct the errors.

Technic of Stool Examination.—In 1918, Kligler and Olitsky[22] reinvestigated the technic of stool examination for dysentery bacilli, and made certain definite recommendations, of which the following are the more important:

"*Selection of Stool Specimens for Examination.*—Too much emphasis cannot be laid on the importance of choosing a satisfactory sample of stool. If possible, one containing blood and mucus with little or no fecal matter should be used. It is essential to plate the stool directly or very shortly after it is collected. Experiments with artificial mixtures of the Shiga bacillus with feces showed a 50 per cent. reduction in four hours and from 85 to 90 per cent. in twenty-four hours, when kept at room temperature."

The two sorts of media which these writers found most suitable are prepared as follows:

"(1) The modified Endo's medium is prepared as follows: To veal or beef-infusion 1.5 per cent. agar, titrated (and this is important) to pH 7.6 to 7.8, is added 1 per cent. lactose and 1 per cent. by volume of decolorized basic fuchsin indicator. The latter is prepared by adding 1 c.c. of 10 per cent. basic fuchsin to 10 c.c. of 10 per cent. sodium bisulphite solution. Of course, the lactose and the indicator are added separately before plates are poured.

"(2) The eosin-blue medium is prepared by adding to the veal-infusing agar, titrated to pH 7.2 to 7.4, 1 per cent. lactose, and 2 c.c. of 2 per cent. solution of yellow eosin and 2 c.c. of 0.5 per cent. solution of water-soluble methylene blue."

It will be noted that both of the new media are standardized according to their hydrogen-ion concentration, which is most important; the colonies on media so prepared are not only more numerous, but relatively larger.

Kligler and Olitsky's procedure for isolation of the bacillus from the stools, as briefly stated by them, is as follows:

"*Procedure.*—On the basis of these tests, and of experience in practical work and class work, we recommend the following procedure for the isolation and rapid identification of dysentery bacilli from stools:

"A fresh specimen of stool, preferably with blood and mucus, is collected and promptly cultured. A shred of bloody mucus, if present, is selected, washed three or four times with sterile saline, to remove all fecal matter, and spread successively on a veal infusion eosin-methylene-blue and a modified Endo plate. The plates are then incubated from eighteen to twenty-four hours at 37° C.

"The plates are now examined and the suspicious, colorless colonies inoculated into each of two differential tubes:

"(*a*) A small tube containing 1 c.c. of a 0.5 per cent. glucose broth.

"(*b*) A double sugar tube, on the principle of the Russell double sugar medium, containing 0.1 per cent. glucose, 0.5 per cent. mannite, and 1 per cent. Andrade indicator.

"The colony is picked off with a small loop and inoculated first into the broth and then stabbed in and streaked on the double sugar tube.

"After from two to four hours the broth tubes are usually sufficiently turbid for an agglutination test with a polyvalent antidysenteric serum. A faint visible turbidity is sufficient, and when it appears, 0.1 c.c. of a 1:50 dilution of a potent polyvalent antidysenteric serum is added and the tubes re-incubated for one hour. A definite clumping is a good presumptive test for the presence of dysentery bacilli.

"The double sugar tube is incubated over-night. A red butt without gas, and a colorless slant indicates a Shiga bacillus. If the entire tube is red and gas absent, it corresponds to a Flexner type. The surface growth is now washed off with saline and a confirmatory agglutination test is made with specific type and polyvalent serum. If desired, an agar slant and various agar mediums may be inoculated for further study, or an animal inoculation made.

"By the use of the two tubes, one can obtain a presumptive diagnosis about a day after the collection of the stool—a matter of great importance for epidemiologic and therapeutic purposes."

Alternative Medium.—A simple and satisfactory medium has been devised by Max Levine,[28] working in the author's laboratory, for the isolation of these organisms from stools:

Distilled water	1,000 c.c.
Agar	15 grams
Peptone (Difco)	10 grams
Dipotassium phosphate	4 grams

The hydrogen-ion concentration of this medium is 7.4 to 7.5. It therefore needs no adjustment, and if the agar is clean and white, need not be filtered. To each 100 c.c. is added:

Lactose 20 per cent. solution	5 c.c.
Glucose 5 per cent. solution	1 c.c.
Rosolic acid (1 per cent. in 90 per cent. alcohol)	1 c.c.
China blue (0.5 per cent. in water)	1 c.c.

The dysentery bacilli grow as luxuriantly on this as on any other medium, and the non-lactose fermenters are readily isolated. Colonies fished from these plates are first agglutinated in a polyvalent serum of high titer and transferred to double sugar tubes in the manner recommended by Kligler and Olitzky (*see above*, page 382).

For a further study of the organism giving the presumptive cultural and serological reactions, it is well to replate the cultures, since those fished from plates inoculated by streaking the surface with material from a stool are frequently contaminated; consequently further study of the organism cannot be carried out until pure cultures have been obtained by replating.

The culture is then transferred to milk, using brom-cresol-purple or litmus as an indicator, to peptone solution and to fermentation tubes containing ½ per cent. solutions of the carbohydrates given below, in Levine's peptone dipotassium phosphate medium, or sugar-free broth. Levine's medium contains peptone 1 per cent., dipotassium phosphate, 0.4 per cent. in distilled water. This should give a pH value of 7.6. which is a satisfactory reaction for this group. The carbohydrates for confirmation of the presumptive test already made, and for further study, are glucose, lactose, sucrose, mannite and dulcite, and to a limited extent maltose and dextrin.

It has, however, been pretty clearly shown, by numerous studies, that the greatest value of carbohydrate fermentations is in the separation of the Shiga from the Flexner-"Y" group by the fermentation of mannite by the latter.

In studying the group by means of fermentation reactions it is essential to have pure sugars, and the best test for their suitability is the use of control fermentations with pure cultures of known dysentery organisms. Impurities in the maltose are not uncommon; but even when pure some of the sugars are easily broken down during the sterilization, which must be carefully controlled. If the Arnold sterilizer is used, i.e., streaming steam, the time of exposure should not exceed twenty minutes on three successive days. If the autoclave is used, an exposure of ten minutes at ten pounds' pressure is sufficient, if the tubes are small. In either case the tubes should be packed loosely in the baskets, to permit rapid and uniform heating. Mudge[24] has shown that the temperature to which the sugar medium is submitted is less important than the time, and he finds that there is less hydrolysis of the sugar when the medium is sterilized in the autoclave than when it is sterilized in the Arnold. As a rule ten minutes' exposure to ten pounds' pressure in the autoclave gives a satisfactory medium. As an indicator of the reaction of the medium either Andrade or brom-cresol-purple will be found superior to litmus.

Cultural Characteristics of the Dysentery Bacillus.—The dysentery bacillus is about the same size as the typhoid bacillus, the difference being that it is slightly shorter and thicker. In a stained preparation from a pure culture considerable variation in size and shape is seen, many bacilli being so short and broad that they resemble cocci. The organism stains readily with all the usual dyes and is regularly Gram-negative. In hanging drop preparations an active brownian movement is seen but no true motility. The absence of motility is readily demonstrated in cultures made in the semisolid medium of Hiss, which shows that the bacillus is unable to grow away from the line of inoculation and consequently leaves the medium clear, in contrast to the motile typhoid bacillus, which causes a diffuse cloud throughout the medium.

Gelatin is not liquefied. On agar plates the colonies resemble typhoid colonies, yet are much smaller and grow less rapidly; they are moreover much more sensitive to the reaction of the medium. Luxuriant cultures on agar plates have a characteristic odor. Milk is not coagulated, but shows a primary acidity with a subsequent reversion to alkalinity.

None of the dysentery cultures produce gas in glucose fermentation tubes. The remaining cultural reactions vary so much with the different strains of the organism that each must be considered separately.

Toxin Formation.—Kraus and Doerr,[25] and Todd[26] have shown that the Shiga strain, unlike the other members of the typhoid-colon-dysentery group, are able to produce a soluble toxin of great power. The soluble toxin is not only fatal to laboratory animals, but reproduces in them many of the lesions of the disease, which are comparable to those found in human beings. The toxin is usually obtained by filtering young broth cultures, but a potent toxin may be obtained by emulsifying agar cultures in salt solution, shaking, for a short period, and then filtering. It will withstand a temperature of 60° or 70° C. for one hour, but is destroyed at 80° if exposed for the same length of time.

The toxin, as will be seen from the symptoms, exerts its effect upon the mucous membranes of the colon, conjunctiva and urethra, on the nervous system, and on the synovial and pleural membranes, and it is probably, therefore, a complex body, consisting of two or more toxins.

Therapeutic Antidysenteric Serum.—This was formerly prepared by inoculating horses subcutaneously with cultures or filtrates of cultures, over long periods of time—nine months or a year. Recently Flexner and Amoss[27] described a rapid method which makes it possible to bring a horse to the productive stage in as short a period as ten weeks. The essential points in this method consist in giving three intravenous injections of toxins, or of killed, and finally of living, cultures on three successive days, followed by a period of seven days' rest, when the three successive doses are repeated and the animal is again allowed to rest. By alternating in the use of Shiga and Flexner-"Y" strains, a potent polyvalent antidysenteric serum which will have a high agglutination titer and which will protect laboratory animals against lethal doses of cultures can be produced in a relatively short time.

Pathogenicity for Animals.—Except perhaps in the case of monkeys it has been impossible to reproduce the disease in animals by feeding experiments. By inoculation with both living and killed cultures, however, dysenteric lesions can be produced in most laboratory animals. The toxin is particularly fatal to rabbits; they develop a paralysis of the hind quarters, which is quickly fatal. The intestinal lesions can also be reproduced: swelling, injection, hemorrhages, necrosis, ulceration and, in occasional cases, scar formation may be seen.

Differentiation of True Dysentery Bacillus from Allied Organisms.—The rapid and exact differentiation of the true dysentery bacilli from allied organisms has been attempted in various ways, and the classification given by Andrews[28] in 1918 seems quite satisfactory.

Cultures die out very quickly on ordinary media, but Andrews finds that it is possible to preserve them on Dorset's egg medium in sealed tubes; he has succeeded in keeping them alive on this medium for months, merely by paraffining the cotton stopper.

As a basis for his sugar media he used the ovomucin suggested by Winter.[29]

The medium consists of 45 grains of dried commercial white of egg, dissolved in a liter of cold water. It is steamed in the Arnold to coagulate the albumin and globulin, and filtered while hot until clear. One-half per cent. of sodium chlorid and the same amount of the sugar to be used is added, together with a suitable indicator; Andrade serves very well. The mixture should be pink while hot, but colorless when cold. The sugars found desirable for a satisfactory differentiation were glucose, lactose, mannite and dulcite. Andrews does not consider that sucrose or maltose is necessary.

The acid agglutination test of Michaelis[30] also proved decidedly useful in his practice. Six stock solutions are made up as follows:

	Normal NaOH	Normal Acetic Acid	Distilled Water
(1)	5 c.c.	7.5 c.c.	87.5 c.c.
(2)	5 c.c.	10.0 c.c.	85.0 c.c.
(3)	5 c.c.	15.0 c.c.	80.0 c.c.
(4)	5 c.c.	25.0 c.c.	70.0 c.c.
(5)	5 c.c.	45.0 c.c.	50.0 c.c.
(6)	5 c.c.	85.0 c.c.	10.0 c.c.

For the test a 24 hour agar culture is suspended in 20 c.c. of distilled water: 3 c.c. or a smaller proportionate quantity is put into each of 6 tubes, then a drop of protein solution is added—a 10 per cent. solution of human serum is satisfactory—and to this finally is added 1 c.c. of each of the stock solutions listed above. After mixing, the tubes are incubated at 27° C. for two hours, and, after half an hour more at room temperature, are read. With this method true dysentery bacilli show no agglutination, while the related organisms are all distinctly clumped, often in all of the tubes. Murray is quite unable to accept this agglutination test, and it seems improbable that it will continue to be used.

Agglutination in specific monovalent sera, when carried on properly to the full titer, must of course be used in any system of identification of these organisms. The reaction must however be carried out systematically, since neither a positive nor a negative agglutination test will of itself establish the diagnosis. For example, some Flexner-"Y" strains may not agglutinate in any available serum, and on the other hand, nonrelated organisms, particularly *Bacillus coli*, may agglutinate to the full titer of the serum. However, when unrelated organisms are excluded by cultures and all the conditions are properly controlled, the agglutination test will establish the identity of the culture in question.

Andrews recognized the Shiga and Flexner-"Y" types as true dysentery bacilli, and separates from them three related organisms called by him, *Bacillus ambiguus* (Schmitz' bacillus), *Bacillus alkalescens*, and *Bacillus dispar*. He gives his results in the following table:

	Lactose	Glucose	Mannite	Dulcite	Indol	Alkali Formation	Acid Agglutination	Specific Serum Agglutination	Pathogenicity for Laboratory Animals
Bacillus of Shiga	−	+	−	−	−	Slow	−	To titer	Very high
Bacillus ambiguus	−	+	−	−	+	Slow	+	Negative	Negative
Bacillus of Flexner-"Y"	−	+	+	−	±	Mod.	−	To titer	Marked
Bacillus alkalescens ...	−	+	+	+	+	Rapid	+	Negative	Negative
Bacillus dispar	+	+	+	−	±	Rapid	+	Negative	Marked

Further work has been done by Murray[81] on the serological reactions of the dysentery group, and his conclusion is briefly that the dysentery group can be divided primarily by cultural reactions into four classes:

(1) *Bacillus dysenteriæ* (Shiga).

(2) *Bacillus ambiguus* (Schmitz' bacillus). This is like the Shiga type, except in the serum reactions and in producing indol. He accepts it as pathogenic.

(3) *Flexner-"Y."* This class contains several varieties which cannot be separated by cultural reactions, but which are evident serologically.

(4) *Bacillus dispar* of Andrews (Class E of Kruse). This organism, besides fermenting glucose and mannite, produces acid in lactose after long incubation—sometimes as long as 14 days—and there is sometimes a late clot in milk.

We see therefore that the dysentery group has been enlarged as the result of the investigations carried on during the war, that Class 2 of

Murray (*Bacillus ambiguus* of Andrews) has been added to the Shiga or non-mannite fermenting type, and that Class 4 of Murray (*Bacillus dispar* of Andrews) has been added to the mannite fermenting type, and further, that Flexner-"Y's" and nearly related strains (Class 3 of Murray, and Flexner-"Y" of Andrews) have been consolidated into a single class. Murray's four classes can be arranged as follows:

Bacillus dysenteriæ (Shiga)	Class 1
Bacillus ambiguus (Schmitz)	Class 2
Bacillus dysenteriæ Flexner-"Y"	Class 3
Bacillus dispar	Class 4

Para-agglutination is an expression which has come into use to express the fact that bacteria other than those used as the antigens in producing the sera will sometimes be agglutinated. For example, *Bacillus coli* isolated from a case of dysentery may be agglutinated in Shiga serum in as high a dilution as the Shiga itself. It has been stated (Fratzek[82]) that *Bacillus coli* and even intestinal cocci may acquire the property of being agglutinated by specific dysentery or typhoid serum, when growing in the body in association with these pathogenic organisms. The inference, on finding para-agglutinable bacteria, is that further search will reveal the causative organism, or that the patient's serum will agglutinate it. Although the direct value of these observations is probably not great, it does serve to emphasize one of the pitfalls of agglutinations in this group. It must not be overlooked that a positive agglutination of an unknown organism in dysentery serum does not identify the culture as *Bacillus dysenteriæ*, and that complete cultural study is always necessary. The para-agglutinins are not group agglutinins, as can be shown by absorption reactions. Furthermore, the para-agglutinable bacilli may lose this property on repeated transfer to culture media.

Pathogenesis.—As with other enteric diseases, the infectious agent enters through the mouth with contaminated food, or drink, or is conveyed to the mouth on the fingers. It passes through the stomach and begins to multiply in the small intestine, where the bacilli can be found in enormous numbers. As they increase in number one or more toxins are produced which are absorbed into the circulation. One of the toxins is excreted by the mucous membrane of the colon, and in passing through its walls, produces characteristic changes and gives rise to the dysenteric symptoms.

Flexner and Sweet[83] made extensive studies on the pathogenesis of the disease, and demonstrated quite conclusively that the endotoxins, which are elaborated in the course of the disease by autolysis of the bacilli in the small intestine, are absorbed, with the aid of the bile, from both the small and large intestines. In rabbits with or without section or ligature of the ducts, absorption of a toxin capable of producing lesions in the colon does not take place, although without the bile the neurotoxin is absorbed in sufficient quantities to produce death from paralysis.

After absorption into the blood, the toxin is excreted by the mucous membrane of the colon, which is greatly damaged in the process. The lesion, as shown in sections of the colon from early cases, begins in the submucosa around the blood and lymph-vessels rather than on the surface. The lesion and the pathological process resemble, in fact, those in mercurial poisoning, from which they differ only in intensity.

Symptomatology.—CLINICAL HISTORY.—*Period of Incubation.*—The exact period is not well established, but there is abundant reason for believing that it is short. Strong and Musgrave [84] report that it is probably less than forty-eight hours in the Philippines. Older statements giving periods as long as seven days are probably incorrect.

Mode of Onset.—The disease usually begins suddenly, often with rigors, headache and vomiting, particularly in the severer forms found in the tropics and southern regions. From the beginning it is characterized by great prostration. Even on the first day of the disease the patient may appear extremely ill and exhausted. The temperature is usually only slightly elevated, although it may reach 103° or 104° F., and it does not show a characteristic curve. A continuously high temperature or marked irregularity in the curve may indicate the onset of some complication. The pulse is increased in frequency and is quite small.

Course of Disease.—The tongue is heavily coated, and as the disease progresses it becomes swollen and shows the imprint of the teeth. If the mouth is not well cared for the coating increases and becomes brown and dry; coating is less in evidence in subacute and chronic cases, and the surface may become bright red, smooth and shining like a piece of fresh beef. The swelling continues to be prominent until well into convalescence.

The characteristic symptoms are of course the *frequent bloody stools* and the abdominal pain, accompanied by great prostration. The number of stools is always large and may reach thirty or forty a day for short periods, except in the acutely toxic cases, when death may occur without much change in the number or character of the stools. The stool itself is quite characteristic, and at the height of the disease is quite unlike the stool in any other disease, not excluding amebic dysentery. It is small and consists exclusively of blood and mucus, without a trace of fecal matter. Under the microscope—and dysenteric stools ought always to be examined microscopically, on the chance of finding ameba, flagellates or ciliates—one sees red blood-cells in enormous numbers, and epithelial cells in masses as they are thrown off by the mucous membrane. These are often to be recognized as columnar epithelial cells, arranged like closely set pickets on a fence, like a typical text-book picture. In addition single epithelial cells in all stages of swelling, degeneration and necrosis are seen; the single swollen cells are often roundish and suggest at first quiescent amebæ, but they do not possess the power of motion, or the ability to send out pseudopods, like amebæ. They may also be readily distinguished from amebic cysts by the large size and different character of their nuclei. If stains are added to the stool,

such as Donaldson's stain, as used by Kofoid,[85] it will be noted that the degenerated and necrotic epithelial cells take up the eosin readily, in sharp contrast to the amebæ, which are stained yellow with the iodin. Everywhere through the microscopical field are enormous numbers of leukocytes. These various elements are embedded in masses of glairy and stringy mucus. As the disease progresses and increases in severity the character of the stool changes from that described above; the epithelial masses increase in size until one sees sloughs of large ulcers, or even a pseudomembranous cast of the entire circumference of the gut. Under the microscope it is no longer possible to make out the structure of the epithelial cells, since the entire mass is coagulated and necrotic. The fluid part of the stool is no longer watery but serous, and dark from altered hemoglobin. Such stools are extremely offensive.

A single stool is often no more than a teaspoonful, yet the patient complains of an incessant desire to go to stool. Vesical tenesmus is also a frequent and troublesome symptom. As a result of the excessive loss of fluid from the body, the patient complains bitterly of thirst, and the need for liquids in treatment is apparent.

In very severe infections, and where the case does not come under treatment early, the patient becomes more and more prostrated and toxemic, and death occurs in the first few days.

Some cases have a striking resemblance to cholera. The onset is sudden, the prostration marked, the stools are frequent and very watery, and soon become of the consistency of rice water; the face and hands, because of the great loss of fluids from the body, quickly become shriveled and shrunken, and the abdomen sunken and boat-shaped. In the presence of cholera it is, of course, impossible to make a differential diagnosis on clinical grounds alone, and such cases are treated as cholera until bacteriological examinations have shown the safety of releasing them from observation.

Milder cases, and those which come under treatment early, may begin to improve toward the end of the first week; the stools become less frequent, and change in character, becoming less bloody and more feculent, showing some staining with bile.

The *pain*, which is so important a symptom of the disease, manifests itself in two forms: tormina and tenesmus. *Tormina* or griping pains (cramps) are felt anywhere in the course of the colon, although they are usually localized in the transverse colon. They occur also during the course of the acute digestive disturbances where the colon is healthy, but in dysentery they continue to occur after the gas and offending food have been passed, and are then probably due to spasmodic contractions of the muscular coat of the inflamed and swollen colon.

Tenesmus is essentially an exaggeration of the usual sensation felt when the bowels are evacuated; due to the inflamed condition of the sigmoid and rectum the sensation becomes an intense and penetrating pain, recurring after every stool, no matter how small.

Vesical tenesmus does not depend upon the severity of the dysentery, but may appear in even the milder cases, and when marked may lead

to retention of urine. In the case of children and of stuporous cases, special attention must be paid to the bladder and catheterization must be performed when needed.

The *urine* is *scanty*, highly colored, and of increased specific gravity. It frequently shows the presence of albumin, hyaline and granular casts and, in rare cases, of red blood-cells. The liver and the bile-ducts may be involved, and jaundice may appear. The spleen may be enlarged and tender.

In adults the disease is usually self-limited and runs its course in from ten days to two weeks, but some cases become subacute and last for a month or more, and of these a few become chronic and last for months or years with periods of remission.

In infants the character of the stools varies greatly. Blood is usually present, although not in every stool, either in small specks or streaks on the surface of the mucous masses, or as fluid blood; the stool may consist entirely of blood and mucus. Mucus is always present, often in large quantities, either alone or mixed with curds and undigested food. As a rule the stools are green in color, and may be quite numerous. Their passage is regularly accompanied by tenesmus, although careful observation is necessary to detect the symptoms in some cases.

The duration of cases of infantile dysentery which recover varies from one to four weeks; death occurs most frequently during the first or early in the second week, although the illness may end in death after as long a period as six weeks.

Relapses occur, comparable to those in typhoid fever, but they are not common or clean cut.

L. Jacob [86] has described a series of cases in which the temperature rose on the nineteenth to the twenty-second day. The period of normal temperature preceding the relapse varied from one to three weeks. The intestinal symptoms were absent, or the stools were milky, amounting to little more than a diarrhea. Nevertheless, he isolated both Shiga and Flexner-"Y" strains from the stools during the relapse. In spite of the mildness of the intestinal symptoms, the fever, malaise and anorexia were marked. Headache and joint pains were frequently present and severe. Relapses after surgical operations (for hernia) have been reported; the thorough purgation preparatory to the operations seemed to be the exciting cause.

At the beginning of the attack the abdomen is distended, but later it is sunken and boat-shaped; palpation of the colon is painful throughout the course, but particularly over the sigmoid, cecum or the flexures.

Chronic Cases.—The symptoms do not differ from those of the acute form except in their severity. The patients are greatly emaciated; in fact, some become mere skeletons before they die. On the other hand, there are periods of remission during which the patient seems to have entirely recovered. Fletcher and Mackinnon [4] call attention to the difference in the symptoms between Shiga and Flexner-"Y" cases, which consists principally in the severity of the symptoms present. Without

exception the patients with the Shiga type were very sick, greatly emaciated, and suffered from mental depression. They had frequent stools, usually containing blood and mucus. The Flexner-"Y" patients, on the other hand, usually looked well, and were often well nourished and had remissions during which the stools were normal. Such men were quite capable of doing ordinary work, and in civil life, where they could choose their occupation, would get along quite well.

Diagnosis.—The diagnosis of dysentery is readily made, but to differentiate this disease from amebic or balantidial dysentery is not possible on clinical symptoms and signs alone. The fresh stool, as soon as possible after it is passed, should be examined under the microscope, in order to exclude the dysenteries which are due to amebæ and other animal parasites. The description of the microscopical appearance of amebæ in dysenteric stools will be found under the subject of Entamebic Dysentery, and will not be referred to further here. It is true that the ameba of dysentery, in the summer in the North and all the year round in the tropics, will preserve its motility for several hours. While vacuum bottles or water-heated containers are desirable for the preservation of specimens, they are not absolutely essential.

The serum reactions are not of much practical value in diagnosis, since agglutinins, for example, do not become evident in the patient's serum until relatively late in the disease. They are rarely present before the end of the first week, and usually not until the second week, and may not appear until the third or fourth week. Bacteriological examination of the stools is of more value, not so much in diagnosing bacillary dysentery, since that can be done by excluding ameba and other animal parasites by repeated microscopical examinations, as in establishing the identity of the particular member of the dysentery group which is the causative organism. The severity and prognosis are much worse in those dysenteries due to the Shiga bacillus than in the forms due to other members of the group. Details of the laboratory methods in use will be found in the first part of this chapter.

The agglutination reaction is of inestimable value in epidemiological investigations of outbreaks in hospitals, institutions and communities, since many mild, unrecognized cases occur, which could not otherwise be diagnosed or identified. The length of time that agglutinins are present in the blood after an attack is not well established, but reports show that they may be present for six or seven weeks, and probably for a much longer period. Agglutinins may be present long after all bacilli have disappeared from the stools.

Differential Diagnosis.—Frequent stools with blood, mucus and tenesmus are caused not merely by the dysentery bacilli but also by organic diseases of the rectum and colon, such as carcinoma, adenomatous polypi, tuberculosis and syphilis. These conditions must be excluded by physical examination and by the history of the onset.

Toward the end of a dysentery epidemic caused by a polluted public water supply, cases of typhoid fever are apt to appear, as has been

shown by Hunt. The pollution of a water supply by sewage would naturally be expected to reproduce all the water-borne diseases which were present in the community from which the contaminating sewage came. Attention must therefore be directed to the possibility of a change in the type of infection. Because of the length of the illness and the higher mortality, the second or typhoid epidemic may overshadow the first or dysenteric outbreak.

Dysenteric symptoms are common in other diseases, and each of these must in turn be excluded before a presumptive diagnosis of bacillary dysentery is established. Malaria, kala-azar and infections with the ciliates, such as *Balantidium coli,* and with the flukes, *Fasciolopsis buskii, Schistosoma japonicum* and *Schistosoma mansoni.* These all produce dysenteric symptoms and are rather easily excluded by proper laboratory examination. The exclusion of amebic dysentery is not always so easy, although close attention to the clinical history, with its slow rather than rapid onset, the character of the stools, and the presence of the ameba in the discharges should make the diagnosis clear. The problem would be easy were it not for the presence of the *Entameba coli,* and of other non-pathogenic species of entamebæ which render careful examinations by an experienced worker quite necessary.

Intestinal disturbances due to eating spoiled food have an acute, stormy onset, and the patient shows great prostration, but the stools are large, fecal and offensive, and lack the dysenteric character.

Foreign bodies, such as fish and small bones of chickens, when lodged in the rectum may cause the evacuation of stools containing blood and mucus, and pain, but the other symptoms of dysentery are lacking in such cases.

In the case of children, intussusception causes an acute illness with great prostration, pain, rapid pulse and stools containing blood and mucus. This condition should be considered in making a diagnosis.

It should not be forgotten that acute bacillary dysentery and some one of the diseases mentioned above may exist in the same patient; for example, there are pathological specimens in the Army Medical Museum showing the lesions of acute dysentery and chronic tuberculous ulceration side by side.

Complications.—Excoriations of the skin surrounding the anus is the rule in severe cases. Prolapsus ani is not infrequent in severe cases, and is more apt to occur in children than in adults. In rare cases a further complication, ischiorectal abscess, may appear.

The diphtheritic membrane in severe cases may extend from the colon to the bladder in men, but this is more commonly the case in women, where it may also involve the vaginal mucous membrane.

During the Civil War and again in the Spanish-American War, and in occasional cases reported in the current literature, typhoid fever and dysentery have been known to coexist in the same patient, the symptoms of dysentery being more or less obscured by those of typhoid, or vice versa. At autopsy the characteristic lesions of both diseases were

seen side by side. Most frequently the dysenteric symptoms preceded those of the typhoid, but terminal infections of typhoid patients do occur and constitute a very fatal complication.

JOINT AFFECTIONS (Rheumatism, Rheumatoid Affections).—In some epidemics these conditions are not uncommon. Woodward reported many cases during the Civil War occurring among northern soldiers. In the World War many cases were reported. Usually there is an interval of three or four weeks between the acute attack of dysentery and the appearance of the joint lesion, which is not infrequently preceded by mild conjunctivitis, lasting a few days only, and by acute urethritis, which is also mild.

The joint most commonly affected is the knee, often the ankle, and less frequently the toes. The upper extremities are not often involved, but the elbow and shoulder are sometimes attacked and the wrist and fingers in rare cases. As each new joint is involved there is a moderate rise of temperature. The heart shows signs of involvement in about one-third of the cases (Stettner [37]) and greatly influences the prognosis. This group of symptoms is spoken of by French writers as the conjunctivo-urethro-synovial syndrome, and the intestinal group as the choleriform syndrome.

SEROUS MEMBRANE AFFECTIONS.—The serous membranes may also be involved and transient effusions in the pleura may appear.

NERVOUS AFFECTIONS.—The complications on the part of the nervous system are important, but they vary in their frequency in different epidemics and on the whole do not seem to be very common in cases occurring in the temperate zone, although they are numerous enough in the tropics. They are usually noticed in the second and third week of the disease, and may take the form of transient paraplegia or monoplegia, or of paralysis or paresis of isolated muscle-groups. Laryngeal paralysis is not infrequent. The nerves of the heart may be attacked by the toxin and a variety of symptoms ensue, the commonest of which is brachycardia. Hiccough and herpes labialis have also been reported.

It is seen that the greater number of these complications are due to the absorbed neurotoxin and not to the multiplication of the bacteria at the site of the complication; the prognosis is therefore excellent. The paralyses pass off in a few months, and all symptoms of joint involvement, which are slower to improve, disappear in four or five months from the beginning of the illness.

Sequelæ.—In the older literature reports of scars from large ulcers in the colon are not uncommon; they contract in healing and cause a puckering, contraction and actual diminution in the size of the lumen of the intestine. Such cases are, however, quite rare. Woodward in his review of almost a thousand cases did not encounter any.

Clinical Varieties.—As Flexner pointed out in 1900, the clinical terms, catarrhal, tropical, epidemic and diphtheritic, are far from signifying sharply defined entities. Other terms are in common use, such as dysenteric diarrhea and chronic diarrhea, yet they merely describe the severity of the symptoms in a particular case. Colitis hæmorrhagica,

colitis necroticans, colitis pseudomembranacea, colitis ulcerosa and colitis fibrinosa are all stages in one and the same disease.

In sporadic cases one may find any of the several varieties of the dysentery bacillus as the causative agent. In small contact outbreaks, presumably starting from a carrier, only one variety is apt to be found, while in the larger outbreaks, which occasionally occur, due to polluted water, any or all varieties may be found in the same group of cases.

Treatment.—PROPHYLAXIS.—As has been pointed out under Etiology, in the presence of **good sanitation** and with average **personal hygiene**, such as we find in the larger cities, the disease tends to disappear. In the presence of a case, careful attention to all the details of personal hygiene and sanitation of the sick room will tend to prevent the infection of others in the same household.

Special measures, such as **vaccination** and **passive immunization** with therapeutic sera, are theoretically correct, and under suitable conditions should give good results. Yet practical experience shows that these measures are rarely used and, in fact, are rarely necessary. Under special conditions, it is conceivable that vaccines might be useful, yet during the World War they do not seem to have been used systematically, at least in the fields where American troops were used, and apparently in those fields they were hardly necessary, as dysentery on the western front was not, except for a short period, a serious disease. In the East, on the other hand, it was a very important disease, and vaccines might well have been used. Detailed reports are not yet available and little is accurately known of the prophylactic measures adopted, or of their results.

The vaccine itself is prepared in much the same way as the vaccine commonly used against typhoid fever, *i.e.*, it is a suspension in salt solution of killed dysentery bacilli of various strains, representing, as far as possible, the members of the group causing the epidemic. The Shiga bacillus secretes a soluble toxin and it cannot be used in as large numbers as others of the group. The vaccines should be given in two or more doses, usually three, at intervals of a week or ten days; an idea of the worth of any particular vaccine may be obtained by testing the blood of the immunized patient for agglutinins after the course of the prophylactic treatment. If the patient has been successfully immunized, his serum will show agglutinins for all of the varieties used in the vaccine.

Sensitized vaccines are reported by Gibson[38] and by Boehncke[39] to be less toxic than the simple saline vaccine, and several favorable reports may be found in the current literature. It is doubtful whether the difference is marked enough to justify the use of the repeated small doses of horse serum used for the sensitization. As immunizing agents they have no special advantage, although the local and general reactions are no doubt less marked; under some circumstances this may be a distinct advantage. Quite recently lipovaccines, that is, suspensions of the bacilli in neutral oil, have been used by Olitsky[40] and by Whitmore, Fennel and Peterson,[41] but the trial has not been extensive enough to justify drawing conclusions at this time as to their value.

In hospitals a most important prophylactic measure is the isolation of the dysenteric cases from all others, and the institution of a ward technic which will prevent the spread of the infection to other patients or attendants.

Treatment of Acute Cases.—*General Treatment.*—Although many mild attacks occur, the disease should always be taken seriously, and the patient should be put to bed, on a **simple, liquid diet** and proper treatment. In this, as in the other acute infectious diseases, early treatment is of the very greatest importance, and there is good reason to believe that the earlier the patient receives proper care, the better the prognosis. The **rest in bed** should be complete, and the patient should use a bedpan and not be permitted to get up to go to stool. Because of the great prostration, special attention should be paid to keeping the patient **warm,** and he should be given enough liquid to allay thirst. **Rice** and **barley water** are satisfactory drinks, and strained **gruels, whey, albumin water** and **clear soups** may be given as bland and liquid foods. When vomiting is troublesome, nothing should be given by mouth, but fluid should be supplied by **enemas or** by subcutaneous administration of **salt solution.**

Most important is early **purgation,** and usually when this is possible the disease can soon be brought under control. The best purgatives are the **salines, magnesium** or **sodium sulphate,** or **sodium phosphate,** and there seems to be little real choice between them; they all act on the colon and clear it of irritating fecal matter, desquamated epithelium, mucus, and inflammatory exudate, and of the toxic products produced by the dysentery bacillus, and the necrotic and fermenting products of the inflammation. Unless these are removed completely and as fast as they are reformed there is little chance of freeing the patient from the exhausting toxemia. It should be remembered that the bacteria do not invade the tissues and that they are not found in the blood, but occur only in the intestinal tract, principally in the lower ileum and the colon, and that the profuse watery exudate from the mucous membrane and the resulting frequent stools are the response of the body to the dysenteric toxin. Our purpose must be therefore to aid in the rapid and complete elimination of the irritating and toxic contents of the colon, and this is best accomplished by frequent small doses of magnesium sulphate or other saline. It is usually given in 8 gram (2 dram) doses, dissolved in an ounce of water, every two hours until the stools lose their dysenteric character and become feculent; then the dose may be reduced one-half or more and continued for another day.

In Japan, Egypt, to a certain extent in India, and in this country, **calomel** has been used in place of salines. Plehn recommends an initial purge of **castor oil,** followed by half grain (0.0324 gram) doses of calomel hourly until 12 grains (0.78 gram) have been taken during the day. Nothing is given at night, but on the second and third day the calomel is repeated, to be followed, as a rule, by **bismuth subnitrate** in half gram doses (7.7 grains) hourly for several days more, after which the dose may be gradually reduced.

Serum Treatment.—In this country serum treatment has not been used extensively, perhaps because the severer forms of the disease are growing fewer each year. In the Army during the year 1917 there were 688 cases of dysentery of all kinds among a total number of 678,579 men, and of these 291 were entamebic. The ratios of the cases per thousand men were: for all dysenteries 1.01, for the bacillary form 0.10, for the entamebic form 0.43, for unclassified forms 0.47. The deaths were 4 in all, of which 1 was charged to the bacillary and 3 to unclassified forms.

An extensive trial of serum in the treatment of infantile dysentery was reported in 1904 by L. Emmett Holt and Simon Flexner,[42] who showed that out of 83 cases in which the serum was used 38 were fatal, and that in only 12 cases did a noteworthy improvement follow the administration of the serum. They did not regard the trial as complete or final, yet very little has been done in this country since that time.

In Japan and the far east, where dysentery in its most severe forms is still relatively common, the reports are quite different. The serum is used from the beginning of treatment to get the best results, as is the case with all antitoxic sera. An **initial purge of castor oil or salts** should not be omitted, nor is there any reason why, if the case demands it and improves under it, the **saline treatment** already referred to should not be **combined with** the use of **therapeutic serum.** As it is impossible to make a bacteriological diagnosis of the variety of the bacillus in much less than a day and a half or two days, it is not practicable to use univalent serum in treatment; therefore, a polyvalent serum is in general use. It is prepared by the injection into horses of several representative strains of the dysentery group. The serum is best given to the patient in large doses under the skin of the abdomen or flank, with the usual antiseptic precautions. Shiga's rules for its administration are as follows:

(1) In mild cases give one dose of 10 mils.

(2) In cases of medium severity give two doses of 10 mils each at intervals of six hours.

(3) In severe cases inject 10 mils twice a day at intervals of six hours for two or three consecutive days.

The tendency is to increase the size of the dose, and 40 and even from 60 to 100 mils has been given daily in severe cases. In very toxic cases the serum has been administered intravenously or intramuscularly; by the latter route absorption is very rapid. Finlayson[43] is particularly positive about the value of large doses; he gives 100 mils of serum intravenously, followed if necessary by another dose of equal size in twenty-four hours; subsequent doses are smaller, about 40 mils, and may be given subcutaneously. When the serum is effective the good results are noted promptly, and as much as 300 or 400 mils have been given in severe cases, resulting in recovery. In order to avoid an anaphylactic shock, about 5 mils of the serum should be given to the patient upon his admission to the hospital.

Serum disease is very apt to follow the administration of these large doses of horse serum, and the patient may show urticarial eruptions and

suffer from pain and swelling in the joints. When the symptoms are severe some relief may be obtained by the administration of **calcium chlorid** in doses of 1 or 2 grams (15 to 30 grains).

The subsequent treatment of acute cases is the same, regardless of whether or not serum has been administered at the beginning. As soon as the blood and mucus have disappeared from the stools and they have become feculent in character, the time has arrived for the administration of astringents, the best and principal of which is **bismuth subnitrate,** alone or combined with **salol,** or with some similar intestinal antiseptic. The bismuth should be given in rather large doses, 2 or, better, 4 grams every four hours (30 to 60 grains).

Dysentery Vaccine Therapy.—Rathery, Ranque and Roux [44] have reported favorable results from the use of polyvalent stock dysentery vaccine in the treatment of acute and chronic cases, and note that in cases in which serum therapy has had little effect, the supplementary use of their vaccine produces good results. The vaccine contains 50 million bacteria per mil, and the organisms are killed by the addition of iodin, which is subsequently neutralized by the addition of sodium hyposulphite.

Local Treatment.—For the pain and abdominal discomfort it is well to apply heat, in the form of a **hot water bag** or **hot fomentations.** The tenesmus may be so disturbing that **morphin** must be given hypodermatically; or **opium suppositories** [½ grain (0.032 gram)] may be substituted. **Atropin** will often give relief when the pain is severe. It is well, however, to avoid the use of opium and morphin as much as possible in the treatment of this diease. As has already been stated, it is an acute infectious disease, as a rule self-limited in duration (most cases run their course in eight or nine days). The bacilli secrete a toxin which is formed in the intestine, absorbed, and again excreted by the colon. During the height of the disease the administration of opium or of any other astringent, by suppressing the excretions, tends to increase the absorption of the toxins and so to make the case more severe. After the acute toxic stage has passed, the intestinal tract is left in a state of acute catarrhal inflammation, and for the treatment of this condition bismuth and other astringents are necessary.

In severe cases which do not show improvement by the third or fourth day, or in cases in which the stools become serous, rather than feculent, it may be necessary to stop the salines and to treat symptoms as they arise. Such cases are apt to do badly, and aside from the use of specific serum there is little more to be done, in the way of general treatment. Local treatment of the colon, however, may give good results.

Enemas of warm normal salt solution are stimulating to the patient, and usually result in giving him a few hours' rest, undisturbed by frequent movements or tenesmus; in many cases they seem to be of distinct value. Incidentally it is worth remembering that the saline solution washings of the colon are particularly good laboratory material for the isolation of the bacillus. Enemas of **silver nitrate,** as described under the Treatment of Chronic Cases, are often effective. Brill[45] reports

the treatment of a series of cases with serum in large doses, which improved under treatment. Being unable to obtain additional serum he substituted enemas of silver nitrate. The mortality of the two series of cases was the same, while a shorter period of convalescence followed the silver nitrate treatment and only one case of recurrence was noted after this treatment. If collapse is threatened, subcutaneous injections of warm saline solution must be given. They should also be given when nausea and vomiting are troublesome and when it is impossible to supply the necessary quantity of fluid to the body by mouth or by enemas of warm saline solution.

In excoriations of the skin surrounding the anus which complicate the disease in severe cases, **soft absorbent cotton** may be substituted for toilet paper to advantage. The skin itself should be **washed with soap and water,** and **alcohol,** and be protected with a **dusting powder.**

In prolapsus ani, the prolapsed part should be reduced by pressure with **compresses moistened in warm saline solution.** Ischiorectal abscess, which may appear, should be treated according to the usual **surgical principles.**

TREATMENT OF CHRONIC CASES.—The first and most important point in the treatment of a case of chronic bacillary dysentery is to be quite sure of the diagnosis. This is never quite so simple as in entamebic dysentery, where finding *Entameba dysenteriæ* clinches the diagnosis. The various diseases mentioned under Differential Diagnosis must each be excluded by appropriate examinations, and finally the dysentery bacillus concerned must be isolated in pure culture and tested against the patient's serum for the presence of agglutinins, together with a known culture of the proper strain of the dysentery bacillus as a control. Work of this character presents many technical difficulties, but it can be done by the laboratories of the better hospitals and boards of health. Clinicians will in the end save much time to themselves and the patient by availing themselves of these facilities.

General Treatment.—It is characteristic of the chronic cases to present alternating periods of remission and exacerbation. During the relapse the treatment should be the same as for the acute cases; during the subacute and chronic stages, the **diet** must be carefully **controlled** and the **patient confined to bed. Milk,** either plain or boiled, peptonized or fermented, full strength or diluted with Vichy water, lime water, or gruels, must be the mainstay of the diet. **Whey, beef juice, thin soups** and **eggs** or, in some cases where the whole eggs cannot be digested, the white only, may be added early; later, dishes made from milk and eggs, and milk toast may be added gradually. **Fruit** must **not be given until late,** except for the **juice** of **oranges** and **lemons.** All these and similar fluids are best given in small quantities at frequent intervals, and should preferably be neither hot nor cold but about body temperature.

Drugs administered by mouth are not of great value, yet **castor oil** in small doses from time to time produces good results. Among the astringents **bismuth subnitrates** has already been referred to; it should be given in large doses, from 2 to 4 grams (30 to 60 grains) three times

daily. **Opium** and **morphin** should be **avoided,** for the reasons already given and because of the danger of forming a habit by their continued use in chronic cases.

Local Treatment.—Local treatment of the colon should be carried out if a proctoscopic examination of the rectum shows ulcers, or if trial treatments are followed by appreciable benefit. The vogue of local treatment in the past may possibly have been due to the failure to differentiate between bacillary and entamebic dysentery, since in the latter disease ulcers low enough down in the rectum to be seen through the proctoscope are common and respond well to **irrigations.**

The simplest of the irrigating fluids is a cleansing one of **normal saline solution** given at body temperature in quantities of a few ounces, at first, and retained as long as possible. Later, as the colon becomes less sensitive, larger and larger quantities up to two liters may be given. **Silver nitrate solution,** beginning at a strength of 1 to 5,000 and increasing to a dilution of 1 to 500 has been used ever since the Civil War, and has given good results. Other astringents may be used from time to time, such as **alum** in a 2 per cent. solution, **tannic acid,** 3 per cent., **salicylic acid,** 1 per cent., or **boric acid,** 2 per cent. All irrigations must be given with the fluid at the temperature of the body, and should be introduced slowly through a large soft catheter or soft rectal tube. The patient should lie on the left side, with the hips slightly elevated, and the enema should be retained as long as possible.

Vaccine Therapy.—Vaccines are sometimes of value in the chronic relapsing cases, and may be given in small, frequently repeated doses over a long period of time, until convalescence is established or, when no improvement is evident, until the patient is highly immunized as shown by an agglutination reaction with his blood serum.

When all other measures have been exhausted a **change of climate** or residence will sometimes bring about improvement or a cure. From the tropics and the South patients are regularly sent to some more northern latitude.

Diet during the Attack.—This has already been referred to in a general way. It remains to be noted that **milk,** particularly in children, is generally agreed **not to be a suitable food** during the height of the disease; **broths, strained gruels, barley, rice** and **albumen water** should be substituted for a time. This is particularly necessary when there is nausea, vomiting or other gastric disturbance. In milder cases and in those past the height of the disease, milk, diluted or modified for children, is necessary to keep up a fair state of nutrition and to prevent the **great loss of weight** which occurs on diets of low caloric value.

When the patient is far enough convalescenced to tolerate them, **fruit juices, fresh fruits and vegetables** are very gradually added to the diet in increasing quantities to maintain the normal intake of vitamins.

Prognosis.—The prognosis varies greatly in different epidemics and under different circumstances. In Japan and in the tropics the mortality reaches 30 per cent. of the cases. In the United States it is rarely

so high. The mortality among children, and among the aged, is high, and as a terminal infection in other diseases it is, of course, very fatal.

As regards chronic infections, the prognosis is not as good in the Shiga type of cases as in the Flexner-"Y" type. The patients with the former type are sicker, have fewer and shorter remissions, and are seldom able to carry on any occupation. Flexner-"Y" cases, on the other hand, tend to improve, and so long as the patient has good surroundings and suitable diet, he is able to carry on his work. In the Army, however, patients suffering from chronic or recurring dysentery are useless as soldiers, since they quickly break down whenever they take the field. The more robust may be given light duties under good surroundings in the home territory, but the others should be discharged from the service and sent to their homes, provided that they can be given proper medical care and that the health authorities will assume responsibility for them. To prevent the infection of others, they should be prohibited from handling food stuffs and be instructed in personal hygiene and taught the measures necessary to prevent the spread of the infection.

The mortality varies much in different epidemics, and in different localities. According to the statistics of Lentz the mortality of Flexner-"Y" infections averaged 0.5 per cent., although in occasional outbreaks it ran as high as from 8 to 13 per cent.; in Shiga infections the mortality was usually from 10 to 20 per cent., although in certain severe epidemics it rose to from 35 to 50 per cent. In the case of children and of elderly persons the mortality is higher than the average. Where the severe forms prevail, as in Japan, the average mortality may be as high as 30 per cent.

Pathology.—The lesions are confined to the colon and, to a lesser extent, to the lower part of the ileum. Blood-cultures, except in very rare instances (Darling), are negative, and no metastatic infections are found in distant parts of the body. The lesion is most marked in the colon. In acute cases the entire extent of the mucous membrane is swollen and injected with small hemorrhagic areas scattered over the surface. The superficial epithelium is necrotic over large areas and comes off in masses, leaving a deeply injected base which may bleed easily. The lesions are most marked on the ridges or the folds of mucous membrane, but the characteristic which differentiates the bacillary from amebic dysentery, is the general diffuse character of the lesion. Ulcers may be absent or extremely minute, yet the whole lining membrane may be thickened, swollen, edematous and hemorrhagic, or the lesions may be well developed only in the sigmoid, splenic and hepatic flexures and in the cecum, where fecal masses tend to accumulate and act as mechanical irritants. In some cases a well-developed diphtheritic pseudomembrane will be found. In very acute, fatal cases the colon may show large or small areas of necrosis and gangrene.

As the necrotic mucous membrane sloughs off, larger or smaller ulcers are left, which may become confluent with the extension of the process. The margin of the ulcer is irregular, but is never undermined to the

same degree as in amebic dysentery. The deeper ulcer may be seen at autopsy through the serous coat of the intestine, which is injected or discolored. Although occasional ulcers may be quite deep, perforation of the intestinal wall is quite unusual.

The picture at autopsy does not in the least resemble dysentery due to the entameba, where the areas involved in the infection show deep ulceration and are isolated from each other, and surrounded by apparently healthy mucous membrane.

Abscesses in the liver are almost unknown in bacillary dysentery, but are common in the amebic form.

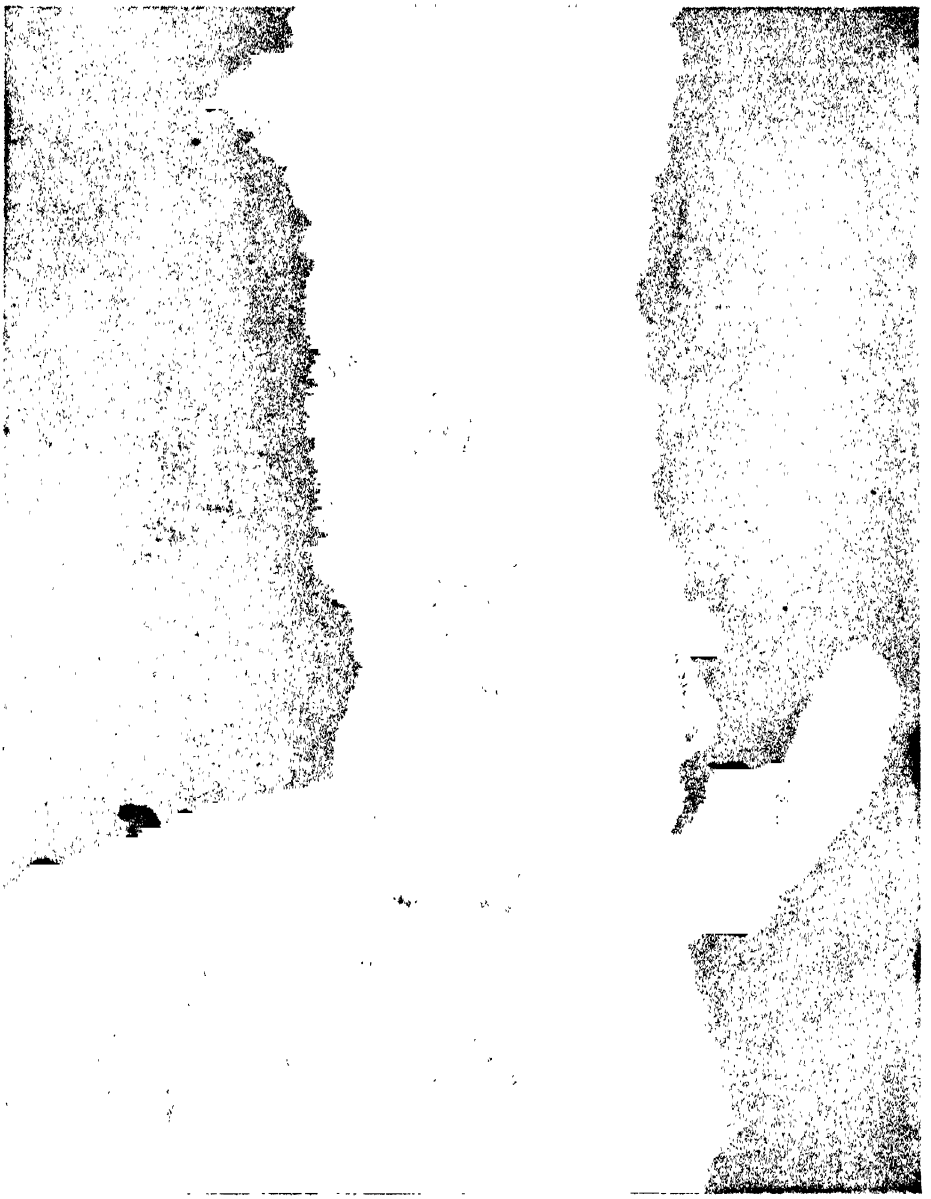
In the chronic cases, many and complicated changes will be found; the glandular coat may be atrophied, or it may be thickened and thrown into corrugations or into irregularly disposed polypoid masses; it may also be replaced by scar tissue. Some cases may show small cysts from the retention of mucus. The connective tissue and the muscular coats may be hypertrophic or atrophic, depending, perhaps, on the state of the disease at the time of death. The ulcers may penetrate the mucous coat only, or invade the submucosa, or even the muscularis. In any case, the resulting inflammation leads to swelling, edema, hemorrhage and necrosis in the surrounding tissues, and ultimately to an increase in the thickness of the wall due to the over-production of connective tissue in the process of repair. It is the subsequent contraction of this newly-formed tissue which leads to irregularities in the size of the lumen of the colon, amounting at times to obstructing bands. When the inflammation has extended to the peritoneal coat, adhesions, more or less extensive, naturally follow.

The following is a condensed protocol of one of Flexner's autopsies done in Manila on an acute case:

"Death ensued on the sixth day of the disease. The colon is dilated and its walls are thickened. The serous coat is injected but otherwise normal. The mucous membrane is swollen and thickened and the normal folds are thrown into coarse elevated corrugations. The general color is red, but there are seen many small hemorrhagic points. No diphtheritic membrane is seen, but there is present an exudate which is readily washed off. The normal velvety character of the mucous membrane is lost and, on close examination, a number of minute ulcers may be seen, particularly on the crests of the coarse corrugations. The lesions, as a rule, are not limited to given areas of the mucous membrane, leaving other areas normal, but the entire lining of the colon and of the lower end of the ileum is involved in the process."

In exceptional fulminating cases the bacillus is found in the blood stream by culture (Darling, Maer). The bacteriemia causes great prostration and toxemia, often with a slight temperature reaction, marked cerebral symptoms, and mild or absent abdominal signs; tenderness, pain and tenesmus may be slight or absent. At the autopsy, nevertheless, extensive dysenteric lesions will be found.

Many of the changes referred to above may be seen in Figures 1 and



(Shiga).

2. Both specimens are from the same case of Shiga dysentery (Army Medical Museum, A. E. F., 1429). The figures show swelling, necrosis, hemorrhagic areas and a pseudomembrane, which is pealing off, leaving a lighter colored base. In this case it will be noted that the lesions extend to the vermiform appendix and to the lower portion of the ileum

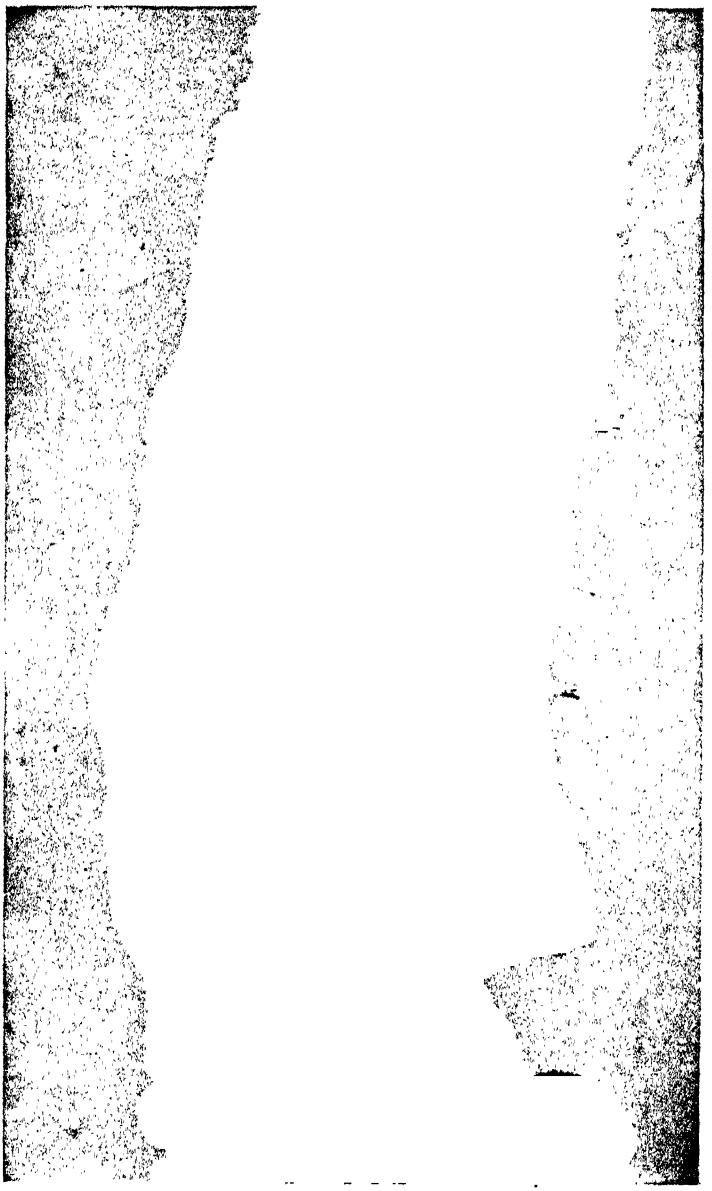


FIG. 2.—BACILLARY DYSENTERY (Shiga).

CASE I.—The clinical history of the case is briefly as follows:

"He was admitted to hospital August 10, 1918, with a diagnosis of 'under observation for appendicitis.' His illness began August 8, with a sharp, cramplike pain across the abdomen at the level of the umbilicus, followed two hours later by vomiting; he has been vomiting at irregular

intervals since. Diarrhea for past four days with eight to ten stools a day. Has taken no food for past twenty-four hours; cannot retain food. Stools bloody and patient complains of burning sensation at defecation. Physical examination showed patient's abdomen to be flat. There is tenderness over ascending colon, but no rigidity. Preliminary diagnosis of intercolitis, severe, hemorrhagic. White blood-cells, at this time, 7,950. August 22, notes indicate that patient has had frequent small bloody stools with tenesmus. No leukocytosis. Reports of feces show much blood and mucus. August 26, *Bacillus dysenteriæ* (Shiga) reported in culture from feces; the diagnosis was made on agglutination with specific sera and on cultural characteristics on differential media.

"*Peritoneal Cavity.*—On opening the peritoneal cavity the collapsed flat condition of the gastro-intestinal tract was found to be remarkable. The small intestine and large intestine showed some congestion of the subserous vessels. The omentum was healthy in appearance and was well down over the coils of the small intestine. It was adherent along the descending colon and sigmoid.

"*Pleural Cavities.*—The pleural cavities seemed remarkably large in comparison to the size of the lungs. After removing the breast plate, it was found that each cavity was apparently empty. There was no evidence of fluid or exudate in either cavity.

"*Pericardial Cavity.*—The pericardial cavity was thin, and even before it was opened one could see that there was excess of fluid in the cavity. This fluid was perfectly clear and of a pale straw color. There was nothing of an inflammatory character in the pericardial cavity.

"*Heart.*—The heart measured 10 x 8 x 4 cm. and weighed 163 grams. The heart was very small and flabby. This was especially marked in the right ventricle. The heart-muscle was pale and the cut surface was swollen. The left ventricle averaged only 1 cm. The valves showed nothing of special interest. The left ventricle measured 12.5 cm.

"*Lungs.*—The left lung measured 17.5 x 10.4 cm. and weighed 167 grams. The lung was remarkably small and had a curious doughy consistency, although it crepitated throughout. The cut surface showed a pale, dry, apparently partially collapsed lung tissue, remarkable chiefly for its dense, almost meaty, and at the same time, soft structure and for its dryness. The trachea and bronchi were clear. The peribronchial lymph-nodes showed caseous and calcified tuberculosis.

"The right lung measured 20 x 14 x 4 cm. and weighed 160 grams. The right lung was in all respects like the left.

"*Spleen.*—The spleen measured 12 x 7 x 4 cm. and weighed 162 grams; it was fairly firm. Its outline was most irregular. On section, the malpighian bodies stood out prominently from a red, firm spleen.

"*Liver.*—The liver measured 23 x 19 x 8 cm. and weighed 1599 grams. The liver showed nothing unusual on the surface and on section showed slight congestion and cloudy swelling. The gall-bladder was negative.

"*Gastro-intestinal Tract.*—The stomach was small and contracted, with prominent rugæ. It contained a quantity of gray-green material.

There was a little hemorrhage beneath the mucosa on the ridges of some of the folds. There was no evidence of ulceration. The small intestine contained a quantity of bile-stained mucus, but was otherwise negative throughout the duodenum, the jejunum and the first part of the ileum. The last 40 cm. of the ileum showed a tense congestion, most marked at the crests of the mucosal folds and about 20 cm. from the ileo-cecal valve; small superficial ulcers with grayish-green necrotic membrane, covering their bases, were found. These were present in rapidly increasing numbers and the last 10 cm. of the ileum showed extensive superficial ulceration with a thick, opaque, grayish-green membrane which could be scraped away in the case of the smaller ulcers, revealing a rough red granular base. The appendix showed an intense swelling and intense congestion of the mucus and a few small ulcerations. The large intestine in the cecum showed less extensive ulceration than did the terminal portion of the ileum, but above the cecum and throughout the remaining extent of the tract there was an extremely intense ulcerative process with diffuse necrotic looking exudate similar to that previously described. At intervals a particularly congested fold appeared, denuded of its exudate. As the descending colon and cecum were reached, the exudate became more extensive and more dense, absolutely covering every portion of the mucosal lining.

"*Pancreas.*—Negative.

"*Adrenals.*—The cortex of the adrenals had lost its usual opaque, yellow color and was swollen and translucent with here and there an occasional yellow patch. The medullary substance was decreased in amount.

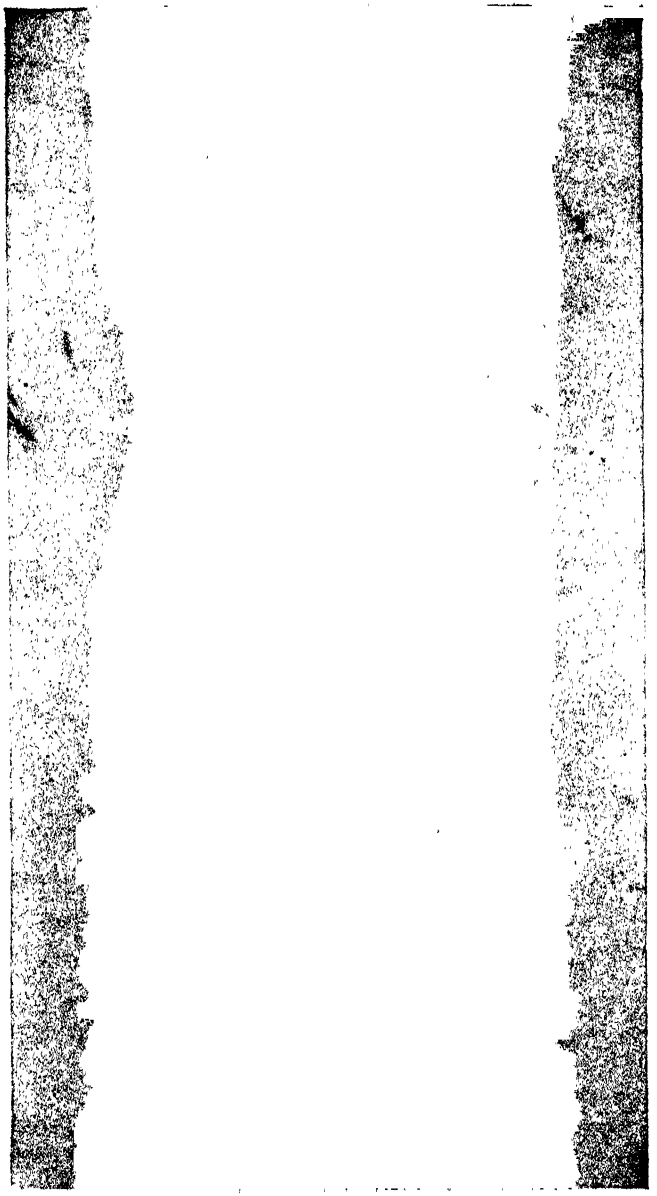
"*Kidneys.*—The left kidney measured 10 x 5 x 4 cm. and weighed 135 grams. The kidney was rather small and soft. The capsule peeled easily, revealing a pale cortex on which the fetal lobulations were somewhat prominent. The cut surface showed a pale, swollen tissue with some congestion of the capillaries and a general haziness of the usual markings. The right kidney measured 9.5 x 5 x 3.5 cm. and weighed 113 grams. This kidney was like the left in all respects. In each instance, the pelvis and ureter were negative.

"*Bladder and Prostate.*—The bladder was distended with urine but was otherwise negative."

The change in the adrenals has also been noticed by Remlinger,[46] in cases from the Argonne, and by many German and Austrian writers, usually, however, in connection with Flexner-"Y" dysentery.

CASE II.—Figure 3 is from a case of mixed entamebic and bacillary (Shiga) dysentery (A.M.M., A.E.F. 1428). The clinical data and autopsy findings are as follows:

The patient was admitted August 11, 1918, with a history of having had a severe diarrhea for the preceding six days, with bloody stools, cramps and vomiting. August 13th, cramps still present. About thirty bowel movements in the last twenty-four hours. August 16th, diarrhea better, but still has very marked pain. August 20th, relapse.



3.—Mixed Bacillary and Entamebic (Shiga).

August 22nd, patient quite prostrated; frequent bloody stools with many clots. Temporary improvement followed administration of emetin, but the drug was continued without further beneficial results. Steady downward course, with rapid circulatory failure a few minutes before death. August 24th, 10.20 P. M., death occurred.

"*Pathological Findings in Gastro-intestinal Tract.*—The stomach was moderately distended and contained thin liquid and air. The gastric mucosa was perfectly smooth and healthy in appearance. The pyloric valve was clear. The small intestine showed duodenum and jejunum clear. The ileum was slightly distended, so that the folds flattened and the walls thinned and there was slight injection of the blood-vessels. The Peyer's patches were clear and the mucosa showed no evidence of necrosis or ulceration. The large intestine showed extensive destruction of its intestinal lining. The condition was well marked throughout the whole of the colon, sigmoid and rectum. The lesions took the form of rounded and irregular punched-out areas of necrosis of the mucosa and submucosa with frequently extension of the necrosis along the submucosa beneath still visible bridges of mucosa. Marked inflammatory reaction was not a feature of the lesions. There was a little congestion in one or two places, but for the most part the grayish necrotic looking mucosa with the numerous coalescing punched-out areas of necrosis was characteristic of the entire large bowel. There was no evidence of perforation or hemorrhage, and there was no exudate on the surface of the mucosal lining. The abrupt line of demarkation at the ileocecal valve between the cecum and ileum was most striking.

"*Bacteriological Findings.*—(1) Cultures from stools of life; *Bacillus dysenteriæ* (Shiga) by cultural characteristics and by agglutination with available serum.

"(2) Cultures from stools at autopsy; negative for *Bacillus dysenteriæ.*

"(3) Feces, in life, by microscopical examination, forms typical of *Entameba histolytica*, but non-motile, always found.

"(4) Sections of colon showed *Entameba histolytica* in submucosa in moderate numbers."

Among troops during the late war, mixed infections were not uncommon, and particular care must, under such conditions, be paid to making a complete diagnosis and to keeping the diagnosis up to date, as the entamebic infection often lags behind the bacillary. If the nature of the complication is not realized, the treatment will be unsatisfactory and the disease will be prolonged.

Sections of the colon show a large amount of small round-cell infiltration, especially around Lieberkühn's glands and around and in the solitary lymph-nodules. The infiltration is especially well marked around the edges and bases of the ulcers. Some of the latter are formed by the sloughing of the coagulated and necrotic mucous membrane and others, which are small and deep, by necrosis of the solitary follicles and overlying epithelium. Around the blood-vessels, particularly the small ones, are seen red and white blood-cells, fibrin and altered tissue-cells, the whole forming a coagulated and necrotic mass. Later in the disease the coagulation necrosis is less marked and the small round-cell infiltration becomes more evident; still later, the connective tissue shows evi-

dences of active proliferation. The ulcers heal over by the extension of the epithelium from the border, but the ulcer remains covered with scar tissue and not with normal epithelium.

Historical Summary.—The disease has been recognized throughout the ages, and the names which Hippocrates gave to the two principal forms of intestinal disturbance, diarrhea and dysentery, have been in continuous use among physicians of all schools up to the present day, although with changes in the definition of dysentery, and such qualifications and limitations as were necessary to exclude symptomatically related conditions. Of course it was impossible, on clinical grounds alone, to separate bacillary from entamebic dysentery, and the differentiation had to wait upon the development of protozoölogy and bacteriology. This did not reach a helpful stage until about 1900, since which time progress has been continuous and rapid. Until recent years, therefore, many diverse conditions producing frequent stools containing blood and mucus, and accompanied by tenesmus, were classified under this diagnosis. From an historical point of view the most important study is that of Woodward[47] in the Medical and Surgical History of the War of the Rebellion, and any student of the history of medicine will derive great pleasure and profit from its perusal.

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CHAPTER XXXVI

TYPHUS FEVER

By Harry Plotz, M.D.

Synonyms, p. 411—Definition, p. 411—Etiology, p. 411—Predisposing causes, p. 411—Exciting cause: bacteriology of the organism, p. 413—Morphology and cultural characteristics, p. 413—Method of culture, p. 413—Occurrence of bacteremia, p. 414—Development of antibodies, p. 415—Rickettsia, p. 416—The virus, p. 416—Epidemiology, p. 420—Experimental demonstration that lice convey typhus, p. 420—Symptomatology, p. 421—The onset, p. 421—Symptoms during the progress of disease, p. 422—Diagnosis, p. 426—Complications, p. 428—Association with other diseases, p. 428—Treatment, p. 428—Prophylaxis, p. 428—General treatment, p. 443—Prognosis, p. 444—Pathology, p. 444—Geographical distribution, p. 444—History, p. 445—Bibliography, p. 448.

Synonyms.—The term "typhus" comes from the Greek (τῦφος) meaning smoke, mist or fog, and was employed by Hippocrates to indicate a confused state of the mind such as occurs in typhus fever. This expression was used with broad application until applied to typhus fever by Sauvage in 1760 and Cullom in 1769. A list of a hundred or more synonyms is given by Murchison. The common ones used in modern literature are, *typhus, typhus fever, exanthematic typhus, pestilential fever, spotted fever, camp fever, jail fever, hospital fever* and *ship fever* by English and American authors; *typhus exanthematique* by the French; *Fleckfieber* by the Germans; and *tabardillo* or *tifo* in the Spanish and Mexican literature.

Definition.—Typhus fever is an acute specific infectious disease, occurring usually in epidemics. It is characterized by a sudden onset, maculopapular petechial eruption, toxemia and high fever. The disease lasts about fourteen days and terminates usually by crisis. It is transmitted by the body louse.

Etiology.—Predisposing Causes.—*Social Condition.*—The older writers all lay stress upon the occurrence of typhus epidemics in times of calamity, during periods of famine and while war raged. The influence of filth and overcrowding and unhygienic conditions generally, were recognized as potent factors in the epidemiology of this disease. Many records relate to outbreaks of typhus occurring in crowded prisons and poor houses, on shipboard, in armies in the field, but especially among the besieged and besiegers. The epidemics in Ireland and England almost invariably followed in the wake of a failure in crops, or periods of distress from famine or strikes. In Serbia, the epidemic of 1915 followed shortly after the capture of 60,000 Austrian prisoners. They were

crowded in stables, houses and camps where the hygienic conditions were bad. Lice swarmed from man to man. Typhus fever broke out among them and as the prisoners were transported from one part of the country to another, the disease was disseminated not only to the army, but the civilian population as well. The Serbian peasants are vermin-infested and live in small ill-ventilated houses. The overcrowding in these huts associated with the vermin-infestation afforded ample means for the propagation of the disease. In Bulgaria in 1916 the typhus epidemic followed shortly after a large number of Bulgarian soldiers deserted and fled to the mountains. Here they congregated in huts and lived under very bad sanitary conditions. When these soldiers were discovered it was found that many of them were suffering with typhus fever. Soldiers who had gone home on furlough to these villages, and had come in contact with the deserters, became infected, and carried typhus back to their regiments. The deserters were finally assembled in prison camps and typhus broke out in epidemic form. From those prison camps the disease spread to the civil population.

Typhus fever is generally considered to be a disease of the poor. Except in epidemics, typhus fever is rare among the better classes. We now know that this is due to the fact that the poorer classes are more apt to be vermin-infested.

Sex and Age.—In epidemics the two sexes are equally attacked. A greater number of cases are ordinarily noted in males because of their greater exposure to contagion. The disease is not generally seen in children, although Soricek reports 23 cases and Moladenkoff 115 cases. The later authors saw none below one year of age, and only 7 in children between one and three. All the cases in children were mild.

Individual Susceptibility.—All races are equally susceptible to typhus fever. One attack usually confers complete immunity for life. A second attack is very rare. Murchison records two cases, and the writer has seen one case in a Bulgarian soldier who had two definite attacks, with an interval of five weeks. Persons who are usually vermin-infested may contract a very mild form of the disease or remain immune. Baehr has demonstrated agglutinins in typhus contacts who have been bitten with infected vermin. He believes the individuals are inoculated with a small dose of virus and are so immunized.

Occupation.—Those who attend the sick, as physicians, nurses, orderlies and priests, are in constant danger of contracting typhus fever. In Ireland, during the epidemic of 1847, 500 physicians contracted typhus fever and died. In an epidemic carried to Breslau by the retreating troops of Napoleon, 18 out of 40 doctors died of this disease. In Serbia, of 340 doctors, 160 died of typhus in the epidemic of 1915, and in Roumania, of 1,200 doctors, 200—or 40 per cent.—died in the epidemic of 1916. This high percentage of infection among those in contact with typhus cases may be explained on the grounds that lice wander away from a patient with fever to the healthy attendant.

Climate.—Typhus is essentially a disease of cool and temperate climates. The seasonal incidence of the disease is from November to April,

although cases may occur in summer. Endemic typhus (Brill's disease) occurs more often in the warmer months. The prevalence of typhus in winter is attributed to overcrowding, scarcity of bathing facilities and the infrequent change of clothing. Lice are susceptible to temperature and are not so prevalent in the summer months. Wilder notes the scarcity of the disease in the lowlands of Mexico where it is warm, in distinction to its presence in the highlands where it is cold; typhus fever is rare in Vera Cruz (lowlands) but common in Mexico City (highlands). Terres states that typhus fever in Mexico is restricted to the cool region in an altitude above 6,000 feet.

EXCITING CAUSE: BACTERIOLOGY OF THE ORGANISM.—Various aërobic bacteria have been described by Rabinowitch, Pretjetschensky, Müller, Füerth, Penfold, Proescher and others as the causative organism of typhus fever, but their work has not been confirmed. In 1914, while studying the bacteriology of endemic typhus fever (Brill's disease) in New York, the author succeeded in isolating an anaërobic bacillus which has subsequently been found with constancy in the blood of typhus fever cases in the United States, Mexico, Serbia, Bulgaria, Germany, Austria and Russia.

In America the organism has been recovered from cases of typhus fever by Bernstein, Blatteis and Lederer, and Gottesman and Klein. Anderson isolated the organism from the blood of guinea pigs infected with typhus fever. In Serbia, Zinsser and Hopkins reported its cultivation in 3 cases and Caldwell reported its occurrence in the spleen of a human case. In Serbia and Bulgaria, Popoff recovered it in 6 of 10 cases, and Mühlens and Ficker in 12 of 20 cases. In Russia, Paneth isolated the organism in 2 of 5 cases, while in Austria, Przygode recovered it eleven times. Ghon, in Germany, recovered the organism from the blood of guinea pigs which had been infected with typhus blood. In Mexico, Olitsky, Denzer and Husk cultivated the organism in 8 cases. The organism isolated in the Balkans, Russia, Mexico and the United States is identical in morphology and cultural characteristics.

Morphology and Cultural Characteristics.—The microörganism is a very small and slender bacillus. It is usually straight, though slightly curved or coccoid forms may occur. The ends are rounded or slightly pointed. It is not motile, not encapsulated, and not acid-fast. Polar bodies are occasionally seen. It is Gram-positive. In early cultures they may be Gram-negative, but subsequently become Gram-positive. Gram-negative forms have been seen in infected lice, but on cultivation they become Gram-positive. Acid is produced from dextrose, maltose, galactose and inulin, but not from raffinose, mannite, arabinose, lactose or dextrin. No gas is formed. The microörganism is an obligate anaërobe. The optimum medium is ascitic dextrose agar. Ascitic fluid and dextrose are necessary for its growth. The organism will not pass through a Berkefeld filter, size N. It has been named the *Bacillus typhi-*

—The Liborius-Veillon method for the cultivation of anaërobes is used. It consists essentially of a deep tube, employing

2 per cent. dextrose, ascitic agar. The agar is a 2 per cent. meat extract agar of 0.9 acidity (phenolphthalein). The choice of ascitic fluid is of importance. It should be clear, free of bile, and of high specific gravity (above 1.015). A filtered ascitic fluid or one which contains a preservative or is sterilized should not be used.

In making the blood culture, the 2 per cent. dextrose agar is divided into eight tubes. Two c.c. of blood and 6-10 c.c. of ascitic fluid are added to each tube. The contents, consisting of glucose agar, blood and ascitic fluid, are carefully mixed so that no air bubbles are introduced. After the agar has solidified, it is layered with 2-3 c.c. of agar. The tubes are incubated at 37° C. The colonies usually appear in from 7 to 14 days in the lower (anaërobic) portion of the tube. Colonies have

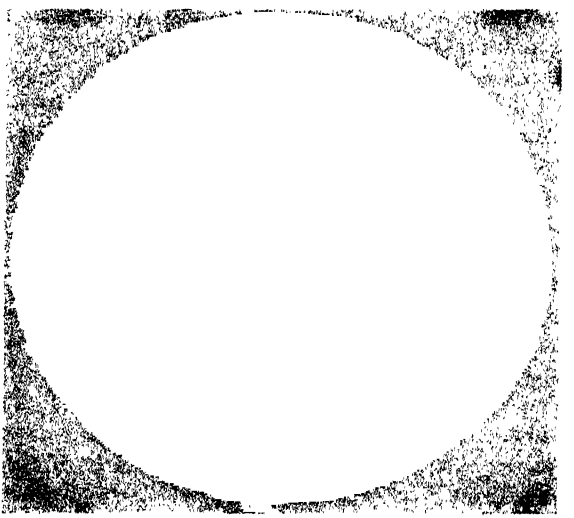


FIG. 1.—BACILLUS TYPHI-EXANTHEMATICI. (Magnification × 1000.)

been found after nineteen days' incubation. Transfers are made by breaking the tube and inoculating the culture on slants of ascitic dextrose agar, which are placed in Buchner tubes containing pyrogallic acid and sodium hydroxid.

Occurrence of Bacteriemia.—The microörganism is recovered only from the blood of persons and animals suffering with the disease. The bacillus is present in the blood during the entire febrile period, and occurs in greater numbers earlier in the disease than later. The intensity of the bacteriemia runs parallel to the severity of the disease. It is therefore more easily recovered from epidemic typhus fever than endemic cases. Baehr found enormous numbers of bacteria on culture during the initial chill. Blood cultures on animals (guinea pigs and monkeys) yield the same results as on human beings.

On culture media the organism loses its pathogenicity rapidly. Cultures recently isolated from epidemic cases produce a febrile reaction in guinea pigs.

Development of Antibodies.—Specific agglutinins, precipitins, opsonins, complement-fixing antibodies and "anaphylactic" antibodies are regularly present in the blood of typhus convalescents. They usually appear during the second week of the disease, increase as the crisis is approached, reach their maximal titer during the first or second week of convalescence and usually persist in the blood for months. In one case they were demonstrable after two and a half years. The curve of the course of development of the antibodies in this disease is typically an immunity curve.

(*a*) *Agglutinins.*—Plotz, Olitsky and Baehr regard an agglutination in a dilution of 1:50 as positive, as does Paneth and Popoff, but Przygode reads an agglutination in dilution of 1:100 as positive. The agglutinins are rarely present during the febrile period but appear at the time of crisis and thereafter. In a series of 43 typhus cases, Plotz, Olitsky and Baehr demonstrated agglutinins in 92 per cent. of the cases after the crisis. On the day of the crisis 33 per cent. of the cases gave positive results. Popoff, Mühlens and Ficker, Paneth and Przygade record the same agglutination results. Cross agglutination, using convalescent sera and bacteria, isolated from epidemic and endemic cases, demonstrates that the various forms of typhus fever are identical.

(*b*) *Weil-Felix Reaction.*—In 1910 Wilson isolated a proteus-like bacillus from the feces of a typhus case which was agglutinated by the serum of a typhus patient. The author did not regard this organism of etiological significance. Weil and Felix in 1915 isolated a proteus bacillus from the urine of two patients suffering with typhus fever, and found that this organism was agglutinated by the serum of patients with this disease. This agglutination phenomenon has been found by other German and Austrian workers. The etiological significance of this organism to typhus fever is not considered by any of the authors. Fairley found that the maximum height of the agglutination curve, with this proteus bacillus, occurs in the second febrile week and the first week of convalescence. This author, using the proteus bacillus as antigen, was unable to obtain complement-fixation, and found that it was not pathogenic when inoculated into two humans. Baehr, using the *Bacillus typhi-exanthematici* and this proteus bacillus, in a series of daily agglutinations found that with the proteus bacillus the agglutination came early in the disease and disappeared early in the convalescence, while with the *Bacillus typhi-exanthematici* the agglutinins appeared later in the disease and persisted for a long time after convalescence. The agglutination with the proteus bacillus was regarded as a co-agglutination phenomenon, while the agglutination with the *Bacillus typhi-exanthematici* represents a true immunity curve. Fairley regards the agglutination with the proteus bacillus as due to a secondary or heterologous agglutinin. Paneth, in an investigation in 300 cases of typhus fever, has studied this reaction thoroughly. This author studied the development of agglutinins with *Bacillus coli, Bacillus proteus, Bacillus typhosus* and *Bacillus typhi-exanthematici*, making daily agglutinations with these bacteria. Paneth found agglutinins in the blood with *Bacil-*

lus coli, Bacillus proteus and *Bacillus typhosus*. These agglutinins were demonstrable in the early part of the second week of the disease and increased until they reached their maximum height at the defervescence of the temperature. They disappear in a few weeks in convalescence. With the *Bacillus typhi-exanthematici* the agglutinins appear in the early part of the second week but develop more slowly and do not attain their maximum until the second week of convalescence. They then persist for several months. The curves for the formation of the agglutinins in the case of *Bacillus coli, Bacillus proteus* and *Bacillus typhosus* are practically identical and differ markedly from that of *Bacillus typhi-exanthematici.*

Rickettsia.—Prowazek and da Rocha-Lima have given the name "Rickettsia" to a class of organisms found in lice infected with typhus fever. Similar organisms have been found in trench fever lice and the parasites found in Rocky Mountain spotted fever may be related. A fourth species has been found by Noller in the "sheep tick."

Rickettsia are very small, from 0.3 to 0.5 by 1.5 to 2.0 microns. In shape they resemble a coccus, diplococcus or short bacillus. They do not retain the Gram stain, are not acid fast, but stain well with Giemsa. They are not motile. Ricketts and Wilder found these microörganisms in the louse in Mexican typhus, and Sergent, Foley and Vialatte, da Rocha-Lima, and Töpfer and Schüssler and others confirmed this. These later observers describe enormous numbers of the organisms in the midgut of lice that had bitten a patient during the height of the fever a few days previously. These bodies develop in the louse in from 5 to 10 days after feeding on a typhus patient.

Töpfer found Rickettsia in typhus and trench fever lice, but claims that he can distinguish the two kinds of parasites, as those associated with trench fever are shorter and thicker than those from typhus lice. da Rocha-Lima distinguishes the Rickettsia in typhus lice from those in trench fever lice in that the former invade the epithelial cells of the gut wall, while Jungmann and Kuczinski could not distinguish differences between them.

Arkwright, Bacot and Duncan have found Rickettsia in stock-bred lice that had been allowed to feed on trench fever cases.

Rickettsia have been regarded as protozoa by Prowazek, and da Rocha-Lima, but Ricketts, Wilder, Töpfer, Sergent, Foley and Vialatte, and Arkwright, Bacot and Duncan regard them as bacteria.

Baehr in Russia, Plotz in Serbia and Bulgaria, and Olitsky in Mexico, found bacilli in the intestinal contents and feces of typhus lice, which are morphologically similar to the *Bacillus typhi-exanthematici.* These bacteria are present in large numbers in film preparations. Olitsky succeeded in cultivating these bacteria from typhus-infected lice, and found them identical with the *Bacillus typhi-exanthematici,* isolated from the blood of typhus cases. The Rickettsia seen in typhus-infected lice are morphologically similar to *Bacillus typhi-exanthematici.*

The Virus.—(a) *Transmission of the Virus.*—The fact that the virus of typhus fever could be transferred from the patient to man or

animals was the first advance made in the experimental study of this disease. Moczutkowski (1900) inoculated himself with virulent typhus blood and after an incubation period of eighteen days suffered with a typical attack of typhus fever. As a result of the disease contracted he suffered with heart disease and died in 1903. Yersin and Vassal confirmed this observation by inoculating two men, who developed the disease after an incubation period of fourteen and twenty-one days respectively. Otero confirmed this human experiment. The recent inhuman experiments of Hamdi, in Turkey, have demonstrated conclusively that the virus of typhus fever is present in the blood during the febrile period, and can be transferred by blood inoculation to man. He inoculated 310 people subcutaneously with 5 c.c. of defibrinated blood taken from typhus fever cases during the febrile period. One hundred and seventy-four—or 56 per cent.—developed the disease, and of them 49—or 28 per cent.—died. The shortest incubation period was five days, and the longest twenty-three days, the usual being twelve days.

Nicolle (1909) first transmitted typhus fever to a chimpanzee by the inoculation of 1 c.c. of human blood, taken from a patient on the third day of the attack of fever. The disease was transmitted from this monkey to another. This was confirmed by Anderson and Goldberger, who also found that monkeys who had recovered from such an inoculation became immune against re-inoculation with typhus virus. Ricketts and Wilder, about the same time, while working in Mexico, succeeded in communicating Mexican typhus to the *Macacus rhesus* by blood injection. Gavino and Girard confirmed this and also found guinea pigs susceptible to typhus fever. All subsequent workers have confirmed these observations, and have found that the virus can be carried from animal to animal for an indefinite period without the loss of virulence.

Typhus fever in animals (guinea pigs and monkeys) is characterized by an incubation period and a period of fever usually terminating by crisis. Nicolle observed a rash in the monkey of his original experiment, but this has not been found by other observers. Loewy recently found an eruption in six of twenty-five guinea pigs. On section these spots showed endothelial degeneration and small-celled infiltration, a lesion which Fraenkel regards as pathognomonic for typhus fever. Following the intraperitoneal inoculation of blood in guinea pigs, the incubation period of seven to ten days is followed by a febrile period of seven to eleven days, which usually ends by crisis. These animals are immune to subsequent blood inoculations. Baehr has found an enlargement of malphigian corpuscles in the spleen of guinea pigs as the only pathological lesion.

Anderson and Goldberger have shown that 56 per cent. of guinea pigs tested failed to react to a first injection of blood from human cases, and that 22 per cent. of monkeys possess a transient or permanent immunity against typhus blood inoculation. For experimental work guinea pigs are preferable to the monkeys, because they are easy to handle, and the possibility of temperature arising from some extraneous disease (tuberculosis) is not so common. In our studies we have always

FIG. 2.—TEMPERATURE REACTION IN GUINEA PIG INOCULATED WITH BLOOD FROM A CASE OF TYPHUS FEVER.

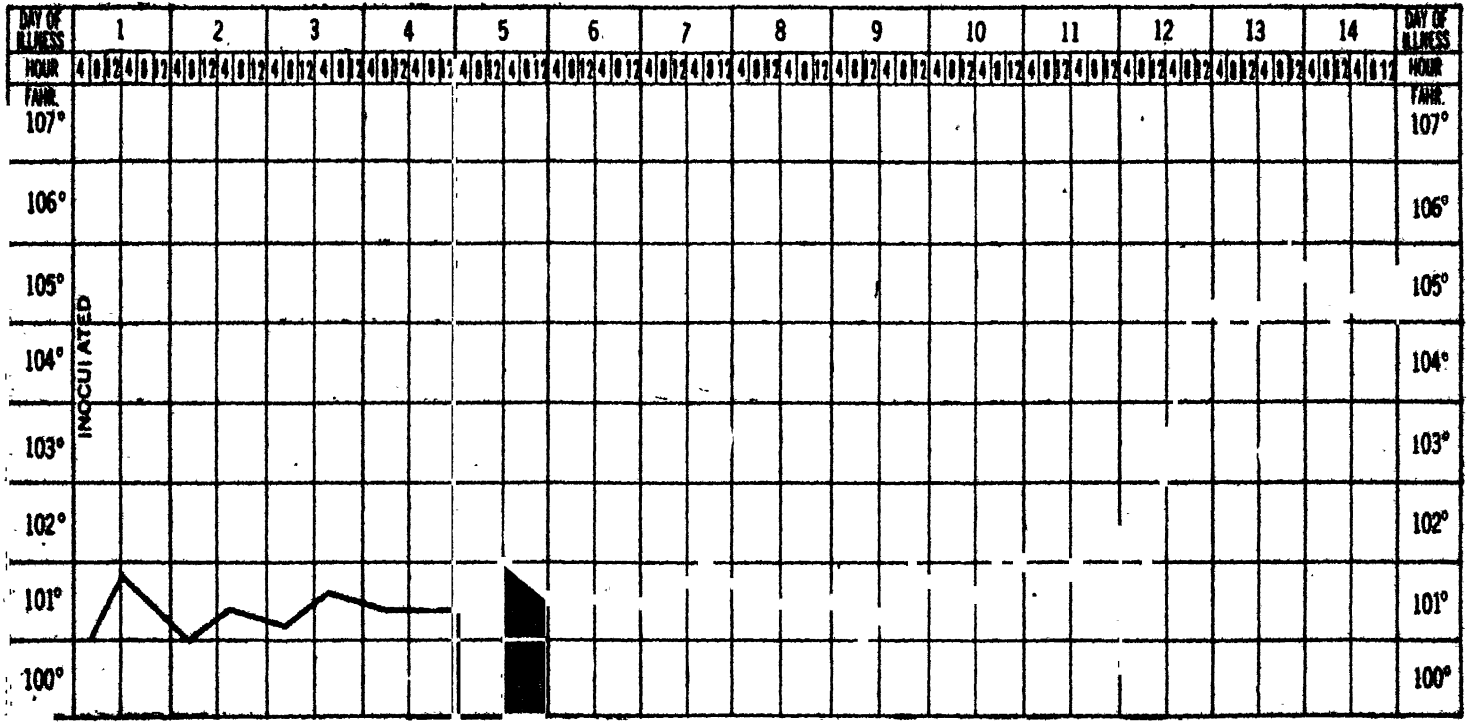


FIG. 2, A

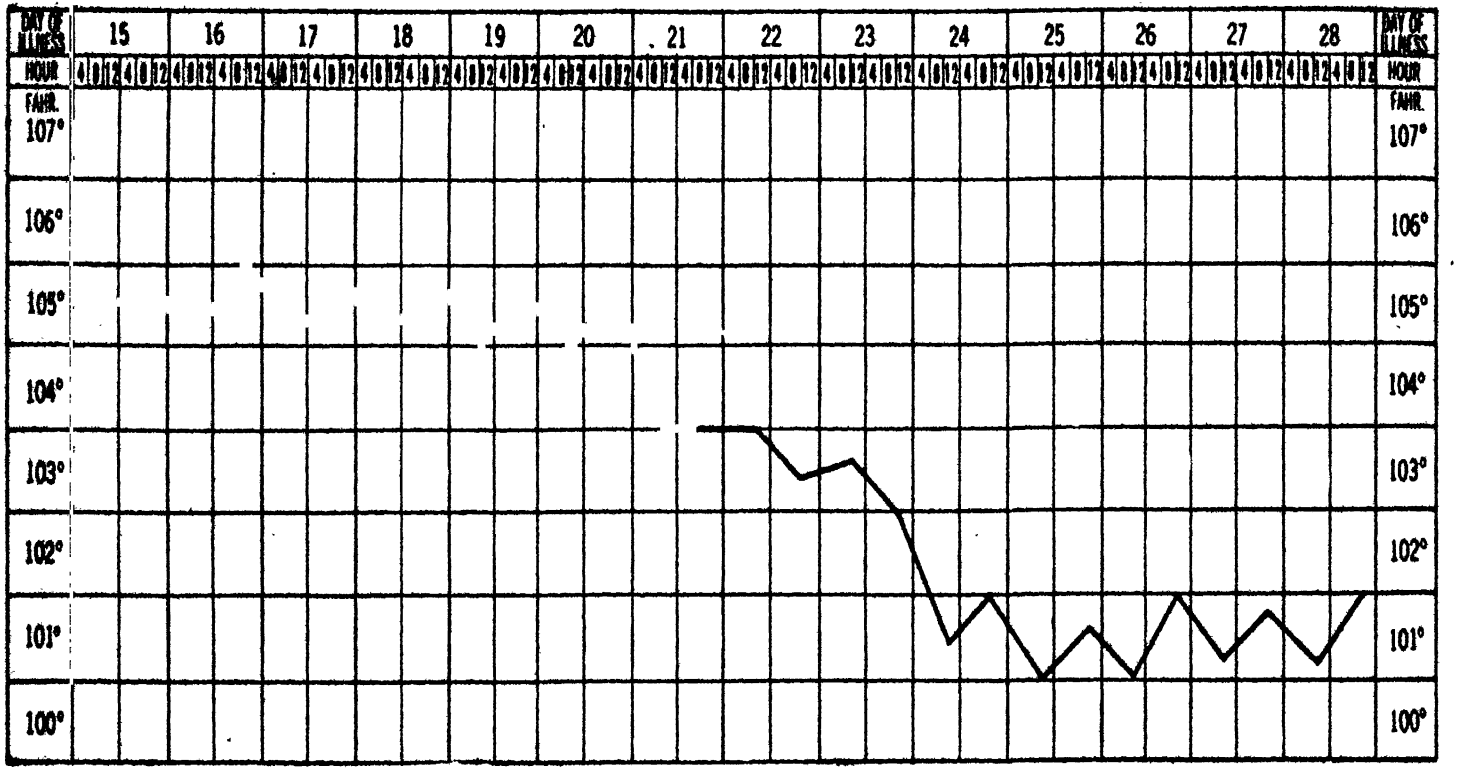

DAY OF ILLNESS
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21
22
23
24
25
26
27
28
HOUR
FAHR.
107°
106°
105°
104°
103°
102°
101°
100°

FIG. 2, B.

used male guinea pigs of 500 grams weight. Female guinea pigs may abort during the febrile period and die. A guinea pig of 500 grams loses about 100 grams during an attack.

(*b*) *Filterability of the Virus.*—The possibility that the virus of typhus fever was filterable was suggested by a doubtful experiment of Nicolle, Conor and Conseil, which neither they, Ricketts and Wilder, Anderson and Goldberger, Gavino and Girard, nor Olitsky, were subsequently able to confirm. In the experiment of Nicolle and his co-workers, he states that a monkey inoculated with Berkefeld filtered serum presented an elevation of temperature of 0.5° C. between the sixteenth and eighteenth days after the inoculation. This animal when subsequently inoculated with typhus blood did not react. Experience with monkeys has shown that a rise of temperature of 0.5° C. cannot be regarded as important. The fact that the animal remained refractory to a subsequent inoculation of virulent blood may have been due to the natural immunity, as shown by Anderson and Goldberger. In the experiments of Ricketts and Wilder, Anderson and Goldberger, Gavino and Girard, and Olitsky, carefully controlled filtration experiments have definitely shown that the virus of typhus fever will not pass a Berkefeld filter.

Epidemiology.—The occurrence of typhus fever during periods of calamity, famine, and while war raged was due to the prevalence of vermin-infestation that resulted because of the bad conditions under which the people had to live. Bernhardi states that the prevalence of louse infestations was observed in the seventeenth century in connection with typhus and relapsing fever. Tobias Cober, in his book on camp diseases, in the seventeenth century, called attention to the close association of typhus fever and the louse, while Hirsch points out the great similarity between the epidemiology of typhus and relapsing fever. Both are now known to be transmitted by lice. The conclusions reached by Murchison (1884) in his classical work on continued fevers, regarding the epidemiology of typhus fever remain as facts to-day. He noted that when typhus appears in a locality or house it usually spreads very quickly; that the number of cases stands in direct relation to the degree of contact between individuals; that persons visiting the sick are prone to contract typhus fever; that the sick convey typhus to clean quarters; that typhus is checked by isolation of the affected; and that it is acquired by contact with the sick, and by contact with objects contaminated in places previously occupied by typhus cases.

Experimental Demonstration That Lice Convey Typhus.—Mackie suggested that lice transmitted relapsing fever, and on account of the epidemiological similarity between this disease and typhus, Smith, Sergent and Foley suggested that lice could transmit typhus fever. It was Nicolle, Comte and Conseil (1909), however, who succeeded in transmitting typhus from monkey to monkey by the bites of infected lice (*Pediculus humanus corporis*) that had fed on a typhus patient one to seven days previously. Ricketts and Wilder confirmed this and succeeded in infecting monkeys through the scarified skin by means of the

gut contents of lice. Goldberger repeated these experiments and also transmitted typhus from man to monkey with the head louse (*Pediculus humanus capitis*). This experimental evidence has since been confirmed by the unfortunate deaths of Ricketts and Prowazek, who succumbed to typhus fever following infection with lice.

The period of infectivity of lice, following their exposure on typhus patients, has been found to vary by different observers. Nicolle, Comte and Conseil found lice infective 1 to 7 days after they had fed on a typhus patient, and Nicolle and Conseil infected two monkeys with lice after a period of 5 to 7 days. Wilder infected monkeys after 7 to 11 days, and Anderson and Goldberger after 1 to 4 days. Prowazek infected a monkey by injecting the contents of a single louse that had fed two days previously on a typhus case. Nicolle, Blanc and Conseil found that the inoculation of crushed lice after 1 to 8 days gave negative results, but after 9 to 10 days, animals became infected. It is difficult to correlate these results at present, and the actual period must remain open, but it is evident that an interval does occur in the body of the louse, between the time of ingestion of typhus blood and the infectivity of the insect.

Many of the earlier experiments state that typhus fever was transmitted by the bite of the louse, but the experiments are not conclusive. The feces of infected lice are infective for animals, and it is believed to be the most common method of transfer of the virus. The virus gains entrance through the puncture wound made by the insect while sucking or is scratched in by the host. Recent work on trench fever suggests that this is the common method in which the louse transmits this disease.

Actual experience in the control of typhus epidemics has shown that, with the eradication of vermin-infestation, the number of cases diminishes. Nicolle and Conseil in Tunis, by carrying on an active campaign in eradicating the louse, have met with remarkable results, as indicated by the following table:

Year	*Cases*
1909	856
1910	148
1911	180
1912	22
1913	6
1914	3
1915	0

Wide experience with recent epidemics in the Balkans and Russia has demonstrated the same results. In hospitals, where all patients were thoroughly deloused before being admitted to the wards, no ward infections occurred, and doctors, nurses and orderlies who previously were prone to contract the disease, remained immune.

Symptomatology.—The Onset.—The period of incubation varies between nine and twenty days, the usual being twelve days. The onset is usually acute with chilly sensations, chill, pains in the back and legs,

severe headache and great prostration. At this stage the expression is dull, the face flushed and the conjunctivæ congested. The conjunctival congestion is a common and constant symptom early in the disease. The tongue is dry and tremulous. The headache is severe, the patient complaining of generalized pain in the head. The bowels are constipated, and thirst is excessive.

Symptoms during Progress of Disease.—The temperature rises rapidly and may reach 103°-104° F. (39.4°-40° C.) in forty-eight hours. The pulse is rapid, rarely dicrotic. The spleen may or may not be enlarged. The eruption appears from the third to the fifth day, usually on the fourth. It appears on the abdomen, lower part of the chest, anterior surface of the shoulders, and arms and legs.

The eruption is rarely found on the face, but may occur on the palms and soles of the feet. The rash reaches its full development in from two to three days. The patient thereupon looks very ill. The face is congested, respirations are shallow and pulse is rapid. Marked mental disturbances are present. He may be lethargic, with sluggish movements, appearing almost in a comatose state, or he may be excited, jumping from the bed, or making suicidal efforts. Sordes appear, and unless the mouth is carefully cared for, parotitis, laryngitis or otitis media appears. Slight hoarseness and deafness are common at this time. The eruption becomes bluish and petechial spots appear. The patient becomes dull and stupid and very weak, lying in stupor or coma vigil.

The temperature continues high throughout the attack, ordinarily being about 104° to 105° F. (40° to 40.5° C.). Should the patient recover, the temperature falls about the fourteenth day and reaches normal in a few days. The eruption, with the exception of the petechial spots which remain as a bluish discoloration under the skin, begins to disappear at the termination of fever. In the event of recovery the patient comes out of the deep stupor, or the delirium gradually subsides, and he appears weak and exhausted. The temperature returns to normal or subnormal in twenty-four to forty-eight hours, and the convalescence is long. In the severe cases death may occur from an overwhelming toxemia early in the disease, but it usually occurs about the tenth to the fourteenth day from cardiac failure.

There is no definite *clinical picture* of this disease, the severity varying with different epidemics, and even in the severe epidemics, mild cases are often seen at the beginning and end of an epidemic which closely resemble the mild form of the disease (Brill's disease) seen in this country. The mild cases do not have such marked nervous symptoms, and the toxemia is not so profound. Petechial eruption is not so common. The convalescence is rapid and recovery usually occurs.

In the Serbian epidemic of 1915, besides the mild cases noted, there appeared the fulminating type and the type marked by circulatory stasis. In the fulminating type the patient goes into coma early and does not come out of it. He displays marked twitchings or *subsultus tendinum,* mutters and picks at the bed clothes. The patient loses sphincter control and usually dies in three days. In the circulatory

type the patient passes through the illness without incident, until about the twelfth day, when the feet and hands become blue and cold. The pulse is small and thready, and the cardiac sounds are distant and weak. Gangrene of the extremity usually sets in. The patient may die of cardiac asthenia or lose an extremity from gangrene.

Temperature.—During the later days of the incubation period a temperature of 99° to 100° F. (37.2° to 37.8° C.) may be recorded. Following the chill, the temperature rises rapidly and may reach 104° F. (40° C.) in forty-eight hours. The temperature then continues high, the remissions being very slight. A fall of more than one degree in uncomplicated cases is rare. The curve shows little change until the later part of the disease. The temperature may fall by crisis on the fourteenth day, reaching normal in twenty-four hours, or may be gradual ending by lysis, with a slight elevation of temperature for three or four days. A precritical or postcritical rise may occur. In mild cases the temperature may not go above 102° F. (38.8° C.) during the entire course. The fulminating cases usually have a high continuous temperature, while in the cardiac type, the remittent temperature may occur. Cases ending in death may have a very high temperature just before exitus.

The Exanthem.—This is the most characteristic symptom of the disease, but during an epidemic the typical eruption does not occur in all cases. The eruption may appear from the third to the fifth day, but occurs usually on the fourth. It consists of a maculopapular eruption followed by petechial spots. The eruption appears first on the upper abdomen, lower chest, shoulders, back and extremities. Unlike typhoid it may be found on the palms and soles of the feet but rarely on the face. The extent of the eruption is variable and bears no relation to the severity of the attack. During an epidemic cases are seen with a very scant eruption, though some cases without eruption are reported. In dark-skinned individuals it is sometimes difficult to see the eruption. The typhus spot must be differentiated from louse bites, which are usually seen in typhus patients. The eruption is usually all out in seventy-two hours, and begins to disappear at the time of crisis.

The spot first appears as a pale red macule, which disappears on pressure. It varies from 1-4 mm. in diameter, and has an indefinite edge. The spot then becomes darker, has a dark reddish or purplish color and does not disappear on pressure. This is due to the deposition of blood pigment, which usually begins at the center and extends to the periphery of each spot. Petechiæ then appear, this being due to the extravasation of red blood-cells. In the Serbian epidemic few of the spots became petechial, the majority disappearing before this stage.

Circulatory System.—The pulse early in the disease is rapid and in the second week becomes small and weak. With the severe toxemia, myocarditis is often present, and cardiac failure may occur. In the circulatory type described gangrene may occur. Toes and fingers are usually affected. Maitland records two cases with gangrene of the nose.

Blood.—There is a decrease of leukocytes in the first few days, but

FIG. 3.— TEMPERATURE CHART OF A CASE OF EPIDEMIC TYPHUS FEVER IN A BULGARIAN SOLDIER, OCCURRING IN THE BALKAN EPIDEMIC OF 1916. (Admitted on the fourth day of the disease.)

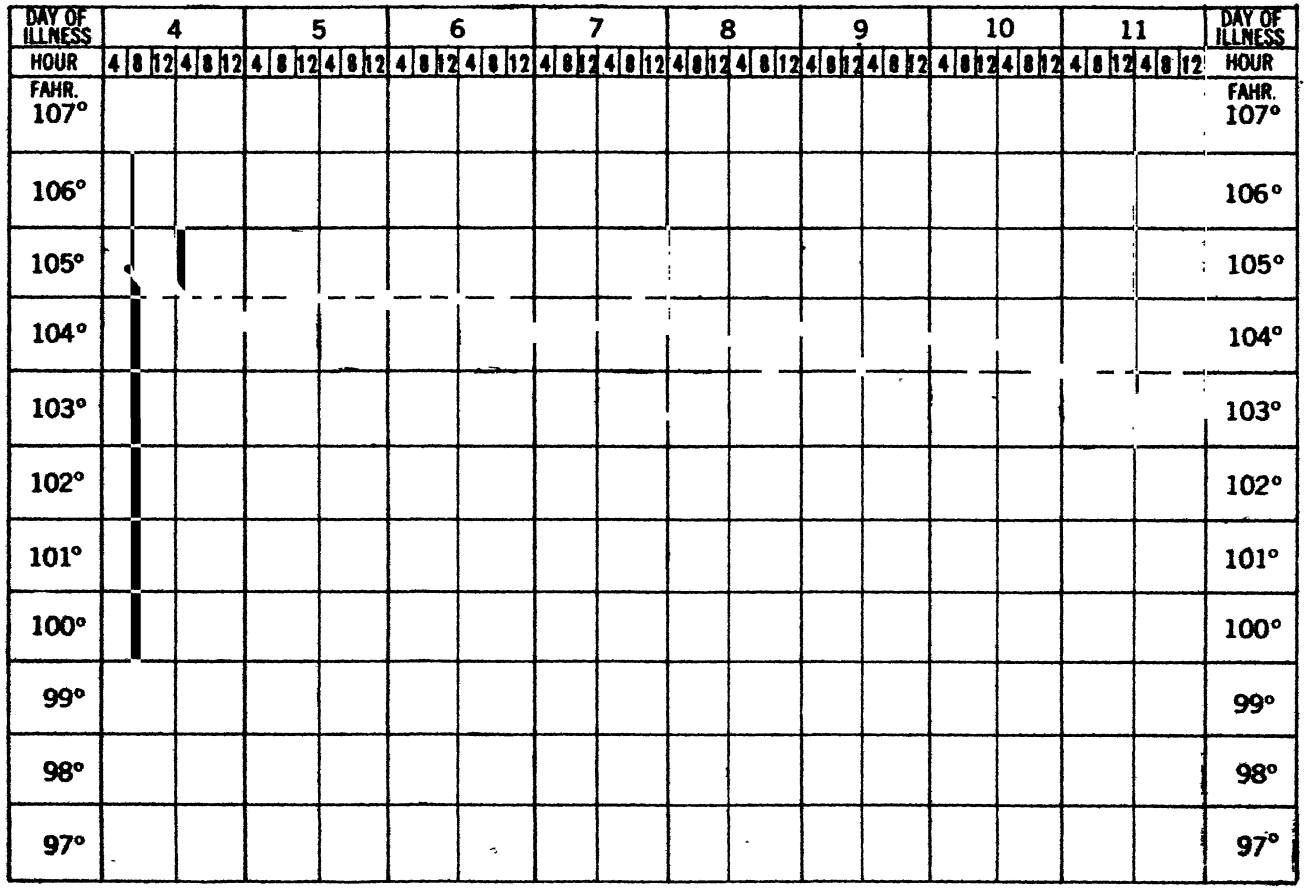


FIG. 3, A


DAY OF ILLNESS
12
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DAY OF ILLNESS
HOUR
4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12
HOUR
FAHR.
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°

FIG. 3, B.

after the third day there is a gradual increase. After the first week the average count is 10,000-12,000 leukocytes with an increase of polymorphonuclear leukocytes. Lichtenstein regards an absence of eosinophils of importance in the diagnosis. In the endemic variety, Brill records 9,000-11,000 as the average count, with sixty-nine per cent. polymorphonuclear leukocytes and thirty-one per cent. lymphocytes.

Nervous System.—The nervous system is involved in the severe cases, because of the toxemia. This may manifest itself by acting on the brain, spinal cord or peripheral nerves. Severe headache is often the first symptom of which the patient complains.

At the onset the mental condition is usually clear, but soon becomes dull and heavy. Violent delirium or marked apathy occurs in the second week. In the delirium the patient seems to suffer from terrifying hallucinations; he may commit suicide by strangling, jumping from the windows or shooting. The type with coma is characterized by marked prostration and coma vigil. Marked tremor is common. The spinal fluid shows an increased number of lymphocytes.

Digestive Tract.—The tongue is coated and dry throughout. Sordes and tremor are common. If the mouth is not properly cared for parotitis, otitis media and laryngitis may occur. Gastric disturbances are rare. Constipation is the rule.

Genito-urinary Tract.—Changes in the kidney are the same as with any acute febrile disease. Febrile albuminuria occurs. Nephritis may remain as a complication. The diazo-reaction is usually positive.

Diagnosis.—The chief diagnostic points are the acute onset, conjunctivitis, continuous temperature, characteristic eruption and toxemia. The disease must be differentiated from typhoid, small-pox, scarlet fever, measles, relapsing fever, malaria, septicemia, Rocky Mountain spotted fever, cerebrospinal meningitis and severe vermin-infestation.

In *typhoid fever* the onset is gradual, the toxemia is usually not so severe, the pulse is slow, the spleen is palpable, the rash appears later than in typhus, and occurs in successive crops. In typhoid there is a leukopenia. A positive Widal or blood culture may be obtained. In *typhus fever* the sudden onset, conjunctivitis, toxemia, rapid pulse, and profuse rash should aid in differentiating the two diseases.

In the *acute exanthemata,* the sudden onset with fever, headache and prostration may cause confusion until the eruption appears. In *small-pox* the eruption occurs in three days, appears on the face, and the temperature drops with its appearance. With *scarlet fever,* there is the sore throat, and eruption in twenty-four hours. *Measles* is associated with coryza, bronchitis, rash on the face, and Koplik's spots. *Relapsing fever* is differentiated by finding the spirochæta in the blood. In *septicemia* a positive blood culture is obtained. *Rocky Mountain spotted fever* occurs among herders in certain sections of the Rocky Mountains. If Rocky Mountain spotted fever and typhus occurred together it would be difficult to differentiate them clinically. The spleen is more often enlarged and icterus is more common in Rocky Mountain spotted fever. *Malaria* can be differentiated by finding plasmodia in the blood and *cerebrospinal*

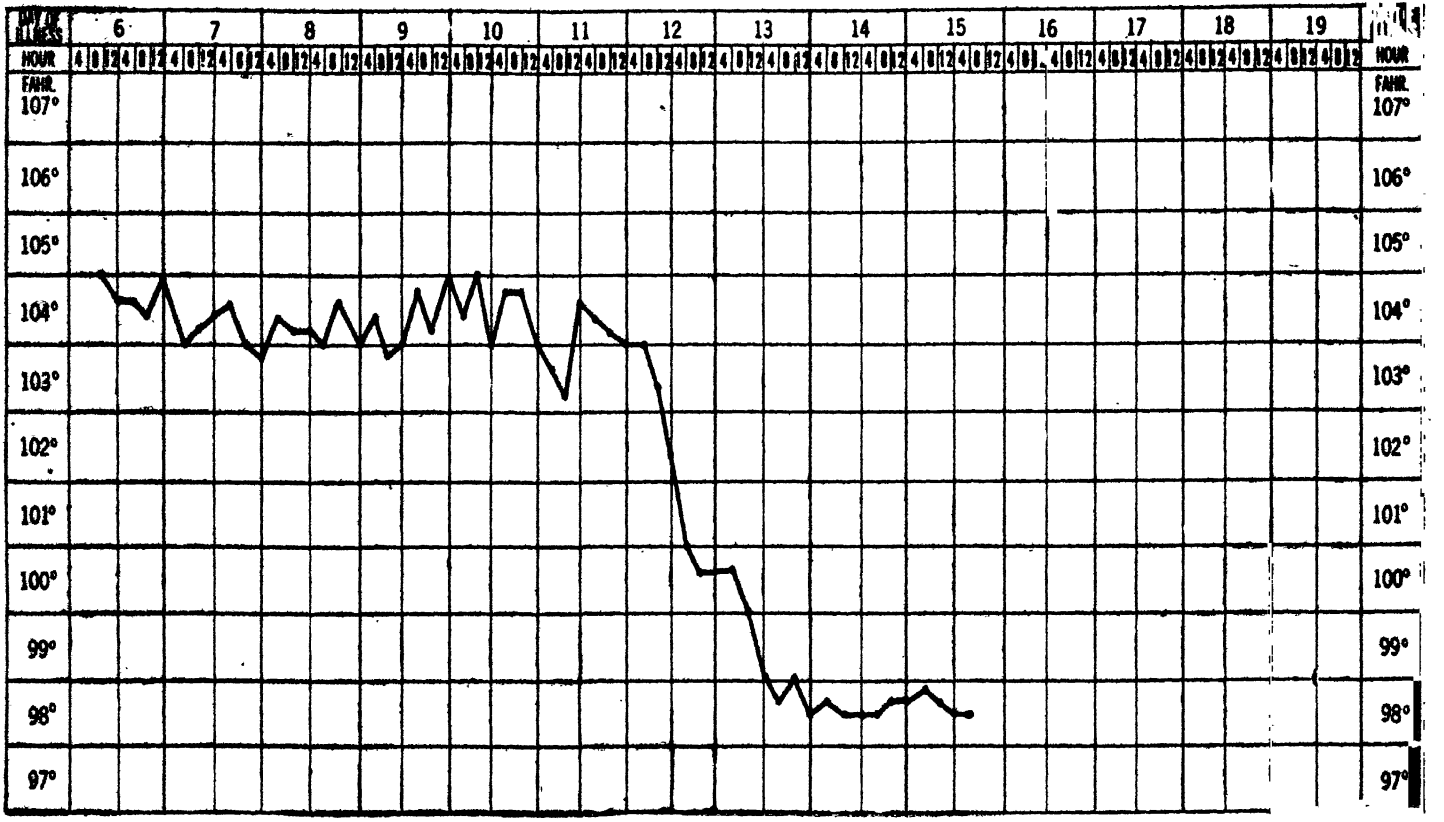


FIG. 4.—TEMPERATURE CHART OF A CASE OF ENDEMIC TYPHUS FEVER (BRILL'S DISEASE.)
Admitted on the sixth day of the disease.

meningitis is diagnosed by lumbar puncture. In severe cases of *vermin-infestation* the patient may present an eruption with temperature which may be confusing. The spot, however, contains a small puncture wound, which does not occur in the typhus eruption, and the temperature is not characteristic, although it may remain for a considerable period of time.

In all instances where the diagnosis is difficult a small quantity of blood (3 c.c. of defibrinated blood and 3 c.c. of saline) may be injected intraperitoneally into a guinea pig to obtain the typical febrile reaction. Blood culture, using the anaërobic method described, should be employed. Agglutination or complement-fixation with the *Bacillus typhi-exanthematici* may give confirmatory evidence.

Complications.—The complications in different epidemics vary. Some epidemics have practically few complications, as occurred in Poland in 1914-1915. In Serbia the more important complications observed were parotitis, gangrene of the feet, polyarthritis, polyneuritis, otitis media and laryngitis. In the Irish epidemic bronchopneumonia was the most common complication. In endemic typhus, Brill records bronchitis, bronchopneumonia, meningismus, phlebitis and otitis media as the complications.

Association with Other Diseases.—Relapsing fever is usually associated with epidemics of typhus fever. This has been noted for many years. Both diseases are transmitted by lice. In the Balkans, in 1914-15, the typhus epidemic ceased in July, while relapsing fever continued. In Poland, in 1915-1916, both typhus and relapsing fever continued through the summer months.

Treatment.—PROPHYLAXIS.—The subject of treatment may be divided into the handling of those exposed to typhus fever and those who have contracted the disease. The subject of prophylaxis is usually dispensed with by saying that it means the control of vermin-infestation. Experience during the World War, with typhus fever, and the handling of large bodies of vermin-infested men has demonstrated that the control of vermin-infestation is not a simple matter.

As with other insect-borne diseases, such as malaria, effective measures cannot be instituted unless the biology and habits of the insect are understood. The World War furnished ample means for the study of this problem, for owing to the unprecedented scale of the war, combined with the conditions under which it has been fought it led to a prevalence of lice among soldiers that has never been equaled before. No army was spared from wide-spread vermin-infestation and diseases transmitted by this pest.

Vermin-infestation in the United States army was prevalent—over ninety per cent. of the troops in the American Expeditionary Forces being infested. Vermin-infestation in European armies is supposed to have been spread from a few infested men. Any large assemblage of soldiers is likely to contain a few such individuals, who are primarily the cause of the trouble, which is greatly aggravated by the limited sanitation under camp conditions.

The effects of the presence of lice upon men differ according to indi-

vidual susceptibility. Persons who are constantly vermin-infested appear to be immunized against the salivary secretion, and the local reaction is very slight. Sometimes only a slight puncture wound is discernible. In persons who have never been infected before the local reaction is intense and indicated by an urticarial wheal or hemorrhagic spot. Fever may result from the mere presence of lice upon the person.

Lice are small wingless insects, and are divided into two groups, according to their method of feeding. The *Mallophagia* include the biting lice, like the bird lice, which feed on the hair and feathers of animals, but do not suck blood. As far as is known, these lice do not transmit disease. The *Anoplura*, or sucking lice, feed by sucking blood, and is the group concerned in the transmission of disease. Human lice have been regarded as belonging to three different species, *Pediculus humanus* (Linnæus) *Pediculus capitis* (De Geer), *Pediculus corporis* (De Geer), and *Phthirius pubis* (Leach).

Pediculus humanus corporis is often called the "body louse," "clothes louse," or the "gray back" of Civil War days, or the "cootie" in the European war. This louse is a parasite which depends upon human blood for sustenance and man's body and clothing, for prolonged life and reproduction. The size varies with its maturity: a newly hatched louse is about the size of a pin's head, while a full grown, well-fed louse is about one-sixteenth of an inch in length. The louse is covered with a smooth, hard substance, known as chitin, which is impenetrable to most chemicals.

The body is divided into head, thorax and abdomen. At the sides of the head are two antennæ; the mouth has a long sharp stylet or stabber, which is used for puncturing the skin, and is adapted for blood sucking. Attached to the thorax are six legs, with a single large claw at each extremity. The first pair of legs in the male differs from those of the female in that a thumb-like projection is present which is much larger than that in the female. The abdomen is divided into eight segments. The terminal one is indented in the female and rounded in the male. The abdomen of the female is broader than the male. There is some evidence that there are more females than males.

The life histories of *Pediculus humanus* (*Pediculus capitis* and *Pediculus corporis*) and *Phthirius pubis* are similar in that the insects, after emerging from the egg, undergo three moults before attaining sexual maturity.

The eggs or nits are laid on fibers of clothing or body hair. They prefer to lay eggs on rough material such as felt, wool or flannel, but will deposit eggs on silk. For this reason the protective value of silk underwear is doubtful. The egg is ovoid, about one-twenty fifth of an inch long with a granular cap or operculum. They are firmly fixed to the hair by the cement, the operculum usually pointing to the distal end of the hair. The freshly laid egg is almost transparent, but as the embryo develops the egg assumes a yellowish color. Eggs are difficult to find on white or gray cloth. The empty shell is hard and remains attached after the louse has emerged. The shell and the cement

are resistant to chemicals: no solution will remove it without first destroying the hair or fiber to which it is attached. At the temperature which ordinarily exists between the skin and the clothing the eggs hatch in from seven to ten days, but if kept in a cooler atmosphere the incubation period is lengthened. Nuttall, in describing the mechanism of

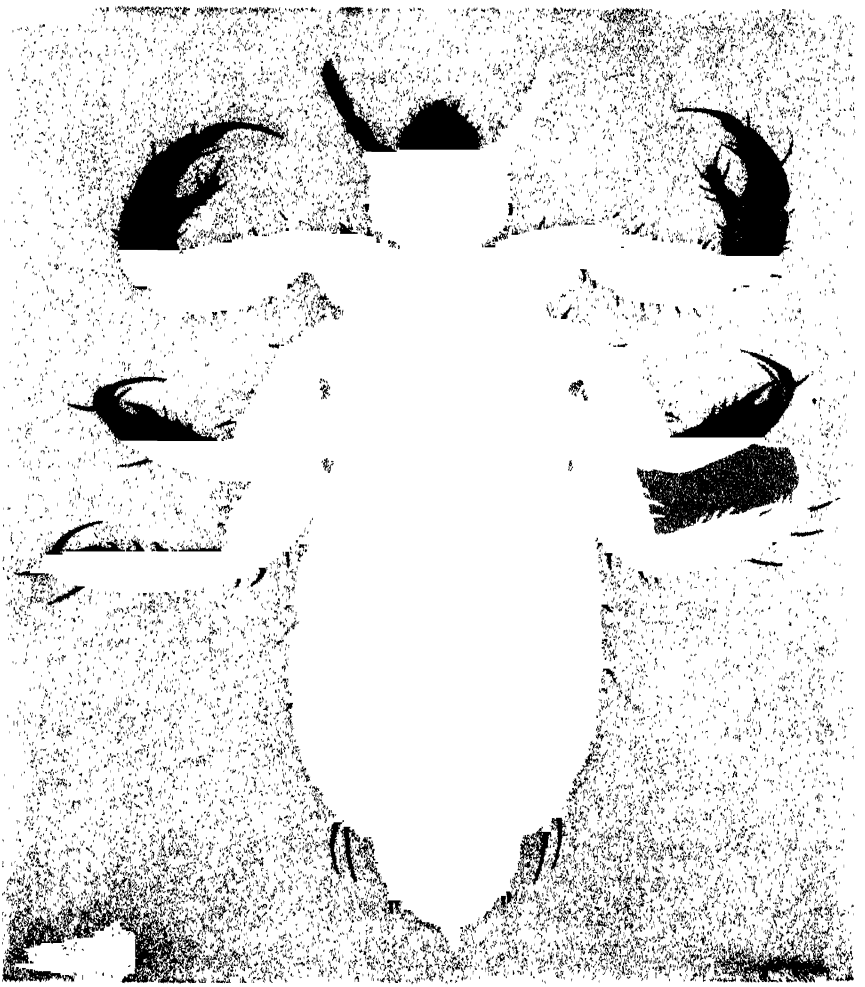
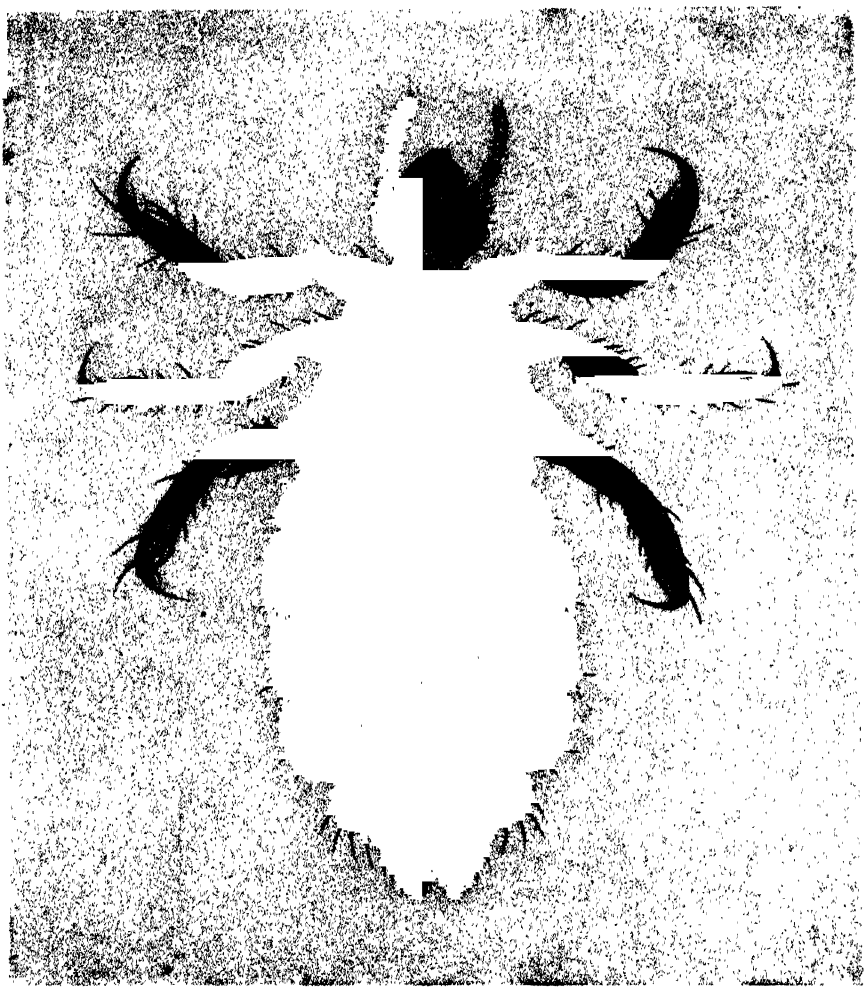


FIG. 5.—PEDICULUS HUMANUS CORPORIS, MALE.

the emerging louse, states that air passes through the operculum which is taken in by the insect and then passes out behind until the air increases and the louse is gradually forced out through the operculum. The first moult occurs after two days, the second, two days later, and the third, after three days. A complete cycle from egg to egg takes about sixteen days.

Oviposition in *Pediculus humanus* commences twenty-four to thirty-six hours after the emergence of the female from the third larval skin. The number of eggs laid depends upon the food supply and the temperature at which the female is maintained. Under optimum natural conditions 300 eggs represent the normal number which a female is



G. 6.—] HUMANUS CORPORIS, FEMALE.

capable of laying. Bacot stated that a female louse under ideal conditions might have 4,000 offspring during her life time. The average life of a louse is from thirty-five to forty days, probably a little less for the males.

Incubation is eight days, at 30° C. (86° F.), which is the optimum temperature. This period may be lengthened or shortened by varying

the temperature. Therefore, infested persons who remove their clothing at night will become less heavily infested than those who wear their clothing continuously. The periodic cooling of the clothing and contained lice leads to their progeny being materially reduced.

The female louse may lay infertile eggs which soon shrivel up. There is no evidence of parthenogenesis.

Lice feed immediately after emerging from the egg. A young louse will die within twenty-four hours if no blood is obtainable, while a well-fed louse can live ten days away from its host. Lice feed a number of times during the day. They feed most frequently at night, when the host is at rest. When lice become ravenous with hunger they feed to excess and may rupture the intestinal canal. The louse depends upon the salivary secretions to dilate the capillaries so that blood flows freely. The feces of lice contain a large proportion of undigested red blood-cells. There is no evidence that lice have an olfactory sense.

Vermin-infestation is spread either by contact with the infested persons themselves, their clothing or their personal effects. One vermin-infested man may spread lice to many of his associates. The soldiers believe that trenches and dugouts were "lousy" and that they obtained their infestation from them. This was not true, for the infestation was obtained owing to the overcrowding in those places. Lice only leave the host voluntarily, when the person has fever or dies. In the first instance the excessive heat drives them off, and in the latter the lack of food supply. Lice may be dislodged by brushing and so fall to the ground. It has been found that lice buried in sand at a depth of four inches will crawl to the surface. They may be blown by wind. Lice are ordinarily not found in bedding and blankets unless recently occupied by vermin-infested individuals.

Lice are most often found in those parts of the garment which are in closest contact with the body, such as the fork of the trousers, waistline, armpits and neck. They are found in the inner as well as the outer garments. Lice may be found on any garment or article worn by an infested man. In conducting inspections for lice it is important to bear this in mind, and remember that the louse may lay its eggs on the hair of the head as well as any other hairy part of the body. This is of great importance in obtaining satisfactory results. The disinfestation of clothing alone is not sufficient.

Pediculus humanus capitis is perhaps the commonest variety of louse in civil life. Sobel states that about twenty-two per cent. of the school children in New York are infested, some 150,000 to 185,000 cases having been reported during the years 1909 to 1912. *Pediculus capitis* shows no material difference in its biology from the *Pediculus corporis,* the only difference being racial. It lays fewer eggs, and is perhaps shorter lived. It is found mostly on children, especially on girls on account of their long hair, and on old people. It is found commonly in the temporal and occipital regions. Although this is the common habitat, it may be found on other parts of the body, in which case it would be difficult to determine whether it was *Pediculus corporis* or *Pediculus*

FIG. 7.—EGGS OR NITS OF PEDICULUS HUMANUS CORPORIS. (Large Magnification.)

itis. This insect is spread by contact such as occurs in schools, and by brushes and hats. The common hook in school houses may be a method of transfer. If hair is worn short infestation is less likely to occur. The experiments of Goldberger indicate that the head louse may transfer typhus fever. Considering that typhus fever is endemic in certain sections of the United States, it is of the greatest importance that the high degree of infestation in schools be diminished.

An effective treatment is to anoint the head with an equal mixture of **kerosene and vinegar** or **kerosene and olive oil**. The head should be wrapped in a towel over night and shampooed in the morning. Repetition of this procedure may be necessary. Combing with a fine comb will remove the nits. In males the hair should be cut.

The *Phthirius pubis* (crab louse) looks unlike pediculi and closely resembles a crab. It is about one-sixteenth of an inch long. It is usually found in the pubic and perianal region, but may be found on the abdomen and chest, axillæ and down over the thighs. They have been found in the eyebrows. The nits are laid near the bases of the hair. *Phthirius* feeds almost continuously. A female lays about twenty-five eggs in her lifetime. Eggs hatch in about seven days. They die rapidly when removed from man. Development is the same as in the case of the pediculus. This insect is transmitted mainly by contact in lodging houses, houses of prostitution, bath tubs and toilet seats. It has not been known to transmit disease. Treatment consists in **shaving the body hair**. If skin irritation is present some **bland ointment** should be applied. The use of blue ointment may cause skin irritation and care should be exercised in its use.

The destruction of lice and their eggs is called "**lousing**" or "**delousing.**" In considering any delousing method, it is important to note that the ideal method is to destroy lice, their eggs and the virus concerned in the transmission of disease. If it were possible to tell non-infected lice from infected ones, such stringent measures would not be necessary. The manner with which delousing can be carried out depends upon the place and facilities put at one's disposal. For instance in armies, the methods employed in front line trenches would be different from those employed in the rear. Lice transmit disease by way of the excreta, the virus gaining entrance through the puncture wound made by the louse while sucking, or is scratched in by the infested individual. Louse-borne diseases, therefore, may be conveyed to an individual even though the lice and their eggs are destroyed.

For the destruction of lice in clothing on a large scale, the most efficient method is **heat**. Dry heat is perhaps more convenient to use, but it is not as effective as moist heat. Dry heat has the advantage in that leather material and rubber goods may be disinfested. Steam is better than dry heat because penetration is better, and it disinfects as well. A temperature of dry heat which would be sufficient to destroy the viruses of relapsing fever, typhus fever or trench fever would also injure woolen materials.

Both lice and nits are destroyed at 55° C. (131° F.) dry heat in five

minutes. In practice, this exposure should be lengthened to thirty minutes at 70° C. (158° F.). In a steam disinfector if the clothing is not tightly packed, exposure should be from twenty to thirty minutes.

The following delousing methods are employed:

1. Mechanical
2. Heat
   - (*a*) Moist
     - (1) Boiling water
     - (2) Serbian barrel
     - (3) Steam disinfector
     - (4) Field sterilizing box
     - (5) Portable sterilizer
     - (6) Trains, locomotives
   - (*b*) Dry
     - (1) Flat-iron
     - (2) Oven
     - (3) Hot-box
     - (4) Hot-air huts
3. Chemical
   - (*a*) Insecticides
   - (*b*) Fumigation
   - (*c*) Sachets
   - (*d*) Powders

Clothing can be freed of lice by storage. Sufficient length of time must elapse for the adult lice to die, and nits to hatch. Nuttall advises that clothing be stored in a dry temperature two or three weeks. Since hatching has been delayed thirty-five days by low temperature, it would be safe to allow thirty to forty days during cool weather. In some armies the men mechanically removed lice from their clothing, but this is never an entirely effective measure.

Lice and eggs in vermin-infested material immersed in water at 70° C. (158° F.) for five minutes will be destroyed. This method is impractical on a large scale. The **field sterilizer box** is an improvised box into which steam is conducted. This box may be mounted or not, as suits the purpose.

The **Serbian barrel** was used with success during the typhus campaign in Serbia and Bulgaria. It consists of a large barrel, the bottom of which is freely perforated, while the top is removed and replaced by a weighted lid. At the lower end is a sand bag collar to prevent the escape of steam, which enters the barrel from a metal boiler upon which it rests, both barrel and boiler being imbedded at their junction in the brickwork forming the furnace. The furnace may be made long and narrow, with a chimney at one end, and the boilers and barrels placed in series. It is important that steam be generated rapidly. The clothing to be deloused is placed in at the top and the lid placed on tightly. After the steam is generated, the clothing remains in the barrel for one hour.

All clothing, except leather material, rubber and celluloid may be

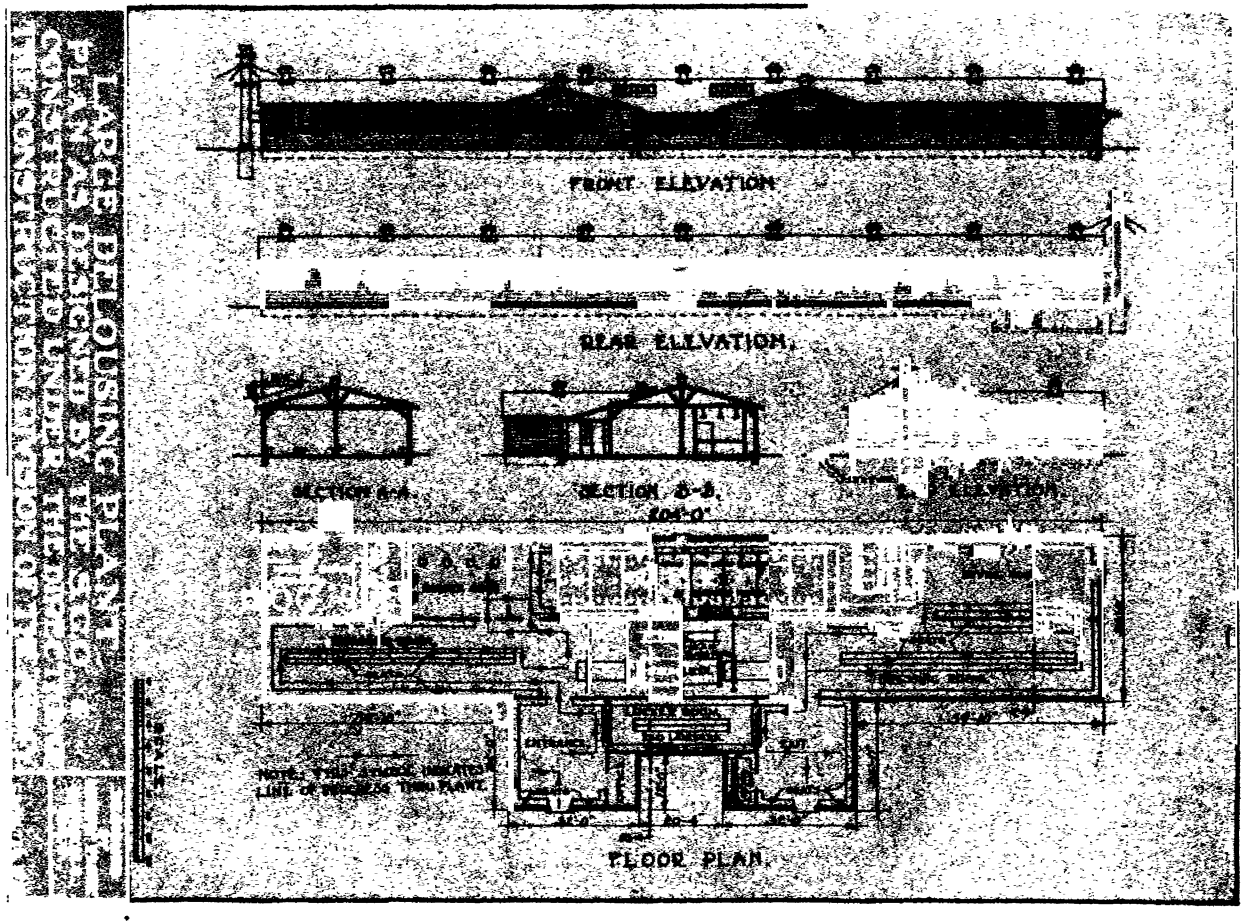


FIG. 8.—PLAN OF DELOUSING PLANTS CONSTRUCTED IN THE UNITED STATES.

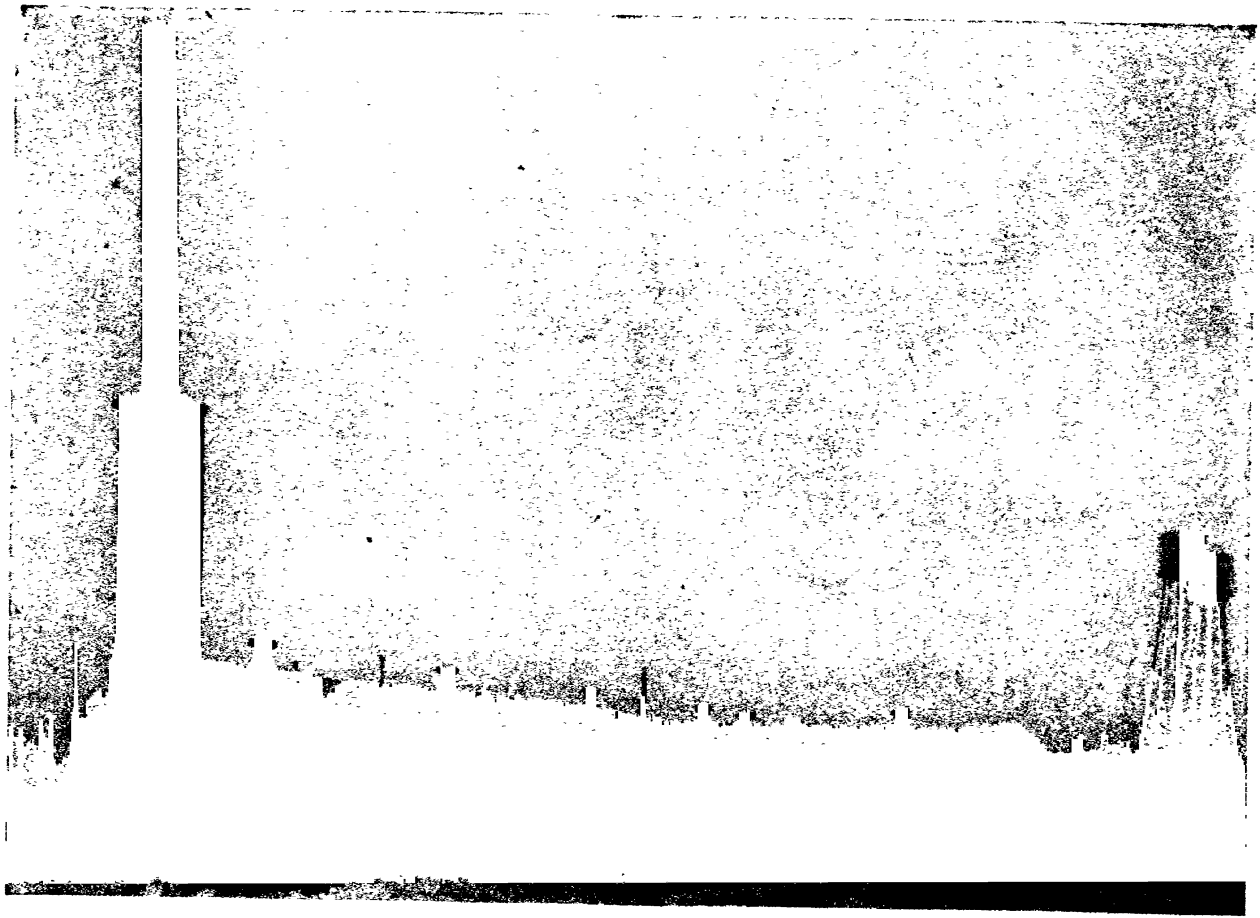


FIG. 9.—DELOUSING PLANT AT A DEBARKATION CAMP IN THE UNITED STATES.

handled in this manner. A portable **steam disinfector** may be employed, and is useful because it can be drawn from place to place. **Locomotives** have been used to generate steam, which is then conducted into sealed trains. A great deal of material can be handled in this manner.

The delousing plant here described was devised by the author for the delousing of all troops returning to the United States. There are certain principles that a delousing plant should observe in order to be successful. The clean men must be separated from the vermin-infected ones; the clothing as well as the body must be treated; the plant must operate rapidly and it should be warm and light. The plant described here could handle about 200 men and all their equipment every hour, or about 5,000 a day, working continuously.

According to the plan, the man enters with his barrack bag, containing all his clothing. The leather material, rubber, celluloid and money are checked in the locker room. The soldier receives two numbered tags, corresponding to the number of the locker, and then proceeds to the disrobing room with his barrack bag. All the clothing is placed in the bag, which is tied and numbered with one tag, the man retaining the remaining one. The bag is placed in the carriage, which is pushed into the steam sterilizer. The sterilizer is 18½ feet long by 5 feet in diameter, and is provided with two cars and transfer tracks, so that one car will be loading or unloading, while the other is in the sterilizer.

The soldier then proceeds to the hair-cutting room. Before entering, he is inspected by a medical officer for vermin and nits. If these are found on the hair of the head, axillary or pubic regions, he passes into the barber-shop. If none are found, he passes into the shower-room. In the barber-shop, the hair is cropped with an electric hair-cutting machine. The axillary and pubic hair can be shaved here also. Following this, he enters the shower-room, where a thorough bath with liquid soap and warm water is obtained. The soap employed is a kerosene soap mixture. A drying-room follows, a table being provided for clean towels, and a receptacle to receive the soiled ones.

In regard to the clothing, provision is made for a pressing-room, as the clothing may be wrinkled following sterilization. If the clothing is carefully folded, the wrinkling is very slight. Wrinkling also may be avoided by placing clothing on hangers. The pressing of garments retards the speed of the plant.

Following the sterilization of clothing, the leather material, etc., is reclaimed at the locker room. In the presence of heavy infestation or an epidemic of louse-borne diseases, everything should be treated and so a small dry-heat plant should be used for the non-sterilizable material. The **steam disinfector** is best operated by applying vacuum, steam, and vacuum in that order. With this process, no shrinkage of woolen materials results and the clothing comes out dry. The floor of the building is of concrete, and two toilets are provided for the clean and infested men.

The **flat-iron** has been employed for the pressing of seams. This method is impracticable on a large scale. **Hot ovens** have been used.

Care must be observed not to scorch the clothing. Penetration with dry heat is not as complete as when steam is used. Stagnant hot air is less effective than circulating hot air.

In the front area, in dugouts and trenches, the **hot-box** may be used. This box was devised by the author, and is based on the principle of the fireless cooker, and is used by heating a piece of metal, and placing the clothing which is protected from the metal over it. The temperature

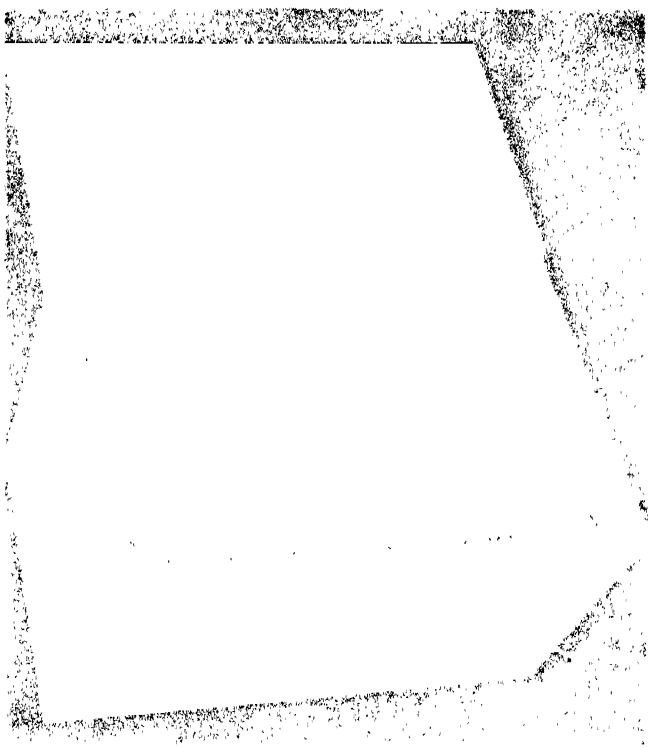


FIG. 10.—HOT-BOX USED FOR DELOUSING.

obtained is sufficient to destroy lice and eggs. The clothing remains in the box for one hour.

The **hot-air hut** is a hut in which air heated to 70° C. (158° F.) is made to circulate in space, either naturally through inlets and outlets, or is kept moving by fans. The objects to be disinfested are hung loosely in the chamber, so as to allow the free circulation of air about and between them.

Chemicals act to destroy lice and nits on clothing and hair, or to repel them. Many of the **insecticides** recommended have been shown to be worthless, as they do not affect nits. Essential oils, such as eucalyptus, anise, oil of wintergreen and oil of cloves act as local repellants, but do not destroy nits. A **powder** employed by the English met with some

success. It consists of **naphthalene** (96 per cent.), **creosote** (2 per cent.) and **iodoform** (2 per cent.). The commercial **naphthalene** was the best. In the studies of Kinlock, and Moore, it was found that the combined powder was more toxic to lice than any of its constituents. The powder acts as a repellant, and does not destroy nits. It should be dusted into the seams of clothing every three days. The fork of the trousers should be avoided, as it may cause smarting. Moore believes that a **powder consisting of talc** (20 grams), **creosote** (1 c.c.) and **sulphur** (0.5 gram) is more effective. In conjunction with the powder the English employed a mixture known as **Vermijelli**, which consists of **crude mineral oil** (5½ pints [3 liters]), **soft soap** (3 pounds [1360 grams]) and **water** (½ pint [.25 liter]). This is smeared in the interior seams of the clothing. **Sachets** have a limited radius of action, and are useless under field conditions.

The practical application of underwear impregnated with chemicals has given unsatisfactory results. Experiments by Hirschfelder and Moore using the sodium salt of dibrominated crude cresol, the monobrom-meta-cresol, and dibrom-meta-cresol indicated that these chemicals have a toxic effect on lice and nits.

Various **fumigation methods** have been employed, but experience has shown many of them to be ineffective, as they do not destroy nits. Sulphur will not destroy nits. **Hydrocyanic acid gas** is effective when used in large amounts. Three to 3½ ounces (90 to 105 c.c.) per 100 cubic feet is sufficient to kill adult lice and nits, when the surface of the clothing is freely exposed to the fumes for one-half hour. When clothes are tightly packed in trunks 6 ounces (180 c.c.) per 100 cubic feet with twenty-five inch vacuum should be used for two hours. This gas is very poisonous. Moore recommends **chlorpicrin** because it penetrates clothing and will kill lice and eggs in proportion of 4 c.c. (1 dram) to 1 cubic foot for thirty minutes.

The method employed by the United States army in excluding vermin-infestation, and diseases transmitted by vermin, from the United States may be cited, as being thoroughly effective. At certain periods over 90 per cent. of our troops were vermin-infested prior to embarkation from France to the United States. All troops were detained for two weeks prior to embarking so as to detect all infectious disease. During this period all troops were supposed to be deloused, but owing to the rapidity with which troops were returned to the United States this was not always possible. Troops were examined at sea, by a medical officer, and they were directed to examine their clothing daily for lice. Vermin-infestation discovered in this way was treated on the transport. On arrival in the United States troops were prevented from coming in contact with civilians, and were immediately sent to the nearest camp. They were received in an "unclean area," and immediately deloused. Following delousing they were assigned to "clean" barracks. Before discharge from the service each soldier was examined again, and infestation noted. From November, 1918, to June, 1919, inclusive, 2,500,665 men were examined and discharged from the service, and only 5 in every 100,000 were found infested. Most of these were *Phthirius pubis*.

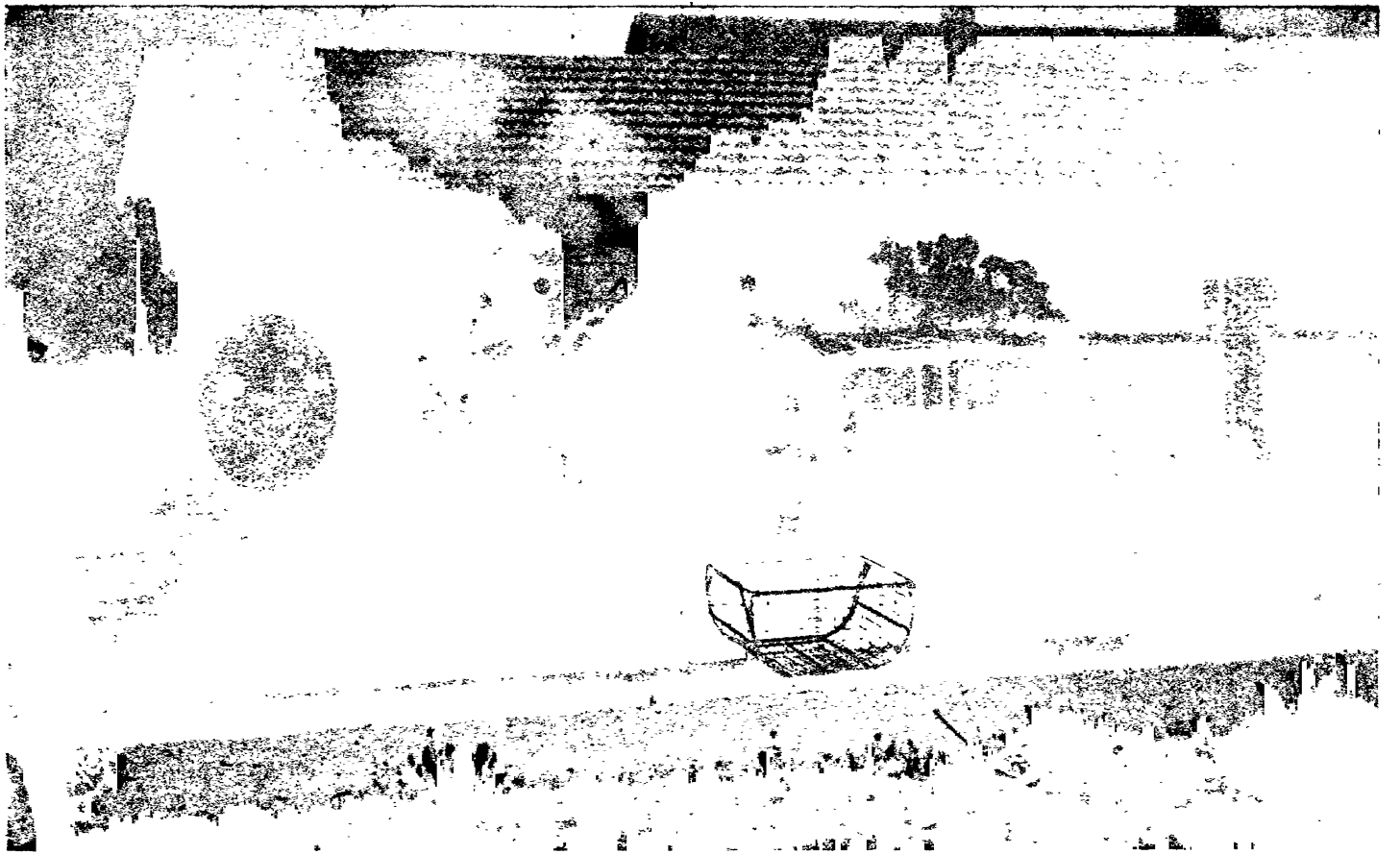


FIG. 11.—FODEN-THRESH DISINFECTOR; DELOUSING IN FRANCE.

Not a single case of a louse-borne disease was brought into the United States.

During a typhus epidemic separate typhus hospitals should be established and separate enclosures for typhus contacts. When a case is discovered the patient should be removed to the hospital—never treated at home. All contacts with the case should be removed to the contact enclosure. On arrival in the hospital all clothing from the patient should be removed in the receiving ward. This should be sterilized by steam and placed in a store-room. The patient should not be allowed to take any of his belongings to the ward. The hair of the head, axillary and pubic region is then cropped with a hair clipper, the hair being carefully collected and burned. The patient is then bathed with warm water and soap, given clean pajamas and removed to the ward. Patients can be rapidly handled if the receiving ward is divided into a receiving-room, barber shop, bath-room, drying-room and examining-room, and the patient is made to pass through in that order. In this manner the patient arrives before the doctor in a clean condition. The wards of a typhus hospital will remain vermin-free only if such a procedure is carried out.

Daily vermin examinations should be made on all patients. All attendants in the wards and receiving department, and all doctors and nurses, should wear the louse-proof suit. This consists of a one-piece garment made of heavy muslin which goes over and covers the shoes, and is tied about the neck. Cotton gloves are sewed on the sleeves. Nurses should wear the same garment, with a skirt worn over it. A sterilized garment should be worn whenever a ward is entered. When the doctor leaves the hospital the garment is removed by an attendant, who places it into a bag and sterilizes it. A shower and clothes closet should be provided near the exit of the ward, where attendants may change. If possible typhus immunes should be employed in the hospital.

Visitors should not be allowed to enter the wards of the hospital. In typhus-stricken countries the hospital attendants are a source of great danger. They usually come from the peasant class, and their habits of cleanliness are generally bad. They should be taught the value of cleanliness, supplied with proper living quarters and repeatedly inspected for vermin. They should not be allowed to leave, as they may bring infestation back into the hospital.

The room from which the patient is removed should be carefully cleaned, and closed for two weeks. It may be **fumigated** with **hydrocyanic acid gas.** All sterilizable material should be disinfected. Carriages and wagons which are used to convey patients to the hospital should be carefully cleaned daily. When patients are carried on trains these should be carefully cleaned. During an epidemic all plush-seated cars should be removed and only cars without upholstery or European third class cars employed. Lice may fall into the crevices of plush seats and are difficult to remove.

All contacts should be isolated fourteen days, in a separate building or camp, being carefully deloused before entering. They should be

directed to examine their clothing daily for lice and should be inspected for vermin by doctors or trained assistants daily. The temperature should be recorded twice daily, and daily inspection made to detect the first symptom of the disease.

An educational campaign should be carried on by lectures in schools, public squares and churches, and by issuing pamphlets on the nature and spread of the disease.

In order that typhus fever may be properly handled in a community, rigid rules and a certain definite procedure must be put into effect. As typhus fever is usually associated with poverty and distress, clothing and food should be supplied the stricken people.

The fact should be kept constantly in mind that the louse is necessary for the spread of typhus fever, just as the mosquito is for the spread of malaria, and our efforts toward prophylaxis should be conducted with this point continuously in mind. Even with the knowledge of the mode of transmission of typhus fever, individual prophylaxis is still somewhat difficult, especially where infected insects abound in thickly populated centers.

For that reason it is recommended that those exposed to the disease should be **vaccinated** with the **polyvalent vaccine** prepared from cultures of the *Bacillus typhi-exanthematici*. The results of studies carried on in the Balkans in 1915-1916, in which over 8,000 people were inoculated with this vaccine, indicate that the reaction is mild, and that some definite immunity is produced. Of this number inoculated only six contracted the disease, although all those inoculated were exposed to typhus fever. Caldwell, the associate director of the American Red Cross Commission to Serbia, during the typhus epidemic of 1915, and director of prison camp conditions in Germany, reports the following regarding the value of the typhus vaccine: "Of the 200 or 300 people not immune to typhus, who found it necessary to go to this part of Europe (Serbia) during the epidemic, all of whom were inoculated with the Plotz vaccine, among which numbers were all the members of the American Red Cross Sanitary Commission with but one exception, and the members of the mission which Columbia University sent to Serbia, and many others who were exposed at some time or another to greater or less degree to the infection, not one case of typhus developed."

The occurrence of mild cases of endemic typhus fever (Brill's disease) in a community like New York does not call for such strict rules as is indicated for the epidemic cases. These cases occur only endemically and can be easily handled, and although usually only one member of a family comes down with it, it must be observed that there is an instance reported where four members of a family had the typical disease in New York City. It should be recognized, moreover, that this disease is typhus fever, and should therefore be quarantined.

General Management.—Treatment is purely symptomatic. **Rest in bed, fluid diet** and **forcing fluid** are the best treatment. **Bromids** or **morphin** may be given for the delirium. **Hydrotherapy** may be employed. Small doses of **digitalis** have been recommended. The essential

thing is **good nursing. Proper care of the mouth** is important. Salvarsan is of no use.

Nicoll and Blaizot have produced a **serum** by immunizing asses with the organs of guinea pigs infected with typhus. This serum has been employed on man and animals and favorable results are reported.

Prognosis.—The prognosis varies with the condition of nourishment, nature of the disease, and general constitution and age of the patient. The older the patient the more severe the prognosis. In patients above forty-five the prognosis is bad. Persons who have never before been infested with vermin apparently suffer more severely than those who have. The mortality in Americans, English and French serving in the Balkans was high. In epidemics the mortality varies from 10 to 80 per cent. Endemic typhus is mild, the mortality being less than 1 per cent.

Pathology.—Typhus fever is characterized by the absence of any definite pathological lesion. The organs show the usual changes that are found in any severe febrile disease. Braur describes a hyperplasia of the follicles in the spleen. Fraenkel describes a skin lesion which he regards as pathognomonic. It consists of a necrosis and proliferation of the endothelial cells of the small arteries and a perivascular infiltration of small round cells. Paultof and others have confirmed this observation. In the Austrian army, in 1916, the diagnosis of typhus fever was often made by finding the typical skin lesion.

Geographical Distribution.—Typhus fever was exceedingly prevalent throughout Europe in former times, but owing to the improvement in sanitary conditions it has become confined to certain endemic areas. Typhus is a disease of cool and temperate climates. It has been found in Europe, Africa, Asia, India and America. The common endemic centers in Europe are Galicia, Russia, Poland, Ireland, Serbia, Bulgaria, Albania, Montenegro, Greece, Roumania and Turkey. The disease is also found in Italy, Scotland, Spain, Bohemia, Austria and Hungary. In Africa it has been recorded from Morocco, Algeria, Tunis, Tripoli and Egypt. In Asia, from Armenia, Persia, Asia Minor, Mesopotamia, Northern China, Korea and Japan. In America, from Canada, the United States, Mexico, Peru, Chili, Brazil, Bolivia, Nicaragua and Argentina.

The following table compiled by Nuttall, from Low, shows the centers where typhus occurs most frequently. The decrease in the number of cases in succeeding years was, no doubt, due to the diminution in the number of vermin-infested persons, and a better standard of living.

England and Wales...	1869-83 (15 yrs.)	1884-98 (15 yrs.)	1899-1913 (15 yrs.)		
	23,702	2,249	390		
Scotland	1865-74 (10 yrs.)	1875-84 (10 yrs.)	1885-94 (10 yrs.)	1895-1904 (10 yrs.)	1905-14 (10 yrs.)
	5,547	2,693	818	308	147
Ireland	1869-83 (15 yrs.)	1884-98 (15 yrs.)	1899-1913 (15 yrs.)		
	11,544	4,703	1,043		

Italy	1887-1900	1901-14	
	(14 yrs.)	(14 yrs.)	
	13,909	1,514	
Galicia	1895-1904	1905-12	
	(10 yrs.)	(8 yrs. only)	
	5,592	2,181	
Germany	1886-95	1896-1905	1906-10
	(10 yrs.)	(10 yrs.)	(5 yrs. only)
	302	81	19
Russian Empire	1905-11		
	(7 yrs.)		

European Russia	45,533
Poland	1,126
The Caucasus	1,546
Siberia	681
Rest of Asiatic Russia	327
Total	49,213

Mexico City	1893-1913
	(21 yrs.)
	14,758

History.—The history of typhus fever is recorded during periods of famine, misery, filth, overcrowding and wars. Typhus fever is a disease of great antiquity and was no doubt one of the diseases to which frequent allusion is made in the Bible under the term "pestilence." The history of this disease has been carefully treated by Murchison and Hirsch.

Some of the cases reported by Hippocrates in his book on epidemics are suggestive of typhus. Fracastorius, in the sixteenth century, clearly described typhus fever under the term "febris pestilens." He describes a red eruption appearing on the arms, chest and back from the fourth to the seventh day. The spots resemble flea bites, but are somewhat larger. The most marked symptoms mentioned are great prostration, feeble pulse, infected conjunctivæ and low muttering delirium. The disease lasted from seven to fourteen days. Before the description of Fracastorius, and for some time afterwards, the disease was confounded with certain epidemic infectious diseases, especially plague. Thus, "the plague" which originated in Cyprus in 1525-28 and ravaged almost the whole of Italy was undoubtedly typhus fever. Hildenbrand believes that a number of other diseases designated as "the plague" (pest) in the sixteenth and seventeenth centuries were undoubtedly epidemics of typhus fever, as, for instance, the plague in Meissen, 1574, the plague in Denmark, 1613-1652, and the plague in Leyden in 1669.

Typhus fever usually follows in the wake of armies, and when it occurs it claims more victims than the casualties of war. In the siege of Granada in 1489 about 17,000 of Ferdinand's soldiers died of a fever

which was designated as "tabardillo," on account of the spots appearing on the skin. Morbus hungaricus appeared in the army of Maximillian II in Hungary in 1566 and then rapidly spread over the greater part of Europe.

The sixteenth century was marked by the prevalence of typhus fever in England. The disease was so common in jails that it spread from prisoners when they were brought for trial to court officers. These court sessions were designated "black assizes." Vaughn describes a notable instance which occurred at Oxford in 1577. "The prisoner was Rowland Jenks, a bookbinder and a Roman Catholic, who was charged with treason and profanity of the Protestant religion. He was sentenced to lose his ears. The trial was held at Oxford Castle, July 4. Several prisoners were brought into court in the course of the trial. The chronicle states that an infectious damp of breath spread through the room. Above 600 sickened in one night; and the day after, the infectious air being carried into the next village, sickened there more than an hundred more. By the twelfth of August 510 persons perished. The infection arose from the nasty and pestilential smell of the prisoners, when they came out of the jail, two or three of whom had died a few days before the assize began."

The whole of central Europe was desolated by war, famine and pestilence during the Thirty Years' War (1619-1648). In 1658, Morton states that England was one vast hospital filled with victims of this fever. The great plague of London (1665) was preceded, accompanied and followed by typhus fever. The eighteenth century was characterized by numerous epidemics. Ireland was particularly afflicted with the disease. Each new outbreak was associated with famine and great want. From 1740-1741, 80,000 Irish died of famine and spotted fever and one-fifth the population of Munster perished. Hirsch divides the eighteenth century into four periods. The first joins on to the war pestilence which occurred in Germany, Austria and Hungary at the end of the previous century and extends to about 1720. During this period three severe epidemics occurred in Ireland, (1) 1708-1710, (2) 1718-1721, and (3) 1728-1731, the last two having affected a large part of England and Scotland as well. During the second period (1734-1744) typhus was spread over a large part of eastern and central Europe. During the third period (1757-1775) we find typhus after the Seven Years' War, and again after the war between England and Spain. The fourth period occupies the last ten years. It begins with the revolutionary wars in France and ends in the second decade of the nineteenth century with the final retreat of the French army across the Rhine, the overthrow of the empire of Napoleon and the restoration of peace. Typhus fever was the terror of the Napoleonic campaigns and decimated the French army already demoralized physically and morally by the terrible retreat from Moscow. Prinzing estimates that from 200,000 to 300,000 persons succumbed to typhus fever in Germany during the years 1813-14, and that 2,000,000 contracted it.

After 1830 the disease abated on the European continent, while in

Ireland and England, where the disease has always been prevalent, it continued unabated, and occasionally broke out in extensive epidemics. From 1816 to 1818 the disease raged throughout England and Ireland. In Ireland alone one-eighth of the entire population was affected and in Dublin as many as one-third of the inhabitants were attacked. Over 40,000 deaths are recorded.

From 1826 to 1848 typhus epidemics appeared in Ireland and England with more or less severity. In 1846, the year of famine, an unusually severe epidemic broke out in Ireland, and was carried to England where it reached its highest point in 1847 and continued until the end of the following year. The last epidemic in England occurred in 1863-1864.

During the nineteenth century typhus fever made its appearance with various wars. During the Crimean War it attacked both the French and English armies. The Italian campaign of 1861 and the Turco-Russian War of 1878 contributed a number of victims; over 100,000 cases with a mortality of 50,000 are recorded.

Typhus fever became epidemic in Mexico soon after the conquest in 1530 and has continued in endemic forms with occasional epidemics to the present time. Epidemics are recorded for 1545, 1575 and 1736 when 192,000 are said to have died of this disease.

Typhus fever was introduced into the United States by Irish immigrants just after the famine in 1846. There was typhus fever in New York in 1850 and 1851. The last epidemic occurred in 1892 when eight of twelve doctors at Bellevue Hospital, New York, contracted this disease and died. In 1910 Brill described a disease of unknown etiology which he has observed in New York since 1896 and which has subsequently been shown to be a mild form of typhus fever. Anderson and Goldberger showed by cross immunity experiments that this disease was identical with Mexican typhus fever. These observers found that a monkey that had reacted with the virus of Mexican typhus fever was immune to the New York disease and vice versa. Plotz demonstrated that the organism isolated from endemic typhus fever (Brill's disease) and epidemic typhus fever was identical. Endemic typhus fever has now been reported in the United States from New York, Massachusetts, Pennsylvania, Maryland, Virginia, Georgia, Indiana, Illinois, Wisconsin, Minnesota, Washington, D. C., and California.

In modern times typhus fever has again made its appearance as a result of the Balkan Wars, and the World War. Following the second Balkan war typhus fever broke out in Serbia, Bulgaria and Greece. As a result of this epidemic nineteen cases were imported into New York by Greek immigrants, but were detected and quarantined. Since the onset of the World War it has been estimated that 1,000,000 persons have died of typhus fever. The Serbian epidemic claimed about 135,000 and the Roumanian, 200,000. At the present time it is impossible to obtain accurate statistics, but the disease has occurred in epidemic form in Russia, Poland, Germany, Austria, Hungary, Serbia, Bulgaria, Roumania, Greece, Turkey, Albania and Montenegro since the beginning

of the World War. The same conditions, namely, overcrowding, bad sanitary conditions and famine have been responsible for these epidemics as they were in the past.

Typhus fever was for many years confused with other epidemic diseases, and even as late as the early part of the nineteenth century typhoid and typhus fever were regarded as the same disease. Gerhard and Pennock, two Americans, definitely distinguished typhus fever from typhoid fever while studying an epidemic of typhus in Philadelphia in 1836. It is interesting to record the fact that although typhus fever has been extremely rare in the United States, many of the important clinical and experimental facts have been obtained by Americans. Among these may be mentioned the keen clinical observations of Gerhard and of Brill, and the scientific studies of Ricketts and Wilder, Anderson and Goldberger, and the work carried on at the Mount Sinai Hospital, New York.

This article would not be complete if some reference were not made to those martyrs of medical science who laid down their lives while studying this disease. The list affords a group of distinguished men in medicine. Tribute should be paid to that large group of physicians who knew the dangers to which they were exposed, and yet were willing to serve their fellowmen. Among the notable examples may be mentioned Moczukowski, Ricketts, Husk, Cornet, Prowazek, Jochmann, MacGruder and Donnelly.

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CHAPTER XXXVII

TYPHOID FEVER

By C. G. JENNINGS, M.D., AND P. F. MORSE, M.D.

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Definition.—Typhoid fever is an acute general infection caused by the invasion of the body tissues by the *Bacillus typhosus*. It is characterized, clinically, by a continued fever of peculiar type, a cutaneous eruption of small maculopapules, a specific enteritis, splenic enlargement and a toxemia with distinctive nervous phenomena; anatomically, by hyperplasia and ulceration of the intestinal lymph-follicles, hyperplasia of the mesenteric glands and spleen and by parenchymatous changes in the various organs of the body. Mutiplicity of symptoms and complications and variability in the clinical history are marked features of the disease.

ETIOLOGY

Prevalence.—Typhoid fever is widely distributed throughout all the countries of the world. It is the most common continued fever. It prevails with about the same frequency in cold as in warm climates. The thickly populated temperate regions have the highest morbidity.

There is a marked variation in the prevalence of the disease in the different countries of the temperate zone, and it may be fairly stated that the typhoid rate of any country is an index of the efficiency and observance of the laws of sanitation. The United States ranks high as an unsanitary country. In the registration area with a population of 71,621,632 the number of deaths from typhoid fever in 1916 was 9,510—a mortality rate of 13.3 per 100,000. On the basis of a case mortality of 10 per cent. there were 95,100 cases of the disease in the registration area in 1916. On the same basis Whipple estimated that there were 353,790 cases of typhoid fever in the whole United States in 1900. In Germany the death rate was 3 per 100,000 in 1912. In England and Wales it was 4.6 per 100,000. Of the other European countries only Spain and Italy show a higher mortality rate than the United States. It is gratifying to note, however, that the disease has been declining steadily in this country since 1906, undoubtedly as a result of an improved sanitary intelligence. The three five-year periods from 1901 to 1915 show a mortality respectively of 32.0, 25.6 and 16.6 per 100,000. The declining rate is graphically shown in Fig. 1.

Typhoid fever is endemic in many districts, especially in cities taking their waters from lakes and rivers constantly polluted by their own sewage or by that of neighboring towns. A continuous high typhoid rate has been the rule in cities situated on the Great Lakes and on the

large rivers of this country. Occasionally in these cities the disease has assumed epidemic proportions. In Chicago, in one year—from April 1, 1891, to April 1, 1892—there were 2,372 deaths from typhoid fever, representing approximately 24,000 cases. In Cleveland, in January, 1903, the disease suddenly increased in prevalence, and during the following sixteen months there were 4,578 cases and 611 deaths.

Many small cities, usually free from typhoid, have had outbreaks of great intensity and short duration due to unusual conditions which caused temporary contamination of their water supplies. An epidemic occurred in the spring of 1885 at Plymouth, Pa., a mining

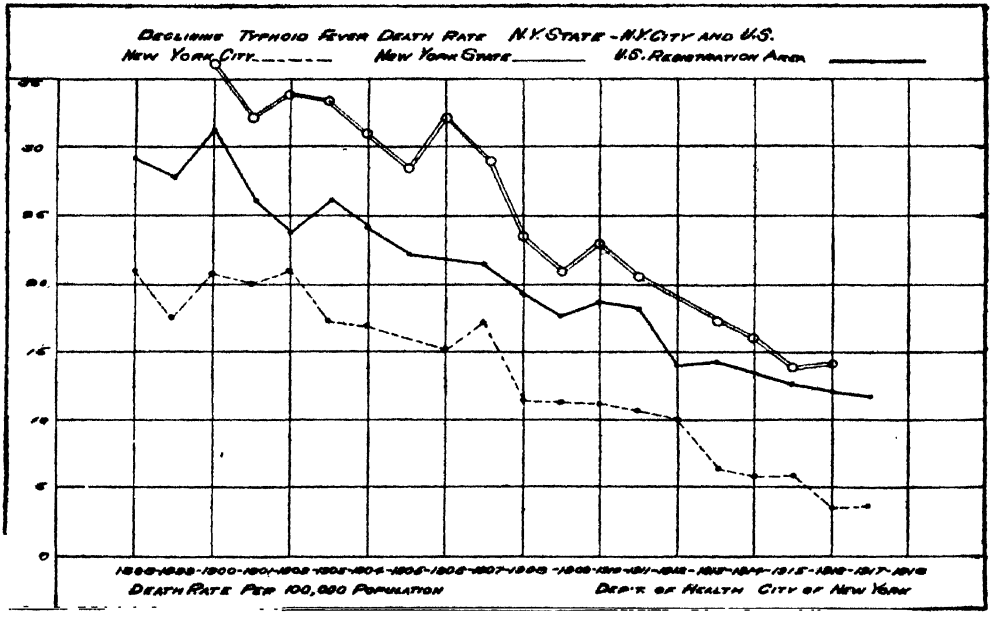


Fig. 1.—Declining Typhoid Fever Death Rate in New York City, New York State and the United States.

town of about 8,000 inhabitants. There were 1,104 cases reported and 114 deaths. The outbreak was caused by the careless disposal of the excreta of a single typhoid patient living in an isolated house on the bank of one of the tributaries to the impounding reservoirs of the water supply of the town. The excreta were thrown on the frozen ground, and were washed into the stream with the first rains of spring.

Such dramatic outbreaks have occurred in many cities; they have fixed the attention of the public upon the dangers of sewage-polluted water, and have hastened the improvement of public water supplies throughout the country.

The special article on typhoid fever in the large cities of the United States, published annually since 1913 in *The Journal of the American Medical Association*, has revealed the sanitary status of the various

cities, and has done much to stimulate health authorities to search out and eradicate the causes of excessive typhoid morbidity.

Occurrence of Typhoid Fever in Armies.—Until the recent great war, typhoid fever was the greatest scourge of armies in the field. In the American Civil War there were 75,368 cases of typhoid fever, with 27,056 deaths, in a field army numbering 431,237 men. The report of the Spanish American War Commission shows that with 107,973 soldiers in the national encampments there were 20,738 cases of typhoid fever, with 1,580 deaths. The British Army in the South African War numbered 557,653 officers and men. There were 57,684 cases of enteric fever during the war, with 8,225 deaths.

The Japanese Army was the first to profit by the knowledge of modern sanitation in the prevention of typhoid fever. In the Russo-Japanese war, where the forces were approximately equal, there were but 5,474 cases of typhoid fever in the Japanese Army as against 21,309 cases in the Russian Army.

Complete data are not yet available for the armies engaged in the recent war. In the American Army, from September 1, 1917, to May 2, 1919, with an average strength of aproximately 2,121,396 men, there were reported only 1,901 cases of typhoid fever, with 213 deaths. In the American cantonments typhoid fever was almost unknown. In twelve of the fifteen camps, not a single case occurred during the six months from September 29, 1917, to March 29, 1918. Camp sanitation, supervision of the water supply and—most important—antityphoid vaccination, practically banished typhoid fever from the camps.

Predisposing Causes

Climate and Altitude.—Climate and altitude have no direct influence upon the typhoid rate. Given the conditions for the easy conveyance of the bacilli from the sick to the well, typhoid fever will prevail regardless of temperature, humidity or other climatic conditions.

Season.—The seasonal occurrence of typhoid fever has been recognized from the time of Hippocrates—hence the synonym "Autumnal fever." The seasonal curve of prevalence in the United States as plotted by the census bureau in 1900 shows a wave with its lowest point about the middle of June. The line rises slowly in the latter half of June, rapidly in July and August, more slowly in September, reaching its crest in October. Then it falls with about equal rapidity, reaching a low point in February. In March there is a secondary low wave and there is another in May. Striking local variations from this typical curve are frequent. The secondary waves of March and May are coincident with the increased surface water contamination of water supplies during the heavy rains of spring. Epidemics from water pollution may cause secondary waves in any month. The adoption of filtration strikingly reduces the height of the secondary waves of winter and spring.

The causes of the summer epidemic are complex. Heat favors the growth of the typhoid bacillus outside the body. This is probably a

minor factor. The fly-pest and the increased possibilities of infection by water and food are the best explanations.

Soil.—In rural districts soil polluted with human excrement may be a medium of infection. The latter may be direct, conveyed by dust, flies or vegetables, or indirect, by infection of the drinking-water.

Typhoid bacilli multiply in the soil only under unusual conditions. They live in soil under ordinary conditions only two or three weeks. In frozen ground they may retain their virulence several months.

Heredity.—There is no satisfactory evidence that susceptibility to typhoid fever is inherited. Several members of a family occupying the same house may contract the disease, but it is quite certain that contagion or a common source of infection, and not hereditary susceptibility, is the predisposing cause.

Personal Conditions.—Individual susceptibility to typhoid fever varies. Of a number of persons exposed, presumably to the same degree, a certain number will escape infection. In an instance under the author's observation, a group of about 200 workmen drank water from a supply accidentally taken directly from the Detroit river, at a point where it is highly polluted with city sewage. Of the number, 156 developed gastro-enteritis within a few days after the incident. Typhoid fever developed in 56 of this group.

There is some evidence that individual immunity may be acquired by repeated infection with small doses of the bacilli which have been overcome by the defensive mechanism of the tissues without producing a frank attack of typhoid fever—an accidental vaccination. This effect of constant association with infectious diseases is seen among physicians and nurses. The most important factor, however, in the production of individual immunity to typhoid fever is antityphoid vaccination or a previous attack of the disease.

Active, robust health is no protection against infection; in fact strong, well-nourished men show a decided susceptibility. In a community, an army or any group of men the strongest and healthiest seem to offer the least resistance to the disease, while those debilitated and exhausted by chronic disease or other acute infections show a relative immunity.

Social Conditions.—Typhoid fever attacks without discrimination the high in rank and the lowly. Filth and overcrowding increase the liability to the disease only when they increase the opportunity for infection. London with its slums has a lower typhoid fever morbidity than the rural communities of the United States.

In the registration states of this country the death rate from typhoid in 1916 was 24.5 in the cities, and in the rural districts 25.4 per 100,000 of the population. Figures from other countries show a similar higher rural prevalence. In cities severe epidemics or localized outbreaks occur at intervals, due to contamination of the general water supply or to milk infection. In small communities scattered cases are continually present the annual total of which exceeds that of the more dramatic outbreaks that attract attention by short-lived virulence. Fulton found that

the death rate increased from 25 per 100,000 in states with an urban population of 60 per cent. or over, to 67 per 100,000 in states with an urban population of 10 per cent. or less. Good water, efficient sewerage systems, well-administered regulations for milk- and food-inspection and a higher general sanitary intelligence help to safeguard the city dwellers.

Newcomers in a district where typhoid is endemic show a greater susceptibility than do the older residents. Both Louis and Chomel observed typhoid more frequently among the new residents of Paris. Of 221 cases cited by these authors 149, or 67 per cent., had lived in the city less than twenty months, and only 6 had lived there from infancy.

Occupation.—Occupation predisposes to typhoid fever only when it increases the chances of exposure to infection. Physicians, hospital attendants, laundresses and soldiers are particularly exposed. However, antityphoid vaccination for persons liable to exposure because of occupation has quite changed this state of affairs. As noted elsewhere the vaccinated soldier is now safer from infection than the unvaccinated civilian.

Sex.—The influence of sex as a predisposing cause seems to vary under different conditions and in different epidemics. In some outbreaks males predominate and in others females. In the typhoid of children boys are in a decided majority. They are more exposed than girls in many ways. The swimming hole is a fruitful source of infection. Men, by occupation and habits, are more exposed than women. In an environment with equal exposure for both sexes it is probable that the difference in susceptibility would be insignificant.

Age.—Typhoid fever is preëminently a disease of youth and early adult life. Approximately from 70 to 75 per cent. of the cases occur in persons between the ages of fifteen and thirty years; about 12 per cent. before the fifteenth and about 18 per cent. after the thirtieth year. Infants under the age of two years are relatively immune, and the disease is quite exceptional after the age of forty years. In children mild cases are very frequent and, as shown by the studies of Koch and his associates, they are not often differentiated from other febrile disorders and do not figure in hospital statistics. It is not improbable that if the mild cases were included the relative incidence in childhood would prove to be considerably higher than is usually stated.

Race.—The question of race immunity is not settled. There is some evidence that the Japanese and Arabs are relatively insusceptible. The practically universal prevalence of typhoid fever makes it more probable that local conditions rather than racial insusceptibility accounts for the low morbidity among these races. The low rate in the Japanese army as compared with the Russian army in the Russo-Japanese War can be accounted for by the more efficient sanitation in the former. Japanese officers knew the value of pure water, the importance of the efficient disposal of excreta and the danger from flies. They put their knowledge into practice and the orders of the medical officers were rigidly enforced.

In the southern states there is a much higher percentage of typhoid fever among the negro population. Bad sanitation among the blacks is

the probable reason, as the difference disappears with general sanitary improvement in the southern communities.

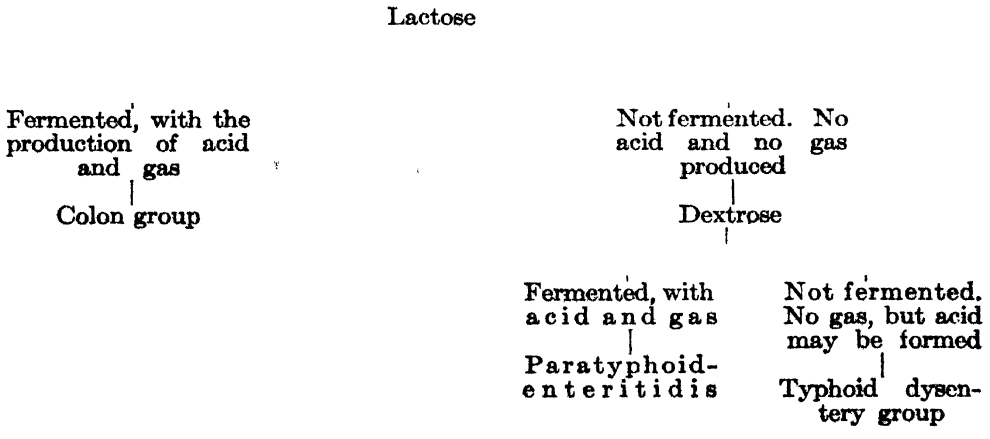
Exciting Cause

Bacteriology: The Colon-typhoid Group of Organisms.—The typhoid bacillus was first described in the tissues postmortem by Klebs, Eberth and Koch in 1880. Pure cultures were obtained by Gaffky in 1884. At this time nothing was known of the large group of bacilli which we now call the colon-typhoid group and which at the present time includes some twenty-odd varieties. Indeed it was not until 1886 that Escherich discovered the colon bacillus, the most important member of the group, considering its wide distribution. At the present time any discussion of the typhoid bacillus either from a biological or medical standpoint must include many other closely related organisms.

Within the colon-typhoid group of bacilli there are three sub-groups more or less sharply differentiated on cultural grounds. Within each sub-group the main types can often be separated by cultural studies, but cultural characters do not suffice to differentiate many individual members, and the agglutination reactions, especially absorption tests, must be resorted to.

In general it may be said that a rod-like organism, either motile or non-motile, which does not form spores, which loses its stain by Gram's method and does not liquefy gelatin, belongs to the colon-typhoid group. Beyond this point the three main sub-groups are differentiated upon their reactions toward two carbohydrates, lactose and dextrose.

Lactose is fermented, with the production of acid and gas, by members of the colon group, while members of the paratyphoid-enteritidis group and members of the typhoid-dysentery group leave lactose unaffected. The paratyphoid-enteritidis group is further distinguished from the typhoid-dysentery group by the ability of the former to produce gas from dextrose. This relationship is made clear by this diagram.



The importance of establishing the identity of any member of the colon-typhoid group of bacilli lies in the fact that some of these organisms cause human disease, a considerable number cause disease in animals or both in animals and in man, and all pathogenic members of the colon-typhoid group, whether from men or animals, are intestinal in origin. It is evident therefore that when the practical problem arises of isolating one of these bacilli from any source whatever a complete differentiation from all other members of the group must be made. Considering the widespread distribution of colon bacilli and the importance of fecal contamination of water and food sources by members of the colon-typhoid group, the practical worker must necessarily exclude all the bacilli of this group whenever he identifies the typhoid bacillus and makes a diagnosis of typhoid fever. The examination of water and food supplies is an important phase of the typhoid problem, tending toward prevention. The colon bacilli found in water supplies may be largely differentiated as to whether or not they are of sewage origin. The important members of the colon-typhoid group are as follows:

COLON-TYPHOID GROUP

Colon Group	Paratyphoid-enteritidis Group	Typhoid-dysentery Group
1. *Bacillus aërogenes*	1. *Bacillus enteritidis* (Gärtner's)	1. *Bacillus typhosus*
2. *Bacillus coli communior*	2. *Bacillus Paratyphosus B*	2. *Bacillus dysenteriæ*
3. *Bacillus coli communis*	3. *Bacillus suipestifer* ("Hog cholera")	(*a*) Shiga
4. *Bacillus acidi lactici*	4. *Bacillus paratyphosus A*	(*b*) Strong
	5. *Bacillus abortus equinus*	(*c*) Park-His
	6. *Bacillus icteroides*	(*d*) Flexner
	7. *Bacillus Psittacosis*	3. *Bacillus Fœcalis Alcaligenes*
	8. *Bacillus typhi murium*	
	9. *Bacillus pullorum*	
	10. *Bacillus sanguinarium*	
	11. *Bacillus danysz*	

In spite of the large number of bacteria in the colon-typhoid group the carbohydrate reactions mentioned above immediately place any particular organism belonging to it in one or the other of the three subdivisions. The first subdivision, viz., the colon sub-group, are comparatively rarely pathogenic and do not cause clinical conditions of a typhoid type. The colon bacillus may at times be a primary invader in local inflammatory conditions of the intestines, such as appendicitis, but even then it is more often present as a secondary invader and not as the primary cause. Therefore, from such a source as blood, urine or feces,

the lactose fermenters are immediately disregarded as causes of disease, and the methods used for isolation of the causative organism in typhoid and paratyphoid fevers are based fundamentally upon this fact.

If we find then from suspected material that bacteria belonging to the colon-typhoid group fail to ferment lactose we have ruled out the colon sub-group and may proceed to the differentiation of the other two, namely the paratyphoid-enteritidis group and the typhoid-dysentery group. This is accomplished by planting of non-lactose fermenting colonies into a medium containing dextrose. Members of the paratyphoid-enteritidis group produce gas from dextrose, while those of the typhoid-dysentery group do not. If we find that we have a gas-producer in dextrose-containing media our problem is now to differentiate between the individuals of the paratyphoid-enteritidis group. If no gas is produced in dextrose media we have a member of the typhoid-dysentery group of organisms to deal with. The latter case is a simple one. Members of the typhoid-dysentery group are easily separated by noting the presence or absence of motility and a few simple biological characters. The members of the paratyphoid-enteritidis group, however, are much more difficult to separate from each other on cultural grounds, and agglutination and absorption tests must be resorted to.

The most important disease-producing organisms of the paratyphoid-enteritidis group are *Bacillus paratyphosus A* and *Bacillus paratyphosus B*. Epidemics of meat-poisoning have occurred from infection with *Bacillus enteritidis* (Gärtner) and with *Bacillus suipestifer* (hog-cholera). Further, at least one epidemic from infection with *Bacillus psittacosis* from diseased parrots has been reported, and we are not certain that even the *Bacillus danysz* (rat virus) and *Bacillus typhi murium* (mouse-typhoid) are altogether non-pathogenic for man. More than this, our knowledge of the bacteriology of this group is still very unsettled and no general agreement has been reached concerning the individuality of some of its members. Some workers deny the identity of such organisms as *Bacillus typhi murium, Bacillus danysz's, Bacillus psittacosis* and *Bacillus icteroides* as separate individuals, but claim that cultures so designated in the past have been impure mixtures of one or more members of the group or have been identical (proved by agglutination and absorption tests) with either *Bacillus enteritidis, Bacillus suipestifer,* or *Bacillus paratyphosus B*. There is quite general agreement that *Bacillus enteritidis, Bacillus suipestifer,* and *Bacillus paratyphosus B* are separate species, giving rise to specific agglutinins and that each can be separated from the others by absorption tests. The separation of these three, especially *Bacillus enteritidis* and *Bacillus paratyphosus B,* from each other has not been accomplished on cultural grounds alone.

The three organisms of the colon-typhoid group with which we are most concerned are *Bacillus typhosus, Bacillus paratyphosus B* and *Bacillus paratyphosus A* in the order of their frequency. However, it

should not be overlooked that *Bacillus suipestifer* and possibly *Bacillus enteritidis* may cause typhoid-like infections in man, although this seems to be very uncommon, especially in the United States.

THE BACILLUS TYPHOSUS.—The typhoid bacillus (*Bacillus typhosus*) is the sole cause of typhoid fever. Closely allied but usually milder clinical conditions are caused by the paratyphoid bacilli. The proofs that the typhoid bacillus is the causative organism of typhoid fever may be summed up as follows:

(1) The bacillus is isolated in pure culture during life from the blood, urine, feces and rose spots, and after death from the spleen, lymph-nodes and bone-marrow of cases of typhoid fever.

(2) The typhoid bacillus is not found in persons sick of other diseases and is not found in the blood or excreta of normal persons except in the stools of rare so-called normal carriers who are not known to have had typhoid fever but who transmit the disease to others.

(3) The typhoid bacillus, when injected into anthropoid apes, or when taken by accident or with suicidal intent by man, produces a typical attack of typhoid fever.

(4) The blood of a patient sick with typhoid fever acquires the property of agglutinating the typhoid bacillus in high dilution. The sera of patients sick with other diseases do not possess this property.

(5) Lastly, the experiments of Metschnikoff and Besredka have shown that it is the typhoid bacillus itself and not an adherent filterable virus which is responsible for the disease.

Bacillus typhosus is a short, plump rod, from 1 to 3 microns long and from 0.6 to 0.7 micron broad. Under various conditions of growth it may vary from short coccus-like forms to long filamentous chains, and under unfavorable conditions may become vacuolated and show many involution forms and pseudo-spore formation. True spores are not formed. The organism is actively motile and possesses from eight to twelve or more peritrichous flagellæ, usually from 6 to 8 microns long but often much longer. The flagellæ are stained with difficulty, because of the ease with which they break off from the cell under the conditions necessary for preparing and fixing the cover-glass film preparatory to staining. The bacillus is imbedded in a delicate matrix or capsule, to which the flagellæ appear to be attached. Gram's stain is not retained. Except for its greater motility, which may vary within wide limits, there is no optical character distinguishing the typhoid bacillus from other members of the group. The number and arrangement of the flagellæ, while usually different from that of *Bacillus coli*, is inconstant, and the difficulty of staining the flagellæ so great as to make this procedure useless in clinical laboratory work.

A. *Growth on Ordinary Media.*—The typhoid bacillus is a facultative aërobe growing at ordinary room temperature as well as in the incubator. On ordinary media it has no distinctive cultural characters, which serve to differentiate it from other bacilli of the colon-typhoid group. In *bouillon*, a diffuse cloudiness, with the development of a

watered-silk appearance, develops. There is usually no pellicle formed on the surface of the bouillon, but the culture soon flocculates and an abundant sediment settles to the bottom of the tube. *Bacillus typhosus* does not liquefy *gelatin*. In stab and stroke cultures the appearance is not characteristic. The growth is rather scanty and does not increase after the first week. Surface colonies on gelatin plates, when examined with a lens, present a rather characteristic appearance. They are about the size of a pin's head, after two days' growth, and are thin and transparent, with an opalescent shine. The edges are indented and sinuous, with ridges extending from the indentations to the center, giving the colony a wrinkled appearance. The center is thicker than the periphery and the picture presented has often been compared to an iceberg.

On *agar* a copious, moist, white streak develops which is in no way distinctive.

On *potato* the typhoid bacillus usually develops as a transparent, almost invisible streak. This was formerly an important differential point distinguishing *Bacillus typhosus* from *Bacillus coli*. The latter organism produces a prominent, brownish or yellowish growth on potato. Occasionally the typhoid bacillus grows on potato like *Bacillus coli*, especially if the potato surface is too alkaline. The growth of *Bacillus typhosus* on potato is no longer resorted to in practical clinical laboratory work for identification, although special media like that of Remy and Suggs have been devised to utilize this characteristic. On these media typhoid and colon bacilli are said to be uniformly differentiated.

In *milk* the typhoid bacillus grows abundantly without coagulating the medium and usually produces slight permanent acidity.

The *Bacillus typhosus* is identified by its various biochemical reactions, which may be discussed under the following heads:

1. Action of carbohydrates.
2. Non-production of indol.
3. Action on basic lead acetate.
4. Influence of various dyes.
5. Agglutination with artificially prepared anti-typhoid serum.

B. *Methods of Identification.*—(1) *Action on Carbohydrates.*—*Bacillus typhosus* does not produce gas from any carbohydrate. Acid is formed in media containing dextrose, levulose, galactose, mannite and dextrin. No acid is formed in media containing lactose, saccharose or dulcite, but in dulcite acid may appear after several weeks. The inability to produce gas from dextrose is the usual character which serves to differentiate *Bacillus typhosus* from the paratyphoid-enteritidis group. A more fundamental and constant character would seem to be the inability of *Bacillus typhosus* to ferment rhamnose, since the *Bacillus sanguinarium* of the paratyphoid-enteritidis group also fails to produce gas from glucose. For practical purposes, working with strains of known human source, the gas production from glucose is a safe character for the differentiation of the bacilli of the paratyphoid-enteritidis group from the typhoid-dysentery bacilli. The *Bacillus*

paratyphosus A was thought to be characterized by its ability to produce permanent acidity in litmus milk without coagulation until Jordan showed that this phenomenon was only quantitative, due to the slower multiplication of para A bacilli. After several weeks the growth of para A cannot be distinguished from para B on milk. Krumwiede has shown that para A differs from all other members of the paratyphoid-enteritidis group in its failure to ferment xylose. The action of the colon-typhoid group on milk has always been of importance. Milk contains coagulable proteins which may be either coagulated or digested by various organisms, and also contains lactose in considerable concentration, besides a trace of glucose. Those bacteria which ferment lactose vigorously, quickly coagulate the milk and produce abundant acid. This reaction is manifested by the colon group. Temporary acidity from the small amount of dextrose present is produced by the paratyphoids and by the *Bacillus typhosus*. These bacteria do not coagulate the milk. In the case of para A the slow growth of the culture produces an acidity which lasts usually several days and is of value as a differential character, although Jordan showed that this is inconstant and temporary rather than permanent, as was formerly believed. *Bacillus paratyphosus B* produces a clearing, with a brownish staining of the fluid within a few days. *Bacillus typhosus* leaves the medium slightly acid or permanently unchanged.

(2) *Indol Production.*—When certain bacteria are grown for from four to six days in peptone water (H_2O 1,000 c.c., peptone 10 grams, NaCl 5 grams), indol. is produced. There are two common methods of testing for its presence in cultures.

Salkowski's Method: To the culture add several drops of concentrated sulphuric acid or 1 c.c. of a 10 per cent. solution, and then overlay with 1 c.c. of 1-10,000 sodium sulphite solution. A pink color develops at the zone of contact which diffuses throughout on shaking.

Ehrlich's Method: This test has proven more reliable. Overlay the culture with 1 c.c. of a 2 per cent. solution of paradimethylaminobenzaldehyd in 95 per cent. alcohol and then add drop by drop concentrated hydrochloric acid until a red zone appears at the point of contact between the culture and the alcohol benzaldehyd reagent. The color may be shaken out with chloroform.

Colon bacilli produce indol. The paratyphoid-enteritidis and typhoid-dysentery bacilli produce no indol. Indol production is no longer of much importance in the practical work incident to the differentiation of strains from human sources. Other methods serve to quickly demarcate the colon bacilli, and indol production may take several days.

(3) *Action on Lead Acetate.*—Jordan and Victorson, following a suggestion of Orlowski and others, showed that members of the colon-typhoid group acted characteristically toward lead acetate when it was incorporated in culture media. Kligler added basic lead acetate to the modified Russell's medium, thus giving us probably the most useful

means we now possess for quickly identifying a particular member of the colon-typhoid group.

Bacillus typhosus and *Bacillus paratyphosus B* give rise to lead sulphid, which forms a black or brown stab in solid media containing lead acetate. *Bacillus coli, Bacillus paratyphosus A,* and *Bacillus dysenteriæ* produce no browning in lead acetate media. *Bacillus paratyphosus B* produces more prompt and extensive browning than *Bacillus typhosus.* This is a simple and valuable means of separating para A from para B types when correlated with xylose fermentation (negative in para A), gas production from dextrose (present in both), and growth on litmus milk.

(4) *Influence of Various Dyes.*—The colon-typhoid group show both group and individual differences in behavior toward various dyes. In general, Gram-positive bacteria, with the exception of the acid-fast group, tend to be inhibited by certain basic dyes like gentian violet. In the Conradi-Drigalski medium crystal violet was used to inhibit cocci and other organisms and to permit the development of colon-typhoids. Dyes are used in colon-typhoid media for three different purposes. The first is to inhibit the growth of certain organisms either outside the group or within it. The use of gentian violet, crystal violet and the like is based upon the principle mentioned above that members of the colon-typhoid group develop in the presence of these dyes while many organisms outside the group are inhibited. More specifically, malachite green in various combinations has been used to inhibit colon bacilli and to allow the development of the typhoids. Bile has been combined with malachite green for this purpose. A more useful dye for inhibiting colon and allowing typhoids to develop is brilliant green, used first in conjunction with picric acid by Conradi but now used alone in the Krumwiede, Pratt and McWilliams plates. Brilliant green may be used as an inhibiting substance in fluid enrichment media also. Paratyphoid bacilli are most resistant to brilliant green and will develop in concentrations which completely inhibit typhoid and dysentery. The optimum concentration of brilliant green for any particular medium and different samples of stool must be carefully determined, and this is usually accomplished by making several sowings from the same material in media containing brilliant green in amounts from 1-500,000 to 1-200,000. Kligler has added neutral red to Krumwiede's brilliant green medium to serve as an indicator of lactose fermenters that succeed in growing and has pointed out the importance of an optimum hydrogen-ion concentration in brilliant green media. Kligler advises that the brilliant green agar be adjusted to pH 7.0-7.2. Holt-Harris and Teague devised a medium containing methylene-blue and eosin which does not inhibit colon but serves to differentiate colon colonies very early by the black centers which they develop. Soon after this Teague and Clurman devised a brilliant-green-eosin plate which combines the advantages of the preceding with the inhibitory qualities of brilliant green. These writers showed also that when eosin was used much larger quantities of brilliant

green could be safely added to the medium without inhibiting the typhoid bacillus. They use a concentration of brilliant green of 1-30,000 in their medium, approximately ten times that of the usual optimum in Krumwiede, Pratt and McWilliams brilliant green agar. In this connection it might be mentioned that caffein has also been used to suppress colon bacilli while allowing free growth of typhoids, although this method has never found extensive use in practical work. Bierast uses petroleum ether (boiling-point 50° C.), which kills the colon bacilli and leaves the typhoids unaffected. The second use to which dyes are put in this connection is to indicate acid formation from various sugars. Andrade's indicator is very useful for this purpose. Basic fuchsin in Endo's medium is well known. Congo-red in lactose media gives colon colonies with blue-black centers, while other colonies are pinkish. Litmus has been very useful in the past, as for instance in Russell's double sugar agar, but on account of its variation in composition and its liability to reduction it has been largely replaced by Andrade's indicator. Methyl-red has been used by Levine in differentiating fecal strains of *Bacillus coli* from non-fecal members of the group, based upon the fact that broth cultures of most non-fecal strains remain alkaline to methyl-red. The eosin-methylene-blue plate of Holt-Harris and Teague differentiates colon colonies early by the development of black centers in them while the other bacteria remain pink. The third use to which dyes are put in colon-typhoid bacteriology is based upon the ability of members at the colon end of the series to reduce and decolorize certain dyes. Neutral red is eventually decolorized and rendered fluorescent by colon strains. Methyl-violet is not acted on by typhoid, but is completely decolorized by colon and partially by paratyphoid bacilli.

(5) *Agglutination.*—The colon-typhoid group of bacteria possesses the property of stimulating the production of agglutinins in the animal body to a high degree. When an animal is injected repeatedly with a pure, killed culture of a bacillus of the colon-typhoid group, the animal's blood serum is found after several injections to possess the property of agglutinating the bacillus used for the injections. This property is manifest even when high dilutions of serum are used. In like manner it was found by Gruber and Durham in 1896, and a few months later by Widal, that the blood serum of patients ill with typhoid fever also possessed this property. When an animal is injected with a particular organism, say the typhoid bacillus, its blood serum acquires the property of agglutinating the *Bacillus typhosus* in high dilution, but at the same time the ability is developed on the part of the serum to agglutinate other organisms of the colon-typhoid group. This property disappears as the serum is progressively diluted, until finally in the higher dilutions only the specific agglutinins for the *Bacillus typhosus* are present in sufficient quantities to effect agglutination. These agglutinins are called specific agglutinins, while those developed non-specifically for other members of the group are called group agglutinins. This phenomenon interfered with the usefulness of agglutinins for determining particular

species of bacteria until the absorption methods first used by Chantemesse were developed.

If an animal is immunized with an organism (A) for the development of agglutinins, the serum will also show more or less power to agglutinate other organisms of the groups (B), (C) and (D). If the serum is now saturated with organism (A) and centrifugated it will be found to have lost its effect on (B), (C) and (D). Thus, saturating with the specific organism removes not only the specific but the group agglutinins as well. On the other hand, if the serum is first saturated with (B), (C) and (D) and centrifugated, the specific agglutinins for (A) will be found to remain in the serum practically unimpaired. On this phenomenon is based the most exact method afforded by bacteriology for definitely detecting the identity of an organism. Without it, it is impossible to differentiate between the *Bacillus paratyphosus B* and *Bacillus enteritidis* of Gärtner. The separation of *Bacillus suipestifer* from these bacilli, while possible on cultural grounds, is rendered prompt and certain by this method. No organism of the colon-typhoid group, no matter what its source, should be said to belong definitely to a particular species for purposes of exact classification, unless agglutination and absorption observations are included in the investigation. For this purpose it is necessary to have on hand sera of animals which have been treated with each of the organisms of the group and whose agglutionation-titers, both specific and group, have been determined. If it then becomes necessary to determine whether a particular organism is *Bacillus typhosus* for instance, the following technic may be observed: Take a serum having a specific agglutinin for *Bacillus typhosus* and, after saturating it with *Bacillus typhosus,* one will find that the group agglutinins have disappeared. On the other hand, after saturating with other bacteria of the group, it is possible to show that the agglutinin for *Bacillus typhosus* is still present, very little impaired. This proves definitely that the organism that is being tested is the same as the one used for immunizing the animal. A table taken from Bainbridge will serve to illustrate this point:

Thus it is plain that the specific organism used to develop the serum

TABLE 1. AGGLUTINATION TEST (Bainbridge)

Serum	Agglutination Limit	
	Bacillus paratyphosus B	*Bacillus suipestifer*
Bacillus suipestifer Original titer	10,000	10,000
Absorbed with *Bacillus suipestifer*	100	100
Bacillus paratyphosus B	100	10,000

absorbs not only its own specific agglutinin but also the group agglutinins, while the other organism absorbs only its own group agglutinin, leaving the specific agglutinin unimpaired.

The earliest really useful methods for differentiating the typhoid from the colon bacillus in clinical material, especially in stools, were based upon the difference in the ability of colon and typhoid to ferment lactose. One widely used method was that of Conradi and Drigalski. A peptone-nutrose-agar is prepared as a base. Litmus-lactose solution is added to indicate the fermentation, and crystal violet to inhibit other organisms. This medium is then poured into large plates and allowed to harden with a fairly dry surface. The material to be investigated, such as a diluted emulsion of feces, is smeared over the surface with a glass rod. The colon colonies are red and opaque while the typhoid colonies are transparent and blue. This medium was later practically supplanted by the much more useful Endo's medium. This has the advantage of being an ordinary nutrient agar very easy to prepare. It contains 1 per cent. lactose, and instead of litmus for an indicator, basic fuchsin decolorized by sodium sulphite is used. On this medium the colon colonies are red and opaque and the typhoid colonies are transparent and colorless. As is apparent from an examination of the properties of the colon-typhoid group, Endo's medium will distinguish only the colon subdivision on the one hand from the paratyphoid-enteritidis and typhoid-dysentery groups on the other. Thus, a red colony on Endo is immediately eliminated, while a colorless colony may be typhoid or any other organism in the last two subdivisions. Given a colorless, transparent colony on Endo, further work must be done to identify any particular colony as one of *Bacillus typhosus*. The use of Endo's medium or of one similar in principle is, however, an indispensable preliminary in the isolation of *Bacillus typhosus* from contaminated material An examination of the diagram of the colon-typhoid group will make these points clear (*see* p. 458).

C. *Isolation of Typhoid Bacillus from the Feces.*—Endo's medium has been frequently modified, in order to make its preparation more simple and to make it more stable and more promptly sensitive to slight changes in acidity. In the authors' laboratory the most uniform results are obtained by following in the main the directions given by Kligler. Kligler pointed out that the ordinary Endo end-point (+ 0.2) was too alkaline, in that after the fuchsin sulphite solution was added in the usual quantity the hydrogen-ion concentration ranged from pH 8.6 to 8.8. Ordinary beef-extract-peptone-salt-agar stock is titrated to pH 7.4 and flasked in 100 c.c. quantities. At this hydrogen-ion concentration the medium is about neutral to Andrade's indicator.

When needed, a bottle containing about 100 c.c. of the stock is melted and adjusted to a pH of 7.8 to 8.0 by adding normal NaOH. Then 10 c.c. of sterile 10 per cent lactose solution is added. The fuchsin sulphite solution is made by decolorizing 1 c.c. of saturated alcoholic

basic fuchsin with 10 c.c. of 10 per cent. sodium bisulphite. One-half c.c. of this fuchsin bisulphite solution is added to each 100 c.c. of the melted agar, to which the lactose solution has been added. Plates are poured after mixing the lactose and the fuchsin-sulphite solutions thoroughly with melted agar, and are allowed to dry uncovered. They are planted within a few hours of their preparation.

Andrade's indicator is made by adding 16 c.c. of (N) NaOH to 0.5 gram of acid fuchsin dissolved in 100 c.c. of water. A substance is said to be neutral to Andrade's indicator when it is pink when hot and just colorless when cold. Andrade's indicator is a valuable means of detecting acid in cultures when added in 1 per cent. quantities to culture media, and it has practically replaced litmus for this purpose. Its disadvantages are that it possesses no color on the alkaline side and is not very sensitive to slight changes in acidity. Furthermore it is very slow in responding to the addition of acid. This latter property is not a disadvantage when it is used as an indicator in growing cultures, but prevents its use as an indicator in titrating media. In general it may be assumed that a medium neutral to Andrade's indicator has a pH of approximately 7.4. The best method of adjusting the reaction of culture media is that of Barnett and Chapman based on the work of Clark and Lubs. For the immediate purpose before us very little equipment is necessary for adjusting the media to be used in colon-typhoid investigations to an appropriate hydrogen-ion concentration.

These workers determine empirically the pH values of various stages in the color change of phenolsulphonephthalein from yellow to red. They set up two rows of six uniform test-tubes. In the front row each test-tube contains 5 c.c. of dilute (1 drop to 100 c.c.) HCl or H_2SO_4. In the rear row each tube contains 5 c.c. of dilute alkali (N/20 NaOH). In tube number one in the front row are placed 9 drops of phenolsulphonephthalein indicator 0.01 per cent. (prepared by taking 1 c.c. [16 minims] from an ampule used for the kidney functional test and diluting it to 60 c.c. with water). In successive tubes of the front row 1 drop less is added each time so that the front (acid) row contains 9, 8, 7, 6, 5 and 4 drops successively. In the back row, beginning with the tube behind number one of the acid row, 1 drop of indicator is placed, and 1 drop more in each succeeding tube of the alkaline series. Thus in any pair of tubes there is a total of 10 drops of indicator, and various shades of color from yellow to red are obtained by looking through the successive pairs of tubes from front to back. Barnett and Chapman determine the pH corresponding to these colors for phenolsulphonephthalein against standard phosphate solutions as shown in Table 2.

A corresponding series for any other indicator can be worked out at will by standardizing against phosphate solutions of known pH by the Clark and Lubs method. This has been done for brom-thymol-blue by the Committee on Descriptive Charts for the Society of American Bacteriologists, with the result that beginning with tube No. 1 the series

DETERMINATION OF HYDROGEN-ION CONCENTRATION FOR PHENOLSULPHONEPHTHALEIN AGAINST STANDARD PHOSPHATE SOLUTIONS

Acid Tubes Indicator Solution (Drops)	Alkaline Tubes Indicator (Drops)	pH
9	1	6.9
8	2	7.2
7	3	7.5
6	4	7.7
5	5	7.9
4	6	8.1

is found to have pH values of 6.2, 6.4, 6.7, 6.9, 7.1 and 7.3 respectively. This committee tested the original series of Barnett and Chapman and obtained values of 7.1, 7.3, 7.5, 7.7, 7.8 and 7.9 respectively. These values are well within the range required for most media reactions and the pairs of tubes are used in the comparator as shown below.

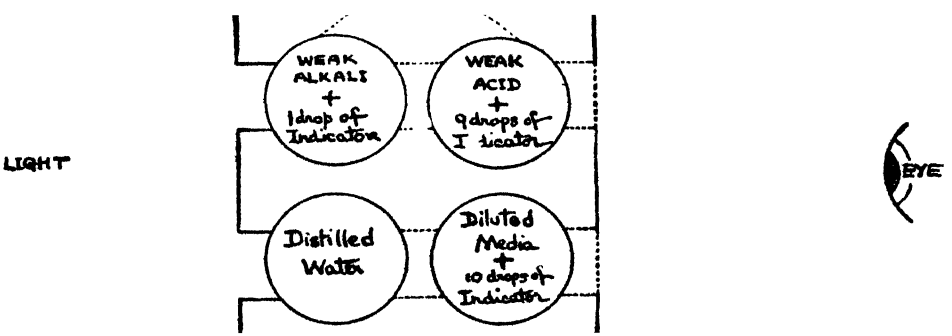


FIG. 2.—DIAGRAM SHOWING COMPARATOR FOR ADJUSTING HYDROGEN-ION CONCENTRATION MEDIA. (Looking down upon the instrument from above. 1.5 × actual size.)

A. Pair of test-tubes (1.25 × 6 cm.) with indicator in weak acid and alkali, giving a color corresponding to that developed by pH of 6.9-7.1.

Five cubic centimeters of media are placed in one of the small test-tubes of the comparator with ten drops of phenolsulphonephthalein indicator and compared with the pair of indicator tubes representing the desired hydrogen-ion concentration. It is noted whether the medium is too acid or too alkaline and the necessary adjustment made to bring the reaction to the desired point.

The surface of the Endo-plate is smeared with a loopful of diluted stool. The author makes a 1-10 and a 1-100 dilution of each stool and, starting at one edge of the plate, gradually works across the surface by making successive streaks. This gives discrete colonies over more than half of the plate. The plates are incubated for about eighteen hours and the suspicious colonies picked and transplanted to the Russell-Kligler medium described below.

Another important plating medium for isolating the colon-typhoid group from mixed material is the brilliant green agar of Krumwiede-Pratt and McWilliams. The authors use this medium as modified by Kligler as follows:

Kligler emphasized the importance of the proper hydrogen-ion concentration. Brilliant green has an optimum inhibiting effect at a pH of 7.0-7.2. Besides this, Kligler adds neutral red as an indicator of acid production and obtains red colon colonies of distinctive appearance, as on Endo's medium.

The medium is made as follows:

Liebig's extract of beef	3 grams
Witte's peptone (the author uses "Difco")	10 "
NaCl	5 "
Agar	15 "
H_2O	1,000 c.c.

The reaction of the medium is set at pH 7.0-7.2. To each 100 c.c. of melted agar, 1 per cent. lactose, 0.1 per cent. glucose and 0.25 c.c. of 1 per cent. H_2O solution of neutral red are added. The brilliant green is added from a 0.1 per cent. stock solution in quantities ranging from 0.1 to 0.3 c.c. to each 100 c.c. of agar. Usually it is best to prepare three plates containing 0.1, 0.2 and 0.3 c.c. of the brilliant green per 100 c.c. of agar. This is necessary because the optimum concentration of brilliant green varies somewhat for different batches of agar and also for different stool suspensions. Paratyphoid bacilli will grow in a higher concentration of brilliant green than will the other members of the group.

The material to be investigated is smeared upon the brilliant green plates in the same manner as upon Endo's medium, and suspicious colonies are transplanted after eighteen hours to the Russell-Kligler medium.

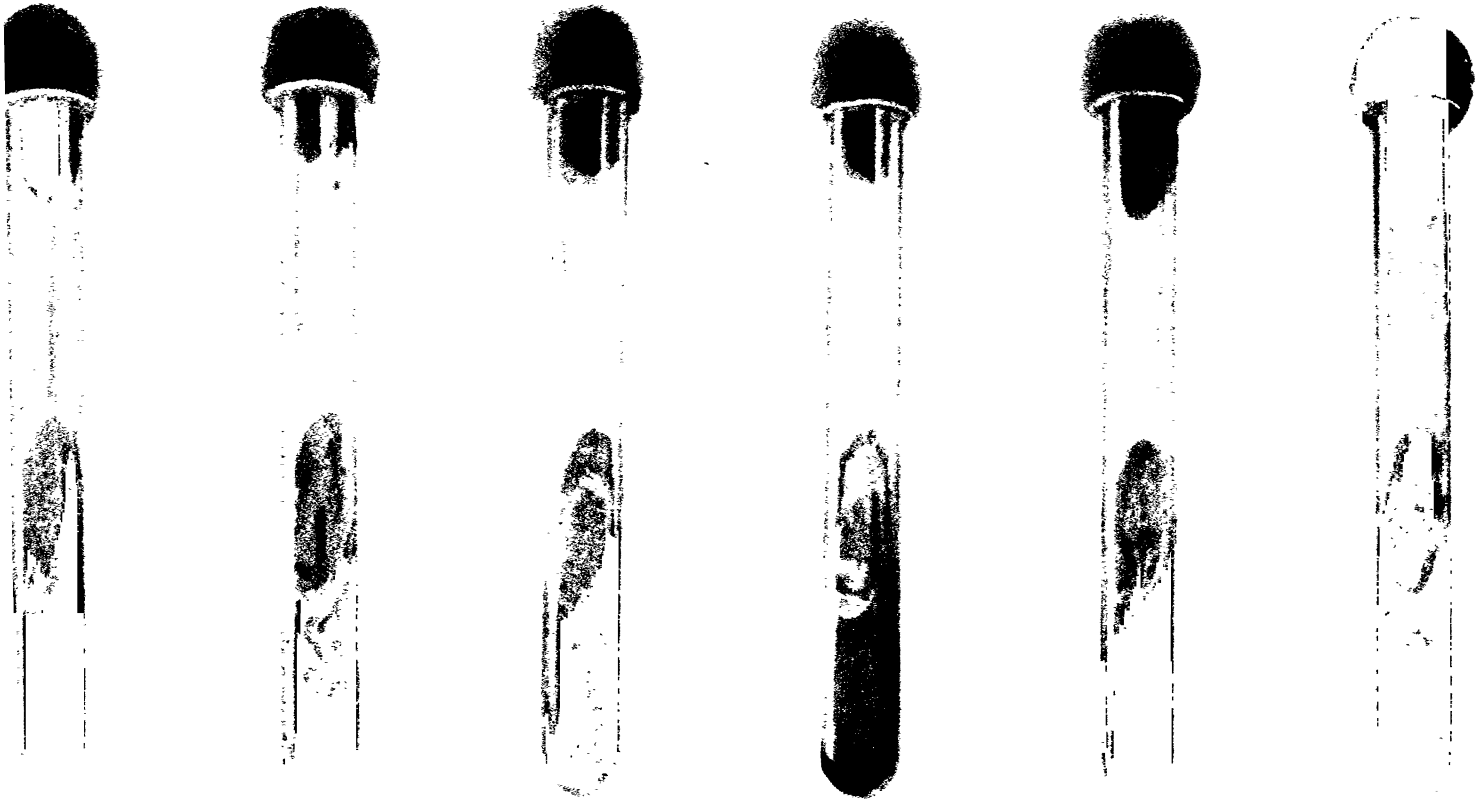
Mention should be made of another plating medium for stools with which the authors claim to have obtained better results than with either Endo's or Krumwiede-Pratt and McWilliams' brilliant green plates. This is the eosin-brilliant-green plate of Teague and Clurman. Following a former eosin-methylene-blue plate for differentiating colon and typhoid colonies devised by Holt-Harris and Teague, Teague and Clurman found that much larger amounts of brilliant green could be added without inhibiting the typhoid bacillus, provided eosin in proper proportion was added to the medium at the same time. On this plate the colon colonies develop dark centers while the typhoid colonies are pink.

Teague and Clurman use meat-infusion agar and warn against the use of beef extract agar as a base for the preparation of this medium. The technic of the preparation is given by them as follows:

Five hundred grams of chopped beef are placed in one liter of distilled water and kept in the icebox over night. The infusion is squeezed through cheese-cloth, heated in the Arnold sterilizer and passed through filter paper. Witte's peptone (1 per cent.), chemically pure sodium chlorid (0.5 per cent.) and agar (1.5 per cent.) are added to the warm infusion, the peptone being first rubbed up into a paste in a little warm water. The flask of medium is then heated in the autoclave for thirty minutes at 120° C. The reaction is adjusted to + 1.0 by the addition of (2N) NaOH and then the medium is heated for half an hour in the Arnold sterilizer. The reaction is again brought to + 1.0, cooled to 55° C. and cleared with egg-white. It is filtered through cotton, flasked in 100 c.c. quantities and autoclaved at 120° C. for twenty minutes. When needed, a flask of agar is melted, and 1 per cent. lactose and 1 per cent. saccharose are added. To every 100 c.c., 2 c.c. of 3 per cent. water solution of yellowish eosin are added. From a stock 1.0 per cent. solution of brilliant green in 50 per cent. alcohol, a 1/6 per cent. solution in distilled water is prepared and 2 c.c. of this added to each 100 c.c. of melted agar containing the lactose, saccharose and eosin. The flask is thoroughly mixed and the plates poured as for Endo or ordinary brilliant green plates. These plates may be kept several days before using, if necessary.

The authors have had slight experience with this medium, but it has seemed wholly satisfactory and at the present time they are using all three types of plates for routine work. The optimum pH of brilliant green media has been stated by Meyer and Stickel to be between 6.4 and 7.0. These writers obtained better results with the Teague-Clurman medium than with any other of a large number of plating mediums. They use a peptonized liver agar as the base. The authors have used trypsinized placenta agar as a base with good results.

Quantities of dextrose up to 1/10 of 1 per cent. in solid media are not utilized by typhoid bacilli growing on the surface of the medium, the oxygen of the air being used by preference. In the depths of such solid media in a stab culture acid is developed. It is upon this property that the usefulness of most practical media used for diagnosis depends. A medium widely used in the last few years for rapid differentiation of the colon-typhoid group has been Russell's litmus-lactose-glucose agar. This medium, as its name implies, contains 1 per cent. lactose, and 1/10 per cent. glucose, besides the indicator litmus. It is tubed with a deep butt as well as with a slant, and in sowing a surface streak and a stab culture are both made on the same tube. The lactose fermenters, like the colon bacillus, redden the medium throughout and break it up with gas. The typhoid-dysentery group redden the butt and leave the slant colorless. This medium has been modified frequently to make it



B. coli. B. paratyphosus B. B. paratyphosus A. B. typhosus. B. dysenteriæ. B. fæcalis alcaligenes

KLIGLER'S MODIFICATION OF RUSSELL'S MEDIUM SHOWING CHARACTERISTIC REACTIONS OF THE COLON-TYPHOID GROUP OF ORGANISMS.

more specific for typhoid. One of the important modifications is the addition of 1 per cent. saccharose to differentiate more quickly the members of the colon group that ferment lactose slowly but attack saccharose more promptly, such as *Bacillus coli communior*. Intermediates are also occasionally encountered in stools which, because of their prompt fermentation of saccharose, are immediately discarded, reducing the number of colonies which need to be further investigated by agglutination methods. The most generally useful modification of the Russell medium, in the author's experience, is that of Kligler. In this modification the two sugars, lactose and glucose, are adhered to, Andrade's indicator is added to indicate the reaction, and basic lead acetate to further differentiate different members of the group by its reduction. The medium is made as follows: Either sugar-free meat-infusion agar or beef extract agar is used as a base. This is made neutral to Andrade's indicator, 1 per cent. Andrade's indicator, 1 per cent. lactose and 0.1 per cent. glucose are added to the melted stock, and when cooled below 60° C., 5 c.c. of 0.5 per cent. basic lead acetate are added for each 100 c.c. The medium is run into small sterile tubes under aseptic precautions, as it cannot be again sterilized. The tubes are slanted to leave a generous butt and allowed to harden. The original Kligler modification calls for double this quantity of basic lead acetate, but the reactions are sharp and prompt as here given. The authors see no objection to adding saccharose to this medium in 1 per cent. quantities, and has frequently done so with uniformly good results. This is after the modification of Krumwiede, who found that saccharose improved the original Russell's medium by picking out some of the rather slow lactose fermenters more quickly.

The Russell-Kligler medium serves to differentiate colon, para A, para B, typhoid and dysentery bacilli from one another. Thus lactose fermenters will produce redness and gas throughout the medium. Those which ferment glucose with gas production but do not ferment lactose (para A and para B) will produce gas and reddening of the butt and a colorless slant. Those which produce acid from glucose but no gas will produce reddening of the butt without gas bubbles and colorless slant (typhoid and dysentery). The para B and typhoid produce browning in the stab from the lead acetate, while the rest do not. These different appearances are well shown by the colored plate (*See* Plate I).

TABLE 3.

DIFFERENTIATION OF TYPES OF BACILLI

Bacilli	Butt	Slant
Colon	Red; gas bubbles; colorless stab	Red
Para B	Red; gas bubbles; brown stab	Colorless
Para A	Red; gas bubbles; no browning	Colorless
Typhoid	Red; no gas; brown stab	Colorless
Dysentery	Red; no gas; no browning	Colorless

A suspected colony picked from one of the three kinds of plates given above will give a reaction on the Russell-Kligler medium which will be immediately diagnostic.

An inspection of Table 3 will make the interpretation of the plate clear.

All that remains is to test the reaction of a culture to known agglutinins. This may be done rapidly by the macroscopic slide method. Some of the suspected colony is rubbed up with a drop of salt solution to make a heavy suspension on the slide. A loop of this is mixed with a high dilution of serum whose agglutinin titer to the particular organism suspected and whose zones of group agglutinins are known. In a positive result the clumping becomes apparent almost immediately. The more accurate macroscopic tube method and microscopic method of testing for agglutinins are discussed under Agglutination Methods for Diagnosis.

The foregoing method of identifying the typhoid bacillus is an example of the procedure for isolating members of this group from the stools in suspected cases or from suspected carriers. It presupposes a fully equipped clinical laboratory and familiarity with bacteriological procedures. The isolation of typhoid bacillus from stools of suspected cases is the most difficult laboratory procedure associated with typhoid fever. Most of the other laboratory work required in the course of the disease can be done by any one with small equipment and the ordinary training in laboratory work possessed by the practitioner.

In seeking to identify a culture as one of *Bacillus typhosus* one should first consider its important characteristics. It will be remembered that the typhoid bacillus is motile, Gram-negative, does not form spores, and does not liquefy gelatin. These characteristics should be tested first. A stab culture is made in gelatin and kept at room temperature. This procedure will save beginners from occasional error, due to the presence of bacilli of the proteus group, which are sometimes present as contaminations. Proteus is motile, Gram-negative and non-sporebearing like *Bacillus typhosus*. Its manner of growth is very different from that of typhoid, and when once seen as a contaminant, especially on agar plates, it will be immediately recognized. Proteus grows very luxuriantly, and after eighteen hours' incubation the colonies are so large as to preclude any possibility of their belonging to one of the colon-typhoid group. Prompt liquefaction of gelatin definitely rules them out of the colon-typhoid group. If gelatin is not at hand the suspected proteus culture may be shown not to be typhoid by the fact that it promptly coagulates and acidifies litmus milk like the colon bacillus.

D. *Isolation of the Bacillus Typhosus by Blood Culture.*—No diagnosis of typhoid fever should be made without an attempt to isolate the offending organism from the blood. With proper methods the percentage of positive cultures from the blood of typhoid fever patients is high, at least 75 per cent. in the first week of the disease. The importance of blood cultures will be realized when it is remembered that a positive blood culture is the only piece of evidence which stands alone incontro-

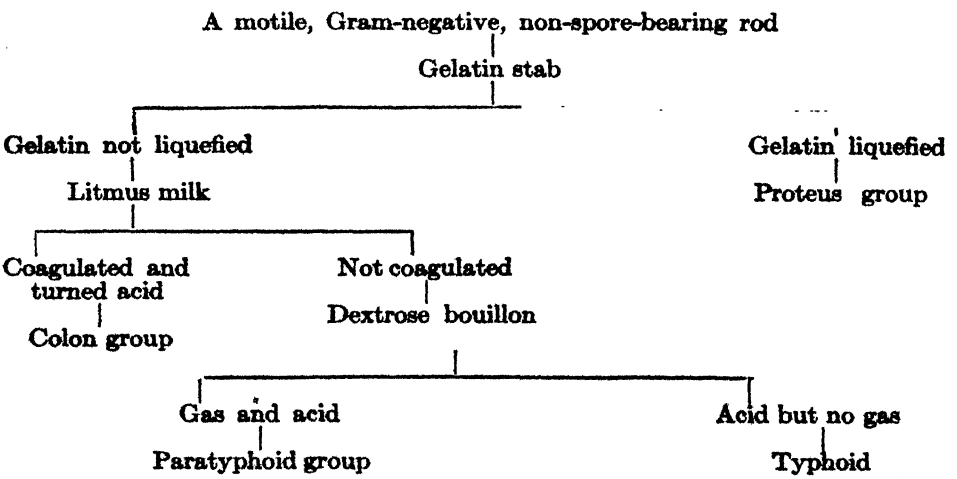
vertible. The Widal reaction is open to occasional sources of error, even when carefully controlled. A culture of *Bacillus typhosus* or one of paratyphoid bacilli obtained from the blood is open to only one interpretation, and that is that the particular bacillus isolated is the cause of the disease. The clinician should always keep in mind that the time to take a blood culture is when he first sees a patient who may be suspected of having typhoid fever. All too frequently the physician observes the case for several days, orders Widal reactions done, which are usually negative for the first week or two, and then, when atypical characters arise in the disease process to shake his faith in his provisional diagnosis, he resorts to the blood culture method. The chance of successful blood cultures in typhoid fever diminishes somewhat after the first week, and diminishes rapidly after the second week. There is a rough inverse relation between the blood culture successes and positive cultures from stools varying with the stage of the disease. The chance of success in culturing the stool of a typhoid patient is greatest in the third week, although Krumwiede found that in paratyphoid A infections the percentage of positives from stools was highest in the first week of the disease.

Of all the methods which have been devised for blood cultures in typhoid fever, the simplest are the most successful. A tourniquet of soft red rubber-tubing is applied above the elbow, just tight enough to impede the superficial venous circulation. The space at the bend of the elbow is painted with tincture of iodin. Under strict aseptic care the blood is drawn from one of the large veins just below the bend of the elbow with a sterile syringe fitted with a needle of about eighteen gauge.

We believe that most blood culture contaminations are due to contaminated syringes. Boiling is not an efficient method for sterilizing a needle for bacteriological purposes. The best method with which the author is familiar is that of suspending the syringe, fitted with the needle ready for use, in a tube of mineral oil. The metal clip at the base of the 20 c.c. syringe rests on the brim of a large 100 c.c. centrifuge tube and serves to support it, so that the needle does not rest on the bottom. The centrifuge tube is filled with mineral oil just immersing the needle and the lower end of the syringe for about a quarter of an inch up the barrel. The top is covered with brown paper tied around the top of the centrifuge tube, making a cap for the whole. This is placed in the dry-heat sterilizer, the temperature run up to 200° C. and the burners shut off, allowing the oven to cool. Such syringes can always be kept on hand for immediate use.

Ten c.c. of blood are delivered into a bouillon flask containing about 200 c.c. of bouillon. The optimum reaction is about pH 7.4. Sterile ox-bile should be added in about 10 per cent. quantity to the bouillon. The author uses a good grade of inspissated ox-gall and adds it in the proportion of 2 per cent. to the bouillon. A blood rich in typhoid bacilli will give a good growth in from twelve to twenty-four hours, but occasionally the bacteria are not present in sufficient numbers for hanging drop recognition until the second or third day. The diagnosis can some-

times be hastened by smearing loopfuls of the twelve to twenty-four hour broth culture over agar slants and incubating from twelve to eighteen hours longer. The organism in the primary broth culture should first be examined in a hanging drop preparation. The typhoid bacilli are very actively motile. The paratyphoid bacilli and the colon bacillus are also motile. If the suspected culture is motile, Gram-negative, non-spore-bearing, and does not liquefy gelatin it should be planted on the Russell-Kligler medium. If this is not at hand a diagnosis can be made by sowing on litmus milk, or in a fermentation tube of glucose bouillon containing 1 per cent. Andrade's indicator. In place of the litmus milk the author uses Andrade's indicator added to the milk in 1 per cent. quantity, or brom-cresol purple. Brom-cresol purple is prepared by making a 1.2 per cent. solution in alcohol and diluting 10 c.c. of this solution to 200 c.c. with distilled water. This solution is added to the media in 1 per cent. quantity. The colon group acidify and coagulate litmus milk, and produce acid and gas on bouillon. The paratyphoid-enteritidis group do not coagulate milk but produce gas and acid in glucose bouillon. The typhoid-dysentery group do not coagulate milk and do not produce gas from glucose bouillon, but do turn glucose bouillon acid. This simple means will suffice to distinguish typical typhoid cultures. Paratyphoid cultures require more extended investigation. The organism isolated should, after transplanting on plain agar for a few generations, agglutinate with the patient's serum in a dilution of at least 1:40 by the third week of the disease. The procedure for making a differential diagnosis of the bacteria found in blood cultures may be understood from the following diagram:



This simple method is sufficient for clinical purposes, especially when fortified by agglutination tests on isolated bacilli. To separate the para A from the para B and these from the enteritidis and suipestifer strains requires careful agglutination and absorption tests, but from material

isolated from blood cultures these latter can be disregarded and para A separated from para B on the ground of lead acetate reduction (positive in para B) and the inability of para A to ferment xylose. Furthermore, the para A bacillus produces an acidity in litmus milk which lasts much longer (7-21 days) than the para B. Para B soon changes the initial acidity of litmus milk to an alkaline reaction, finally clearing the milk and leaving a clear brownish liquid with a copious sediment. Final identification is made by agglutinating with a high dilution of a homologous serum.

E. *Isolation of Bacillus Typhosus from Urine.*—The urine of typhoid fever patients commonly contains typhoid bacilli. When typhoid bacilli are present albumin is usually found, indicating some degree of kidney injury. Typhoid bacilli are occasionally present in such enormous numbers that the conclusion must be drawn that they have multiplied actively in the bladder. Under hospital conditions, where the urine can be procured easily under aseptic conditions, it may be smeared directly on Endo plates with a large platinum loop. Under conditions where the urine must be brought to the laboratory in an ordinary receptacle without special precautions against contamination, Kanichiro Morishima and Teague have found it advisable to add one-half volume of nutrient broth to a given quantity and incubate over night, and then to inoculate a Teague-Clurman plate.. Any other medium such as Endo, or Krumwiede's brilliant green plate, can be used. The inoculation is made by smearing different dilutions from 1-10,000 to 1-1,000,000 over several plates, or by inoculating successive portions of a single plate without sterilizing the wire between segments, thus making the dilution on the plate. The later method is the more practical.

F. *Isolation of Bacillus Typhosus from the Gall-bladder.*—The cultivation of the typhoid bacillus from the bile offers no difficulty. Bile aspirated from the gall-bladder at operation is delivered directly into bouillon, and usually when the typhoid bacillus is present it is in pure culture. The *Bacillus typhosus* has also been obtained from the interior of gall-stones. The gall-bladder is the most accessible and unfailing source of the typhoid bacillus at autopsy. Lymph-nodes, bone-marrow and spleen pulp inoculated into bouillon also give positive cultures.

Distribution outside the Body.—The typhoid bacillus has no normal breeding place in nature outside of the human body. When the organism is discharged from an infected person, either in the urine or the feces, it tends to die out. The duration of the life of the bacillus outside the body is widely variable and subject to many environmental conditions. The more important of these are temperature, moisture, reaction of the material in which the bacillus finds itself, and the presence of other bacteria. The difficulty of giving definite rules for the disappearance of *Bacillus typhosus* from any material rests upon the fact that in all typhoid-infected material there are usually a few resistant organisms that survive the adverse conditions and remain alive in small numbers for weeks or months. Thus, though most typhoid bacilli

succumb to drying within a few hours, Park finds that a few may live for months.

Temperatures widely different from that of the human body tend slowly to destroy the typhoid bacillus. It survives longer in warm than in very cold water. Like other non-spore-bearing bacilli, a temperature of 60° C. (140° F.) for a very short time is sufficient to kill the organism. Park has also shown that a resistant minority of typhoid bacilli may withstand freezing for as long as five weeks; but, in spite of this, ice is a negligible factor in the epidemiology of typhoid fever.

In Feces.—The feces, after discharge from the body, harbor the bacilli for a variable length of time. Park has shown that the majority die in a few hours, while Levy and Kayser isolated typhoid bacilli from a cemented privy vault five months after their excretion. Gay thinks that the reaction of the stool is a factor in determining the longevity of the bacillus.

In Sewage.—In sewage the typhoid bacillus disappears directly in proportion to the amount of the contamination of the sewage with other bacteria. In heavily contaminated sewage the organism dies out quickly because of the presence of antagonistic bacteria and because the oxygen is consumed by these bacteria and other organic substances. On the other hand, Gay states that the organism has been found to persist even in the effluent from septic tanks.

In Water.—In running streams the bacillus dies out more readily than in still water; and in thin layers of water, in the sunlight, it dies very quickly. In relatively pure water, such as well water or ordinary drinking water, the organism may persist for several months, though it probably does not multiply to any extent. Park and Williams think it usually disappears in river water within seven days.

In Soil.—Under usual conditions typhoid bacilli live only a short time when buried in soil. The abundant bacterial life in surface soil is quickly destructive to the bacilli. In sterile soil their life is longer. Thrown upon frozen ground they may live several weeks and ultimately may be washed into a well or stream and become a source of infection.

Milk.—Milk is commonly considered a good culture medium for *Bacillus typhosus* and is a common medium for transmission. Gay is of the opinion, and quotes Chapin to the effect, that milk in the raw state definitely inhibits the growth of the *Bacillus typhosus* for several hours, and further, that this source of infection is of more importance in small towns over short milk routes than in larger communities.

Other Foods.—Various other foods may be contaminated and harbor the bacilli for indefinite periods; and, as in the instance of the Hanford outbreak cited by Gay, due to spaghetti infected by a carrier cook, the organism may multiply enormously under favorable conditions.

Fomites.—The bacillus may live for several weeks on blankets, bed clothing and various other articles soiled by typhoid excreta.

Modes of Conveyance.—Every case of typhoid fever is caused by infection with *Bacillus typhosus,* conveyed directly or indirectly from a previous case of the disease. Infection may be conveyed by any route

which permits the bacilli excreted by a typhoid patient or carrier to reach the mouth and gastro-enteric tract of another individual.

(*a*) *Water.*—Water is the most important medium of conveyance. In the temperate zone at least, typhoid fever is the most important water-borne disease. The reduction in the morbidity from typhoid fever, following the introduction of a pure water supply, in a city in which the disease is endemic, is one of the striking facts of modern sanitation; and the marked general reduction in the typhoid rate in the United States, which has taken place in the last ten years, is due largely to improvement in the public water supplies of the cities. In New York State the typhoid rate has decreased from 19 per 100,000 population in 1906 to 3.3 per 100,000 in 1919, coincident with, and—according to the Health Department—directly resulting from, the wide extension of the use of purified public water supplies.

Various authorities estimate that from 35 to 80 per cent. of the cases of typhoid fever are conveyed by infected water. Seventy-two per cent. of 640 epidemics recorded by Schüder were water-borne.

Water supplies may be infected by typhoid bacilli in a number of ways. The most important mode of pollution is by the discharge of the raw sewage of cities and towns into lakes and water courses. Excreta may be discharged directly into the water, or washed into streams, lakes or wells from the surface of watersheds. Sewage may reach a drinking water by percolation through a porous soil. Many outbreaks have been the result of the accidental connection of sewers with water mains, or to the dumping of infected refuse above intakes of water supplies. In 1892 an extensive outbreak in Detroit was traced to the discharge into the St. Clair River of a great volume of mud and sewage dredged from a small river at Port Huron, fifty miles above the Detroit intake.

Water-borne epidemics are usually explosive in character, restricted to areas supplied by the polluted water, and are apt to occur at periods out of the regular typhoid season. The occurrence of an outbreak in the winter or spring is presumptive evidence of water-borne infection.

A large majority of the cases directly due to contact, or to fly or food infection, have their origin indirectly from infected water. A few small outbreaks have been found to be due to ice contaminated by the typhoid bacillus.

Even highly polluted water may be made relatively safe for public consumption by filtration or chlorination. All water supplies liable to sewage pollution should pass through filtration plants. *Chlorination* is a safe and inexpensive temporary substitute for filtration and is always available. The reduction of the typhoid fever rate of Milwaukee, Detroit and other lake cities, since the introduction of chemical purification of their water supplies, is evidence of the efficiency of this method.

The recent outbreak at Alpena, Michigan, well illustrates the value of chlorination. The city is supplied by lake water, continuously or intermittently polluted by city sewage. The water is treated by chlorination and for a long period the city was free from typhoid fever. On March 16, 1920, an explosive outbreak began, in which 106 cases were

reported. The outbreak quickly subsided and no secondary cases developed.

The epidemic was caused by an interruption in the chemical treatment of the water, extending from February 29 to March 8. The first case of the outbreak developed sixteen days after the untreated water reached the city mains.

(*b*) *Contact Infection.*—The recent work by health authorities in tracing the source of individual cases of typhoid fever has shown that conveyance by contact is much more frequent than was formerly thought. Estimates of the percentage frequency of contact cases by different observers vary widely. Rosenau attributed from 6 to 17 per cent. to contact infection; Whipple, 30 per cent.; and Frosch, 65 per cent. In Detroit, during the three years ending December 31, 1919, 562 cases of typhoid fever were reported which originated in the city. The Department of Health traced 81 cases—or 13.9 per cent.—to contact infection.

In contact infection the bacilli usually reach the mouth by hands soiled by the excreta of the typhoid patient. An attendant may infect himself or may carry the bacilli to a healthy person or another patient. Physicians, nurses and hospital attendants are particularly liable to this form of infection. Unclean thermometers, spoons, cups and other objects used by a typhoid patient may convey the infection directly to the mouths of other persons. Contact infection may occur in the same way from a chronic carrier. Kissing is a possible mode of contact infection.

(*c*) *Infection of Food.*—From 10 to 25 per cent. of the cases of typhoid fever can be traced to food infection. Food may be contaminated directly by the typhoid patient or carrier, or indirectly by an unclean nurse or attendant. Conveyance from chronic carriers most commonly occurs through the medium of food contaminated by them in its preparation or distribution. The bacilli may be introduced from a typhoid-infected water, which has been used in the preparation of the food or for washing dishes or other containers in which it is served or stored.

Milk is the food which acts most frequently as a vehicle for the conveyance of the typhoid bacillus. Of 638 epidemics investigated by Schüder in Germany, 17 per cent. were caused by milk infection. Trask, of the United States Public Health Service, collected reports of 317 milk-borne epidemics up to 1908. In four years' study of typhoid fever in Washington, Rosenau found that 10 per cent. of the cases were due to milk infection. In large cities the sanitary regulations which are now enforced in the production and distribution of milk, have reduced milk-borne typhoid to a minimum. In Detroit no case of conveyance by milk has been traced since the adoption, in 1915, of an ordinance requiring the pasteurization of general milk supplies. Milk epidemics are still common in smaller towns.

The number of cases in a milk-borne outbreak is usually small and their distribution is restricted to the territory supplied with milk from the infected dairy. An extensive milk-borne epidemic occurred in Boston in March and April, 1908, in which 410 cases were reported.

Milk may be infected from a typhoid-polluted water used to dilute the milk or to wash the containers; or by dairy employees who are convalescent or chronic carriers, or who are nursing a typhoid fever patient.

Milk outbreaks develop abruptly, like water-borne epidemics, and subside quickly. Often two or more members of a household are taken sick at the same time. Children and women are chiefly affected. It appears that under certain conditions the typhoid bacillus multiplies in milk and becomes less virulent. Therefore cases due to milk infection may have a short period of incubation and may be mild in type.

Cream, ice cream, buttermilk, butter and new cheese produced from infected milk may retain and convey the typhoid bacillus.

Oysters and other shellfish grown or fattened in sewage-polluted bays or inlets have been the medium of transmission of typhoid fever in a number of outbreaks.

In 1894 an outbreak of 25 cases occurred among the students of Wesleyan University at Middletown which was traced by Conn to infected oysters. Isolated cases of oyster-borne infection, widely separated from one another, undoubtedly occur, which are not traced to their common source of infection. Typhoid bacilli survive for several days in infected oysters, although there is no evidence that they multiply there.

Vegetables, which are eaten raw, such as celery and radishes, if grown in typhoid-infected soil or washed in polluted water, may carry the disease.

(*d*) *Contamination of the Soil.*—Contamination of the soil by typhoid-infected excreta is frequent in rural districts, in newly built unsewered towns, in camps and in territory occupied by armies in the field. In some countries extensive soil-infection results from the use of untreated human excrement as a fertilizer. Under ordinary conditions of heat and moisture typhoid bacilli live in soil from one to two months. In frozen ground they may remain virulent for several months, as shown in the Plymouth and New Haven epidemics. There is no evidence that the bacilli multiply in soil.

The bacilli may be conveyed from soil to mouth by one of several routes. The most important route is by way of water infected from the soil of the watersheds of streams and wells supplying communities or isolated houses. Some of the most striking of the water-borne epidemics have had this origin. The bacilli from infected soil may be carried to the mouth by fingers contaminated by handling dirty boots and clothing. This was a frequent mode of indirect contact infection in the camp epidemics which occurred during the Spanish American War. Flies may carry the infection from soil to food, and vegetables grown in bacilli-laden ground may be the medium of transmission. Typhoid bacilli in dust from infected soil may be carried directly to the alimentary tract by inhalation or indirectly by the contamination of food.

(*e*) *Flies.*—Sedgewick, in 1892, and Kober, in the same year, suggested that flies were an important factor in the transmission of typhoid fever. The report of the Typhoid Fever Commission of the Spanish American War—Reed, Vaughan, Shakespeare—emphasized the rôle of

flies as the medium of indirect contact infection in the typhoid-infested camps of the American Army. Vaughan believed that about 15 per cent. of the cases of camp typhoid were due to fly transmission.

It is difficult to estimate the percentage of fly-borne cases in civil communities. It may be high in small villages with open latrines and unscreened homes, in mining and lumber camps and in crowded and filthy tenements. In well-sewered cities it is probable that only an occasional case is due to fly transmission.

Flies carry enormous numbers of microbes on their bodies, wings, and feet, and in their alimentary tracts. Typhoid bacilli have been isolated from flies captured in the immediate vicinity of a house occupied by a typhoid patient. Flies are infected by contact with the typhoid-bearing excreta on the patient or sick-bed or by feeding on excreta in unprotected vessels or privies. They have been found to retain the bacilli as long as twenty-three days after infection. The route of infection is: flies—to food—to mouth.

As a rule flies infect only at short range. It is possible, however, for them to transport the bacilli for long distances. In open country and over water they may travel several miles. On the Great Lakes the author has many times sailed through swarms of house and stable flies from ten to fifteen miles off shore. Other insects may convey infection in the same manner as flies.

(*e*) *Fomites.*—Articles of clothing or bedding soiled by typhoid excreta may convey typhoid fever. Washerwomen may be infected from unsterilized linen, hospital inmates from soiled towels and clothing, and soldiers from infected blankets. Such articles have been shown to harbor living bacilli for two or three months.

SYMPTOMATOLOGY

Clinical History

The commonly accepted division of the clinical history of typhoid fever into weekly periods, while arbitrary, is convenient and practical. In the average uncomplicated case of moderate severity the first week is the period of onset or invasion, during which there is a gradual increase in the severity of the symptoms. The second and third weeks correspond to the fastigium, the period of the height of the disease. The fourth week is the period of decline. The fifth week marks the period of beginning convalescence. The course of the specific pathological changes in Peyer's patches, roughly follows this division into weekly periods.

Typhoid fever is a disease of remarkable variability in symptoms and course. Epidemics and outbreaks show many differences in type, and the character of the disease endemic in a certain community is apt to change from year to year. Individual cases in the same outbreak are often so erratic in onset and progress that identification

from the symptom-complex alone is very difficult, often impossible. No symptom or sign is necessarily present and no symptom or combination of symptoms is impossible.

Sudden severe outbreaks may occur which show such bizarre symptomatology that health authorities and physicians are in doubt as to the identity of the epidemic until accurate laboratory methods of diagnosis reveal the true nature of the malady. In a disease of such protein manifestations it is impossible in a single continuous description to include the multitude of symptoms it may present. It will be well to give a short sketch of the clinical phenomena of the disease as it is commonly observed in communities where typhoid fever is endemic, describing in fuller detail under separate headings the various individual symptoms and their variations from type.

The Period of Incubation.—This is the interval between the time of infection and the onset of the symptoms of the disease. The exact time of these two events is so difficult to determine that the duration of this period is more or less a matter of speculation.

Ingestion of the typhoid bacillus and infection of the body by the organism are not synchronous. A longer or shorter interval may elapse between the entrance of the pathogenic organism into the intestinal tract and the actual invasion by them of the body tissues through some portal of entry. That this interval may be indefinitely prolonged is shown in the case of healthy carriers, who may harbor the bacillus for long periods. It is not improbable that cases showing an unusually long period of incubation are instances of delayed invasion of the intestinal wall.

The average time for symptoms to appear is from ten to fourteen days after exposure to infection. The period may be as short as two days or prolonged to twenty-three days. In 750 cases studied by the Spanish-American War Commission the average incubation period was ten and one-half days, the shortest six days. In an outbreak in Hanford, Cal., reported by Sawyer and cited by Gay, ninety-three people were infected by eating spaghetti prepared by a typhoid carrier. One-half the cases showed symptoms before the eighth day, 1 on the third, 12 on the fifth, and 19 on the sixth day. In 56 cases in an outbreak observed by the author among the employees of a local manufacturing plant, distinctive typhoid symptoms appeared in from ten to twenty days after the ingestion of highly polluted water. Murchison has reported a small outbreak in which the period of incubation in 20 out of 22 cases was not longer than four days.

In a number of instances of laboratory infection reported in recent literature the period of incubation has been determined with greater accuracy than is possible in ordinary clinical observation. An assistant working in Gay's laboratory received from a blocked syringe a mass of a thick suspension of recently isolated typhoid bacilli on the left cheek and conjunctiva. On the third day she felt a distinct malaise and on the fifth day she was ill with a temperature of 104° F. (40° C.). A blood culture taken at this time was positive.

Kissalt's study of 50 cases of laboratory infection gives the usual

incubation of about fourteen days, although cases developing in five, six and eight days are mentioned. Voisin reported two interesting cases of laboratory infection. A girl aged nineteen years swallowed a virulent culture of typhoid bacilli with suicidal intent. On the third day headache and fever developed; on the seventh day abdominal pain, and on the eighth day rose spots. The fever ran a typical course. In the second case a young physician accidentally aspirated a small amount of a bouillon culture of typhoid bacilli into his mouth while making a Widal test. Although he promptly rinsed his mouth with bichlorid solution, typhoid fever developed. The first symptoms appeared on the fifth day and splenic enlargement and rose spots on the thirteenth day.

Usually no symptoms mark the period of incubation, although careful inquiry often brings out a history of headache, lassitude and loss of appetite for a few days before the onset of the fever. These symptoms tend to increase in severity and are merged into the more well-defined illness of the onset of the disease. Often no sharp increase of symptoms marks the beginning of the period of invasion. There is an insidious aggravation of all the feelings of discomfort, and the patient finally stops work and takes to his bed. Without temperature observations and a clear history of the beginning of fever this event must be taken as indicating the first day of the stage of invasion.

Course of the Disease.—First Week.—Chilliness followed by the flush and general aching of fever will often identify the first day of onset. A well-defined chill occurs in a small percentage of the cases. In Osler's series of 79 cases treated in one year at Johns Hopkins Hospital 13 were ushered in by a chill. In addition, there are excessive fatigue, dizziness, anorexia and abdominal pain or discomfort. Occasionally there is vomiting. The bowels are constipated, or there may be a diarrhea, usually excited by a cathartic. Headache, severe and unyielding, is a most important and characteristic symptom. Epistaxis is common on the second or third day.

The temperature taken on the first or second day shows an evening rise to 100° or 101° F. (37.8° or 38.33° C.). The pulse is 90 to 100, full and soft, becoming dicrotic in the last days of the week. The pulse rate is slow in comparison with the height of the temperature and the severity of the general symptoms. The tongue is moist and coated, the breath heavy. A mild bronchitis with unproductive cough, and sometimes dyspnea, is a common initial manifestation.

The symptoms continue and increase in severity. The temperature rises a degree or more each day, with morning remissions and evening exacerbations, until, toward the end of the first week, it reaches from 103° to 104° F. (39.4° to 40° C.) in the evening. The daily range of the remissions is from one to two degrees. The headache continues and is complained of bitterly by the patient. Sleeplessness is frequent and a dreamy confusion makes the nights restless. The skin is hot and dry, with occasional short periods of perspiration. Thirst and anorexia increase. The abdomen is slightly distended and there is usually tenderness in the right lower quadrant with gurgling on pressure. Constipa-

tion persists, or there may be one or two loose stools a day. This group of symptoms, all of which are more or less common to the febrile state from any cause, continue for about seven days, the first week of the disease.

SECOND WEEK.—In the beginning of the second week, from the seventh to the twelfth day, the characteristic rose rash appears upon the skin of the abdomen or chest and enlargement of the spleen can often be demonstrated. The symptoms of the first week continue and some of them increase in severity. The fever reaches from 103° to 105°F (39.4° to 40.6° C.) each evening, with slight or no morning remission. The pulse becomes more rapid and is soft and dicrotic. The subjective symptoms tend to increase up to the middle of the second week. The headache then diminishes or ceases and the patient becomes dull and apathetic. In the severe cases there is delirium, especially at night. This is usually of a mild muttering type; occasionally it is more noisy. The lips are dry and crack easily. The tongue is coated and may be dry. The abdomen is distended and the gurgling and tenderness in the right lower quadrant become more pronounced. The rose rash continues, appearing in crops of a few macules each day or two. Diarrhea, if present early, is aggravated, with several pale yellow, offensive movements of characteristic pea soup consistency during the day; or it may first show itself at this time. Constipation requiring measures for its relief is equally or more frequent. The urine is scanty and often shows a febrile albuminuria with a few casts.

The second week may end the period of continuous high temperature and defervescence may begin (Fig. 3). This mild course is rarely seen except in the typhoid fever of children. Death may occur late in the second week from intense toxemia or from hemorrhage or perforation.

THIRD WEEK.—Usually the foregoing symptoms continue into the third week, the patient failing under the continued high temperature and toxemia. Toward the end of this week the temperature may begin to show more decided morning remissions. The pulse becomes weaker and faster, 100 to 130, loss of flesh is rapid and prostration is great. The face is pale with occasional flushings, the pupils are dilated and the expression is dull and heavy. The mouth and tongue are dry, the tongue often red and glazed. Without constant care the lips and teeth become covered with sordes. Diarrhea continues and involuntary evacuations may occur. Profuse perspirations are common; excoriations and bed-sores may appear. Delirium persists, with subsultus tendinum and picking at the bed clothes in highly toxic cases. This is the condition designated as the "typhoid state." Inefficient nursing and bad feeding are often responsible for the severity of some of these symptoms. Intestinal hemorrhage, perforation, bronchopneumonia and other grave complications are most frequent at this time. Progressive asthenia or one of these complications may cause death.

FOURTH WEEK.—This is the period of decline. Defervescence is by lysis, the disease ending gradually as it began. In rare cases a crisis

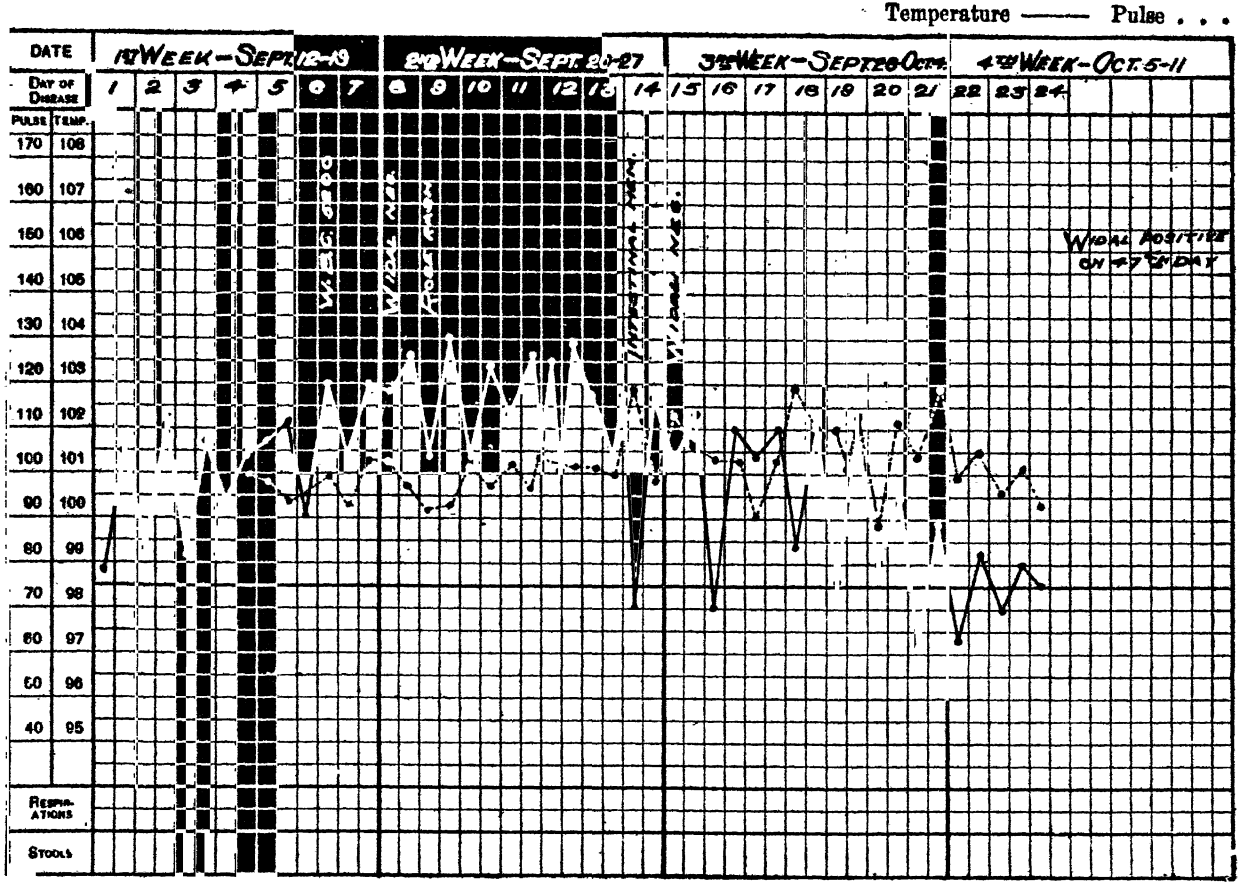


FIG. 3.—CHART IN MILD TYPHOID FEVER.

Hemorrhage on 14th day. (Personal observation. Patient aged 36.)

terminates the period of high temperature, and convalescence begins abruptly (Fig. 4).

The temperature curve shows characteristic oscillations or "spikings." Increasing morning remissions with sharp evening rises give a daily range from 101° to 104° F. (38.3° to 40° C.), the maximum diminishing each day by a degree or more. The pulse becomes slower, or it may increase in rapidity from myocardial weakness.

The tongue moistens and cleans off, the appetite begins to return, the thirst lessens. The diarrhea abates, the abdomen becomes flat and the spleen shrinks. The general symptoms improve, delirium ceases and natural sleep replaces the wakeful and restless nights.

Fifth Week.—With the fall of the temperature to normal convalescence begins. The pulse becomes slower and stronger. The appetite is keen, often ravenous. Nutrition improves and weight and strength increase. Diarrhea abates and a troublesome constipation obtains. The urine increases in amount and the albumin and casts disappear, if previously present. The temperature remains low, with fluctuations below and above the normal line. In children and nervous adults the afternoon temperature often holds at from 99° to 100° F. (37.2° to 37.8° C.) for several days. Recrudescences are common, with a rise of 101° to 102° F. (38.3° to 38.9° C.). They are excited by slight disturbances of digestion, physical exertion or nervous excitement, and last two or three days. The skin may desquamate and the hair fall out. The spleen is no longer palpable. Should it remain large the possibility of a relapse must be borne in mind. Murchison considered convalescence established when the temperature remained normal for two successive evenings.

Variations in Symptoms and Course.—Divergence from the ordinary type of typhoid fever outlined above is common. There may be variation in the mode of onset, or in either the severity or the duration of the attack. Again, the brunt of the attack may be borne by a particular system or organ. Such localization of the infection gives a special character to the symptoms and course. An intercurrent complication may hold the field during part, or throughout the whole course of the disease. The use of complex terms like pneumotyphoid, meningotyphoid, etc., to designate some of these unusual types is becoming obsolete. Although occasionally used, these terms are unnecessary and may be confusing.

Variations in Mode of Onset.—1. Abrupt Onset.—Instead of the gradual accession of the symptoms of the period of invasion the onset of typhoid fever may be abrupt. With but insignificant premonitory symptoms the fever may rise sharply to 102° or 103° F. (38.9° or 39.4° C.) on the first day, with or without a chill, and the general symptoms reach a severity that in the usual cases is not attained until the end of the first week. Sharp remissions or intermissions in the fever, during the first week, are not uncommon.

2. Onset with Pharyngeal Symptoms.—Severe sore throat with red pharynx, swollen tonsils and nasopharyngeal catarrh may usher in an attack. Severe facial neuralgia from invasion of the accessory sinuses

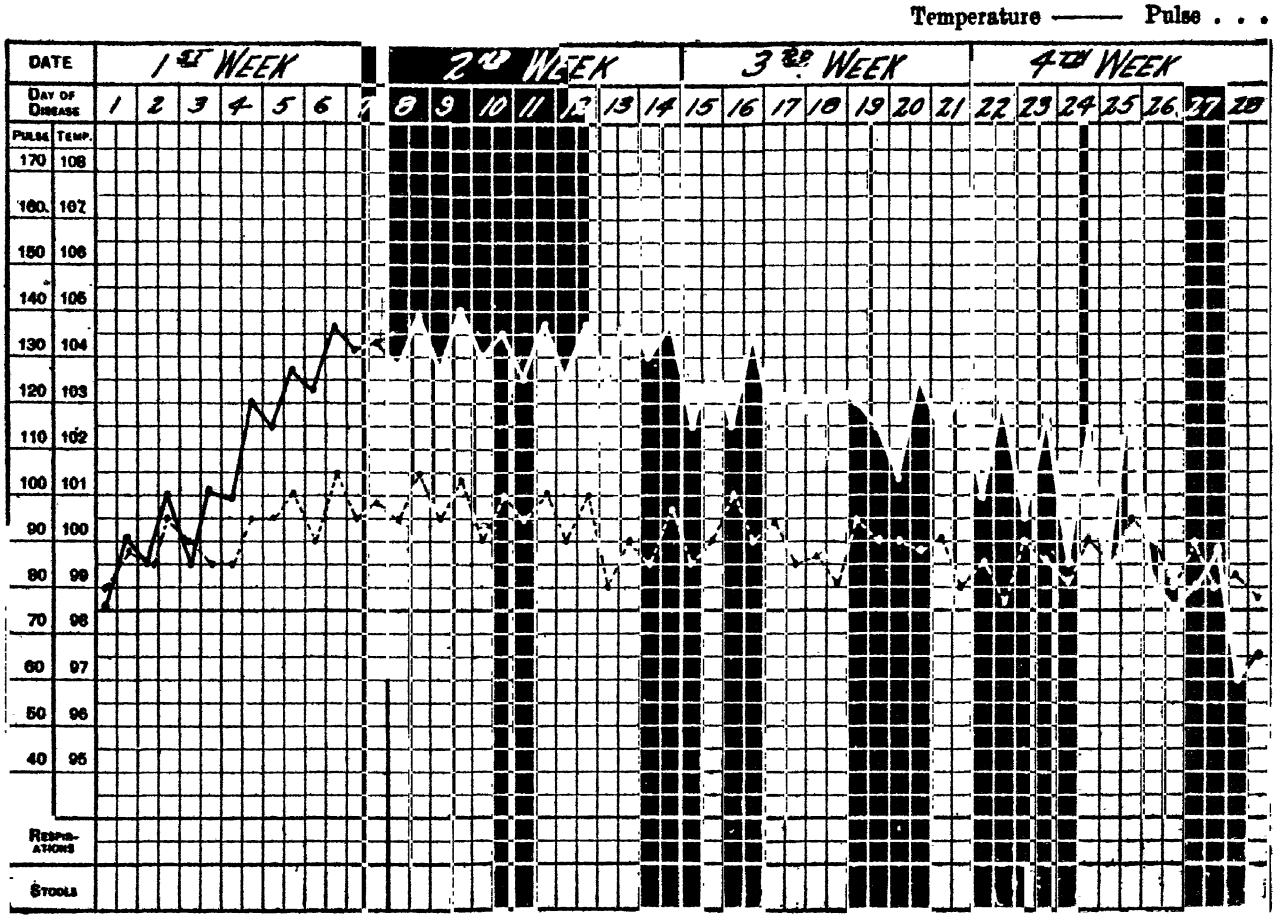


FIG. 4.—CHART IN UNCOMPLICATED, MODERATELY SEVERE TYPHOID FEVER. TYPICAL TEMPERATURE CURVE.
(Personal observation.)

of the nose may still further confuse the clinical picture and lead the practitioner astray.

3. Onset with Abdominal Symptoms.—Sudden pyrexia with nausea and vomiting, abdominal pain and rigidity may mask the onset of the disease and simulate acute gastritis or peritonitis. The impetuous surgeon may be led to open the abdomen, expecting to find a diseased appendix or other variety of acute abdomen.

4. Onset with Respiratory Symptoms.—Respiratory symptoms may dominate the onset. The initial bronchitis may be of unusual severity. The high fever and sweats, rapid pulse and respiration, with the physical signs of a general bronchitis may closely resemble acute pulmonary tuberculosis. The first symptoms may be those of pneumonia, with chill, pleuritic pain and the physical signs of lobar consolidation. The typhoid bacillus has been recovered from the lung in some of these cases; others are examples of coincident infection by the pneumococcus and the typhoid bacillus.

5. Onset with Renal Symptoms.—In rare cases, an acute nephritis with a scant, smoky urine containing albumin, blood and casts may replace the usual symptoms of onset. The increasing and persistent fever, with abatement in the severity of the renal symptoms, should lead to the suspicion of typhoid fever.

6. Onset with Nervous Symptoms.—Severe, suddenly developing nervous symptoms may usher in an attack. The symptoms may be those of a meningitis; headache, vomiting, delirium, photophobia, retraction of the head and positive Kernig sign. Or drowsiness, stupor or coma may develop after a day or two of the usual symptoms, and fix attention upon the nervous system.

Very rarely, in patients with a psychopathic tendency, delirium may develop with the onset of the fever, taking the form of a confusional or maniacal psychosis. In a dazed state such a patient may wander from home and end up in a hospital in some distant city, quite unable to reveal his identity; or he may be found hidden in some building where he has gone to escape fancied persecution.

Special and Characteristic Symptoms.—The Temperature.—The ordinary form of typhoid fever shows a temperature curve which, while subject to various irregularities, is fairly characteristic and is an important diagnostic feature. The typical chart (Fig. 4) shows a gradual rise with ascending oscillations during the first week. Normal in the morning, the temperature rises to 100° or 101° F. (37.8° or 38.3° C.) on the evening of the first day. On the following morning there is a remission of a degree or more, succeeded by an evening rise of about one degree higher than the maximum of the first day. This step-like ascent continues until about the end of the first week, when the temperature attains a height of from 103° to 105° F. (39.4° to 40.6° C.), depending upon the severity of the case.

The classical textbook ascent is perhaps exceptional, and various irregularities are the rule. Because of the insidious onset, the physician rarely sees a patient on the first day of the fever, and a temperature

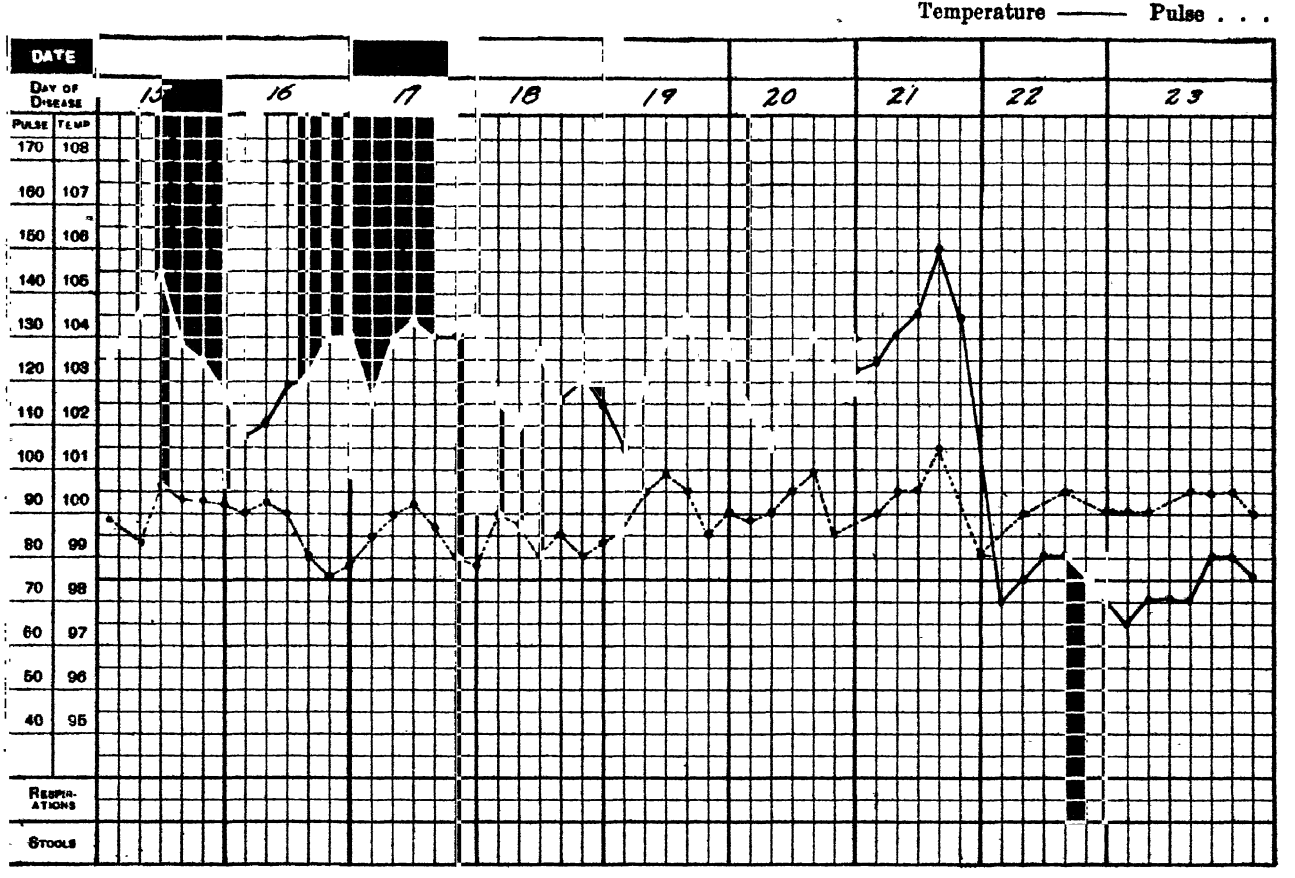


FIG. 5.—CHART IN MODERATELY SEVERE TYPHOID FEVER.

Crisis on 21st day. Four-hourly temperature. (Personal observation. Patient aged 52.)

observation is not often made until the disease is well advanced. Patients under the author's (Jennings') observation who had been taken ill while in bed in the hospital, have shown the typical gradual rise of temperature. The period of ascent may be shortened to three or four days, or in severe cases the onset of the disease may be by chill followed by a persistent high fever. It is very unusual for the ascending period to be prolonged beyond the eighth day. Remissions of great amplitude or actual intermissions in the fever are occasionally observed and may be a feature of the case throughout its whole course.

During the course of the second and third weeks of typhoid fever the temperature, as a rule, tends to hold a continuous high range with small oscillations. Without apparent reason it is quite common for the temperature to rise sharply above or fall below the average line. The study of a large number of temperature charts will emphasize the fact that every variety of curve may be met. During the height of the disease in cases of moderate severity a daily maximum of from 104° to 105° F. (40° to 40.6° C.) is the rule. The two hour temperature chart will show two or more distinct elevations during the twenty-four hours. A midday maximum is often observed. Occasionally a reversal of type is seen, the remissions coming in the evening instead of in the morning. This is more apt to occur in children, in the aged and in persons occupied with night work.

The end of the third week or the beginning of the fourth brings an increase in the amplitude of the daily remissions. Each day the remission is greater and the maximum and minimum points lower. As the fever comes to an end the remissions decrease in range from day to day until the normal is reached. This *period of descending oscillations* is a fairly constant phenomenon of both mild and severe cases. In very rare cases convalescence begins at the end of the third week, with a sudden critical fall of the temperature to normal (Fig. 5).

The therapeutic cold bath disturbs the normal curve, and causes transient falls (Fig. 6). This is particularly the case toward the end of the fastigium. Sudden, unexpected temperature changes should always excite suspicion of the onset of some complication. Hemorrhage usually causes a drop of several degrees (Figs. 3 and 7). After perforation it may either rise or fall. The complicating pus infections so frequent in typhoid disturb the fever curve, giving rise to many irregularities. Thrombophlebitis is a not uncommon cause of disturbances in the normal curve of the third and fourth weeks. The rise often begins several days before the local signs of the phlebitis show themselves. Osler has noted wide oscillations of temperature following a severe hemorrhage. Hyperpyrexia is not common. In only 4 or 5 per cent. of the cases is the temperature above 106° F. (41.1° C.) and very rarely does it rise above 107° F. (41.6° C.). Hypothermia may be observed in protracted cases with great emaciation, the temperature persisting below normal for a week or more. Fever with irregular oscillations from complications and causes not always demonstrable may continue for weeks and indefinitely

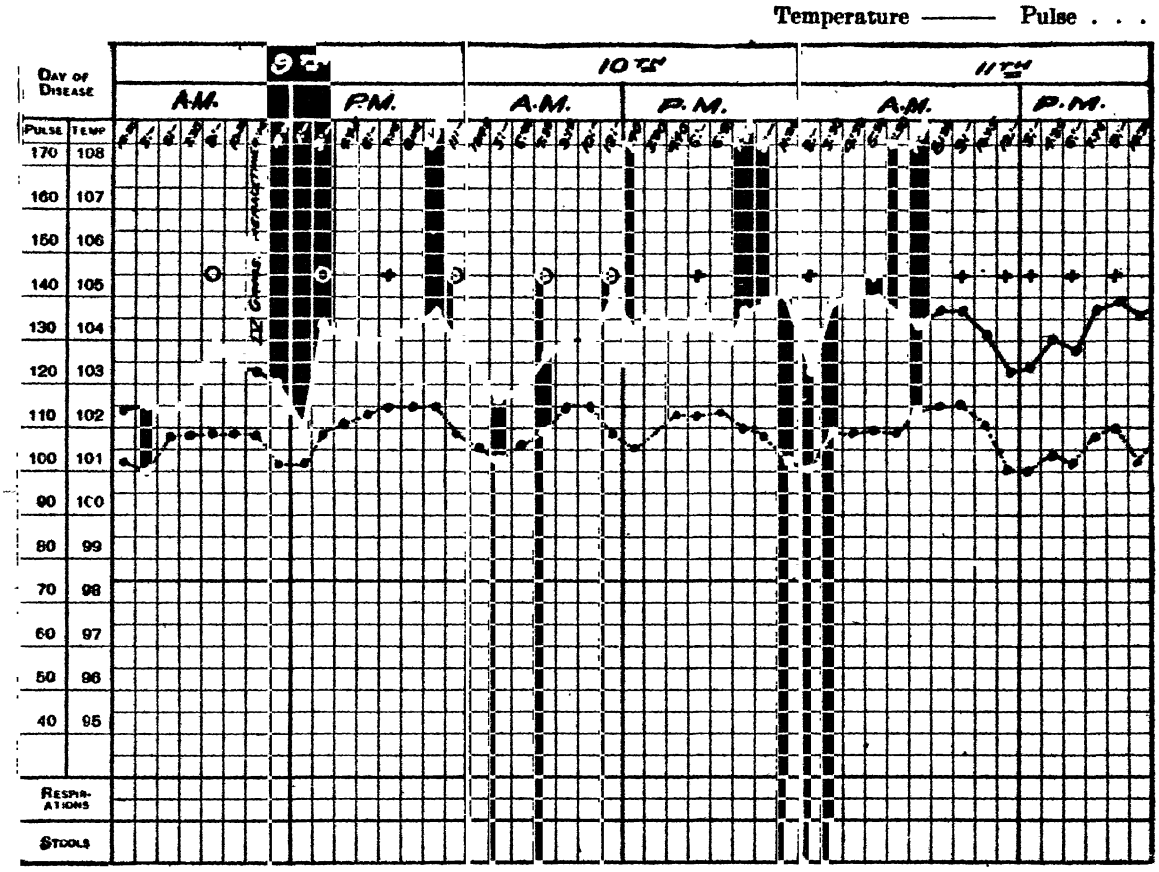


FIG. 6.—CHART IN MODERATELY SEVERE TYPHOID FEVER.

From 9th to 15th day (inclusive), showing effect of bath on temperature and pulse. O, bed bath; × tub bath. (Personal observation.)

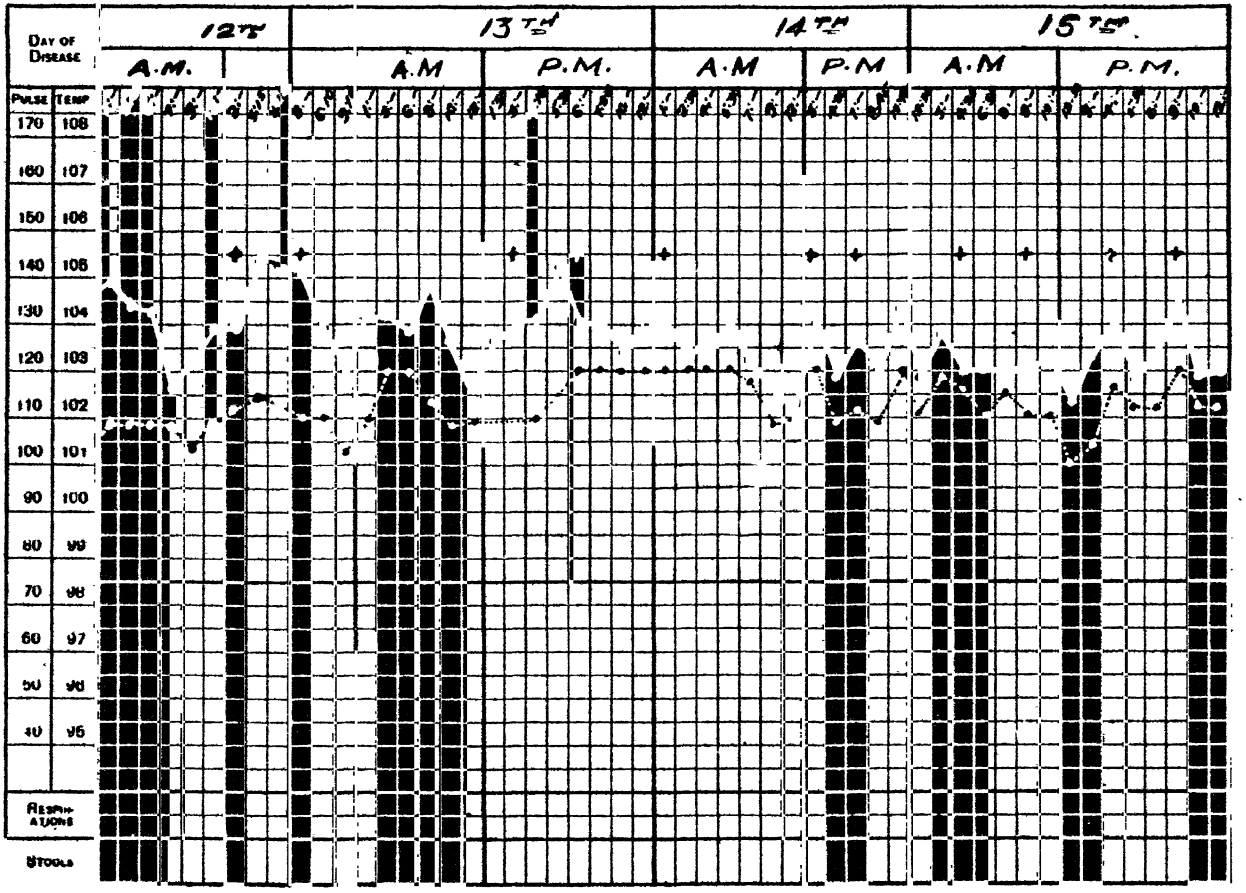


FIG. 6 CONTINUED.

delay convalescence. The temperature curves of recrudescence and relapse are considered elsewhere.

CHILLS.—A chill, sometimes repeated, not infrequently marks the onset of typhoid fever and at this period has no special significance. In rare cases a relapse is ushered in by the same phenomenon. Occasionally chills occur during the course of the disease, and at this time they are always startling and may be of grave import. Osler has made a detailed study of the cases with chills under his observation at Johns Hopkins Hospital. They may occur under a variety of conditions. Most common is the chill resulting from the use of drugs, notably antipyretics. In the author's (Jennings') early experience with antipyrin he saw two instances of rather alarming chill and depression from moderate doses of the drug. Chills have been caused by hypodermic or intravenous injection of typhoid vaccine, a legitimate result of the direct entrance into the circulation of a foreign protein. Two of Osler's cases resulted from the application of guaiacol to the skin.

A chill may serve to announce a complication. Pneumonia, perforation, appendicitis, thrombophlebitis or other complicating infections may begin in this way, although temperature variations without chills are more frequent. Occasionally a chill may precede a rapidly fatal hyperpyrexia. In a few cases a concurrent malarial infection has been proven to be the cause by the demonstration of the plasmodium. Chills may occur throughout the course of the fever and the most searching investigation may fail to reveal a local infection, a complication or any cause other than the typhoid septicemia itself. Conner asserts that chills in many of these obscure cases are due to a latent thrombophlebitis. The author (Jennings) saw a case of this kind in consultation with Doctor Bruce of Saginaw. The patient, aged 37, was taken ill with typhoid September 26 (Fig. 7). The disease ran the usual course of a case of moderate severity; the maximum temperature was 104° F. (40° C.). The Widal reaction was negative on the sixth day, positive on the twelfth day. On the seventeenth day the patient had a severe chill lasting half an hour, followed by a temperature of 105.5° F. (40.8° C.). The pulse was 120. After a profuse sweat the temperature returned to its former height—103° F. (39.4° C.). The phenomenon recurred on the twentieth day and again on the twenty-first day, and then throughout the subsequent course of the disease at varying intervals. After the chill of the twenty-first day there was a hemorrhage of moderate amount, followed by a period of subnormal temperature and slow pulse lasting nearly twenty-four hours. Repeated complete physical examinations and laboratory investigations failed to reveal any complication, except the hemorrhage. The Widal reaction at this time was negative. The white blood count was 2850. The plasmodium was absent. Blood culture was positive. Although the repetition of the chills was very alarming, the other symptoms were not unusual and the case went on to good recovery.

PULSE.—The pulse characteristics in typhoid fever are the slow rate in relation to the temperature and the early appearance of dicrotism.

At the first examination of a typhoid patient the physician's attention

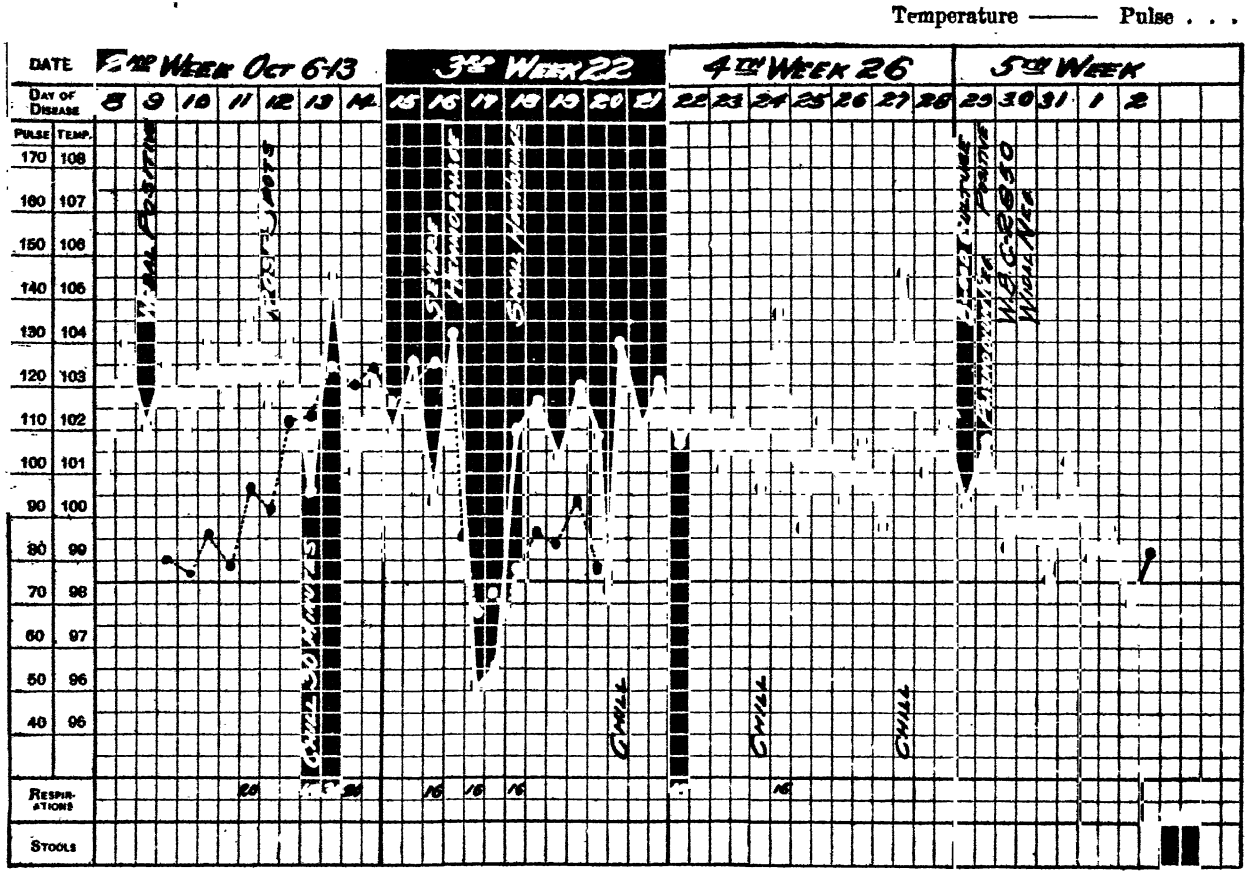


FIG. 7.—CHART IN CASE OF MODERATELY SEVERE TYPHOID FEVER.

Repeated chills during course; hemorrhage on 16th day, followed by subnormal temperature and slow pulse. (Personal observation. Patient aged 37.)

is usually arrested by the full, soft pulse, which may be elevated slightly or not at all above the normal rate. With a temperature of 103° F. (39.4° C.) and higher, a pulse rate of 90 to 100 is not unusual. The disproportion between temperature and pulse is most marked after the first few days and continues into the second or third week. Then the rule is for it to become more rapid and variable, and to follow more closely the irregularities of the temperature curve. In many cases of moderate severity the low rate holds throughout the entire course of the disease. In 500 cases studied by McCrae, there were 176 cases in which the pulse rate did not rise above 100.

The pulse may be rapid at the onset or become so at any period during the course of the disease. In a general way the rapidity is an index of the gravity of the case. Above 120 it is always looked upon with apprehension. It may be 140 or higher in the seriously ill. In adult patients with a pulse of 150 or more the mortality is very high. An intercurrent complication is often announced by an unexpected rise. Hemorrhage of any amount quite uniformly causes a sudden jump to 120 or higher. A rapid running pulse accompanies perforation. As noted elsewhere typhoid fever of infancy and early childhood usually shows a rapid pulse, which is not necessarily of grave import. In the period of decline and during convalescence the pulse is extremely susceptible to nervous and other disturbing influences and may show wide diurnal oscillations.

At the end of the febrile period, when the temperature is subnormal, a very slow pulse, as low as 50 or 60, is not uncommon and a true bradycardia may be seen with a rate of 40 or lower. No serious import is attached to this slow pulse. Irregularity and intermittence sometimes attend the slow rate.

The dicrotic pulse is more frequent in typhoid fever than in any of the acute infections. It appears early in the first week and may continue throughout the disease. It often disappears in the second or third week, gradually becoming less pronounced as the pulse becomes more rapid.

Therapeutic measures, particularly the cold bath, change the quality and rapidity of the pulse. A reduction of ten beats or more is usual after the bath, the pulse losing its full compressible character and becoming smaller and firmer.

Blood-pressure.—The blood-pressure in typhoid is almost invariably below the normal range for the individual infected. In 115 cases studied by Crile the highest systolic pressure was 138 mm., the lowest 74 mm. and the mean 104 mm. The hypotension increases as the disease advances. Crile's cases showed a mean pressure in the first week of 115 mm.; second week, 106 mm.; third week, 102 mm.; fourth week, 96 mm. To be of practical value readings must be taken at frequent intervals and continued during the course of the disease. For this reason blood-pressure studies have not been popular.

Blood.—*The Red Cells.*—During the first week the number of red blood-cells remains about normal. In the second week a reduction in the count is evident and this gradually increases and becomes greatest

about the end of the febrile period. Thayer found the fall frequently accentuated in the fourth week. Regeneration of the blood begins with convalescence, or even before, should a mild fever prolong the period of decline into the fifth or sixth week. The average maximum loss is 20 per cent. of the red-cells. Sudden loss of body fluids from diarrhea, vomiting and profuse sweats may cause a transient, apparent increase. A sudden fall is the usual result of any considerable hemorrhage. The reduction of the hemoglobin percentage is about the same as the percentage loss of red cells.

Leukocytes.—Uncomplicated typhoid fever shows a characteristic reduction in the number of leukocytes in the peripheral circulation. In the first few days of the fever the number is normal, or there may be a slight increase. The number then progressively diminishes during the period of pyrexia, the extent of the fall depending upon the severity of the toxemia. A fall to 2,000 or even lower is not uncommon, and may indicate a feeble defense and be of grave significance. The average number at the height of the disease is from 4,000 to 5,000. In exceptional instances, from 8,000 to 10,000 may be found in uncomplicated cases. The differential count shows (1) a progressive reduction in the percentage of polymorphonuclear cells, (2) a progressive increase in the percentage of the mononuclear cells, especially of the large forms, and (3) a constant reduction in the percentage of the eosinophils. With the establishment of convalescence the number of white cells returns to the normal, although the characteristic differential count may continue for some time. A moderate leukocytosis is not unusual during the convalescent period, often caused by some mild or hidden secondary infection.

Cold baths cause a sudden but transient increase in the number of leukocytes. The number may be increased to three or four times what it was before the bath. The relative percentage in the differential count remains unchanged. This transient increase is not a true leukocytosis. It is dependent upon the changed surface circulation. For this reason a white cell count for diagnostic purposes should not be taken for three or four hours after a cold bath.

Inflammatory complications and secondary infections by pyogenic organisms quite uniformly cause leukocytosis. The leukocytic count, therefore, is a most valuable aid in the differentiation of typhoid fever from septic conditions and in the recognition of the onset of septic and inflammatory complications. In very severe and malignant infections no increase in the number of leukocytes may take place. A high white cell count often immediately follows hemorrhage from the bowels, reaching a maximum inside of twenty-four hours and returning to the former number inside of a week.

Perforation of the bowel also is marked by a leukocytosis which may precede the perforation by several hours. Usually it begins a few hours after the accident and rises rapidly to 10,000, 15,000 or higher. With the onset of general peritonitis there is often a rapid fall. The rapid changes in the number of leukocytes following perforation render

an hourly leukocyte count essential to the proper determination of the significance of this symptom. In perforation complicating profoundly toxic cases there is either no change or, frequently, an actual reduction in the number of cells.

THE TYPHOID RASH.—The characteristic cutaneous symptom of typhoid fever is the rose-rash, a maculopapular eruption appearing chiefly upon the abdomen, chest and back. The rash can be demonstrated in from 80 to 90 per cent. of cases. McCrae's white patients showed it in 93.2 per cent. It is distinctive of typhoid fever and is eagerly looked for by the physician as the earliest conclusive clinical diagnostic feature.

The rash consists of a number of discrete, circular, rose-colored spots from 1/12 to 1/8 inch in diameter. They are slightly elevated above the skin surface, perceptible to gentle palpation, and disappear with pressure. A minute vesicle sometimes forms at the apex of the lesion, and in severe cases some of the spots may become hemorrhagic. The eruption usually first appears at the end of the first week or the beginning of the second week—from the sixth to the tenth day. It may appear as early as the second or third day or as late as the fifteenth. In exceptional cases it is delayed until late in the attack, even after the end of the febrile period. The spots come in successive crops, a few at a time, and the individual lesion lasts from two to five days. The spots fade away, leaving a faint discoloration covered with a fine desquamation.

The duration of the rash as a whole is from one to two weeks; or it may persist during the whole febrile period. The average number of lesions present at one time is not large—from five to twenty. Only three or four may be found, or they may be very numerous: one hundred or more. The site of the rash is usually the abdomen and lower thorax, often the back and more rarely the neck, arms and legs. In quite rare cases spots have been found on the face. The typhoid bacillus can often be recovered from the blood taken from the rose-rash.

TONGUE AND MOUTH.—In the early days of the disease the tongue is moist and covered with a white fur. As the disease progresses the coating becomes thicker and discolored. The oral secretions are diminished and thick and the tongue tends to become dry and cracked, often red and glazed. It is tremulous and protruded with difficulty. The red, dry, baked tongue is particularly noted in cases with severe diarrhea and great prostration. The condition of the mouth and tongue is often an index of the quality of the nursing. With modern hospital care the dry tongue and foul mouth are much more rarely seen than formerly. Any great collection of sordes on the gums or teeth is certainly an indication of neglect.

COUGH.—Bronchitis is quite a constant feature of typhoid, and shows itself by an infrequent cough in the early days of the disease. It is usually restricted to the upper bronchi and causes no other symptoms. A few coarse râles are heard over the front and back of the chest. It may be more severe and attended by a frequent, distressing cough and by dyspnea. Abundant coarse and fine râles fill the entire chest.

CONSTIPATION AND DIARRHEA.—Either of these conditions may be

present throughout the whole course of the disease, or there may be alternating periods of constipation and loose movements. In the endemic typhoid of the large cities of this country constipation predominates. In two outbreaks recently observed by the author (Jennings), the ingestion of highly polluted river water was followed in from three to five days by a severe gastro-enteritis with diarrhea. About 20 per cent. of these cases developed typhoid fever later. Instead of persisting, the diarrhea usually abated with the onset of the typhoid fever and was replaced by constipation. This would tend to show that the diarrhea was the result of a general intestinal catarrh, and that the typhoid lesions themselves did not produce diarrhea. In general, diarrhea is present in some stage of the disease in from 20 to 30 per cent. of the cases. It occurs as a prodromal symptom in a small number of cases. It may appear in the latter part of the first week, or not until the second or third week. The administration of cathartics may precipitate the onset of the condition. The influence of bad feeding is very great, and the onset of loose movements after a period of constipation usually calls for a careful revision of the diet. When diarrhea is present the number of movements varies from one or two in the twenty-four hours to as many as six or eight or more. The movements are large, thin and of a dull yellow color. The reaction is alkaline and the odor is offensive. The characteristic typhoid stool has the consistency and appearance of pea soup. After it has stood, a thin, turbid fluid layer overlies a thicker, flocculent, opaque stratum. Severe diarrhea is an unfavorable symptom. It drains the tissue fluids, dries up the tongue, seriously interferes with nutrition, and aggravates the exhaustion and wasting of the late period of the disease.

Abdominal Tenderness and Pain.—Abdominal tenderness accompanied by or without pain, is one of the group of symptoms that help to make up the commonly recognized clinical picture of typhoid fever. The tenderness may be general over the whole abdomen or, more frequently, it is restricted to the right lower quadrant. It can often be elicited early in the period of invasion, and, in that case, may be an important suggestive symptom; or it may be found at any time during the course of the fever. The specific bowel lesion is of itself an adequate cause for the symptom. Neither the tenderness nor the pain due to this cause alone is usually severe. In diarrheal cases the tenderness is greater and more widely spread over the abdomen. In these cases pain of a colicky character may precede the bowel movements or may be continuous and harassing to the patient. In certain cases severe abdominal pain may be present, with tenderness, distention and rigidity, but with no complication that can be demonstrated. Many conditions incident to the course of a prolonged fever may cause periods of pain of longer or shorter duration. Attacks of indigestion, vomiting, colic, diarrhea or constipation, and distended bladder belong to this group. Pain over the enlarged spleen is quite common. Various thoracic and abdominal complications are manifested by abdominal pain and tenderness and these symptoms, if at all severe or persistent, demand critical

search for their cause. In the presence of unusual abdominal pain, perforation and hemorrhage should always be uppermost in the mind of the attendant, because of the urgent necessity of prompt diagnosis. McCrea found pain and tenderness from various causes and complications in three-fifths of 500 carefully studied cases.

TYMPANITES.—Intestinal paresis, the result of inflammatory exudate in the musculature of the bowel wall, favors the development of tympanites, which is present at some time in the course of the disease in most cases of typhoid. Gurgling from intermittent pressure over the right iliac fossa may be elicited in the first week of the disease. It is found so frequently in other acute abdominal conditions that it cannot be considered a distinctive typhoid symptom, but it may complete the symptom-complex of the first week of the disease, and thus aid in arousing suspicion of the onset of typhoid fever. Mild and moderately severe cases, if properly nursed and carefully fed, rarely show tympanites of any severity. The development of the condition in these cases, as in diarrhea, calls for a revision of the dietary and attention to the alimentary tract. A clean colon is an efficient preventive.

Severe meteorism is an indication of toxemia and may be of grave import. It seriously interferes with the digestion and absorption of food, and it may precipitate hemorrhage or perforation. It may also seriously embarrass respiration and the action of the heart. A single deep ulcer has been thought to be the cause of severe intestinal distention.

SPLEEN.—The spleen is invariably enlarged. Swelling begins with the onset of the disease but can rarely be demonstrated by palpation until the end of the first week or the beginning of the second week. The spleen may not become palpable until late in the disease, or not at all. The enlargement can be determined with certainty only by palpation. Percussion is notoriously unreliable. In Osler's studies the organ was palpable in 71 per cent of all cases. It is, therefore, an important member of the group of clinical findings that permit a presumptive diagnosis of typhoid fever.

HEADACHE.—This is a constant early symptom, occurring in from 70 to 75 per cent. of the cases. It may be a dull, heavy ache or an intense stabbing or boring pain. It may be frontal or occipital, more rarely parietal. It comes early, and by fixing the attention of the patient it is very useful in directing investigation to possible typhoid infection. It continues throughout the first week and lessens in severity in the beginning of the second week, when increasing mental hebetude tends to blunt the sensibilities of the patient. Headache continuing or increasing later than the end of the second week should excite suspicion of meningitis or other intracranial complication.

THE TYPHOID STATE.—This term is used to designate the symptom-complex expressing the profound asthenia that may result from severe infections or intoxications. It is not distinctive of typhoid fever. It may be met in the course of any severe and prolonged infectious disease, in abdominal inflammations, in urinary tract infections, intracranial

diseases and in some intoxications like acute phosphorus-poisoning. In the second week of severe cases of typhoid fever, earlier in the worst forms, the patient passes into a state of extreme physical and nervous prostration. He lies in bed relaxed and in a more or less profound stupor. Consciousness is obliterated and the special senses dulled. He responds sluggishly to mental and physical impressions. He is aroused with difficulty and takes food and drink only when urged. The temperature is usually high, although in the aged and in alcoholic, diabetic and other debilitated patients the pyrexia may be of a low type. The pulse is rapid and weak. The respiration is quickened because of passive congestion of the base of the lungs. The tongue is brown and dry, the lips cracked, and there is abundant dry secretion on the teeth and gums. There is a low muttering delirium, twitching of the tendons, picking at the bed clothes and grasping after imaginary objects. Involuntary discharge of the excretions may occur. This condition, when pronounced, is always a very grave one.

Relapse.—Recrudescence or Spurious Relapse.—The convalescent period is not infrequently interrupted by short periods of pyrexia. The typhoid convalescent is peculiarly sensitive to fever-producing influences. No adequate cause may be found, but usually the disturbance can be traced to an indiscretion in diet, constipation, a return of the diarrhea, physical exertion, or nervous excitement. An indiscreet visitor will often excite a transient rise of the patient's temperature. A careful search should always be made for a complication.

The important feature of the recrudescence is the rise of temperature. Malaise, headache and a return of the lassitude are the usual accompaniments. The temperature reaches the maximum in from one to three days and quickly begins to decline. The duration of the febrile period is from one to five or six days. Apprehension that the apparent recrudescence may be the onset of a true relapse is always in the mind of the attendant.

True Relapse.—The true relapse is a re-infection of the patient with the typhoid bacillus, after convalescence is apparently established. It occurs after a few days of normal temperature, usually before the end of the second week after the termination of the original period of fever. It may begin as early as the second day after the temperature has fallen to normal, or its appearance may be delayed until the fourth week or longer. The longest interval in McCrea's series was 43 days. In Curschmann's experience it was 53 days.

The frequency of relapse varies in different epidemics and it is stated by writers to occur in from 3 to 16 per cent. of the cases. In a collection of 28,057 cases by McCrae from European and American sources relapse occurred in 8.8 per cent.

Liability to relapse is as great or greater in mild as in severe primary attacks. Often the mild and abortive cases are followed by severe relapses from which the diagnosis of the original attack may first be made in retrospect.

The cause of relapse is not settled. The authors are in accord with

Gay, who believes that they "are undoubtedly due to the overflowing of typhoid bacilli from their localized metastatic or ultimate foci in the body." Among these foci, those which have been considered to be particularly concerned in the etiology of relapse are the gall-bladder, spleen and bone-marrow. These tissues serve as reservoirs for the re-infection of the circulation.

Except when it follows a very mild or abortive attack, the relapse runs a shorter course than the first infection. The relapse may be multiple, two or more attacks succeeding each other at varying intervals. Osler records a case with six relapses. The onset of a relapse is usually gradual, with the step-like ascent of the temperature as in the primary attack; or it may be sudden, with chill and rapidly rising fever. The symptoms are practically the same as in ordinary typhoid. The pulse is usually more rapid and dicrotism is less frequent. The rose-spots may reappear, and the spleen enlarge. It has frequently been noted that relapse is very apt to follow if splenic enlargement persists after convalescence from the original attack. A new crop of intestinal lesions may occur, and the typhoid bacillus may again be recovered from the blood.

The duration of the relapse is from one to three weeks. In exceptional cases a moderate irregular pyrexia persists for several weeks without evidence of a pus focus or other complication.

The mortality of true relapse is low, from 2 to 5 per cent. Shattuck met with one death in 21 cases. McCrea, in 172 cases of relapse, observed 5 deaths, or 2.9 per cent. In the Hamburg epidemic cited by Curschmann the death rate in 496 relapses was 4.9 per cent.

Intercurrent Relapse.—This is a term applied in this country to an exacerbation of the disease that begins during the period of decline, before the temperature has become normal. Curschmann, Sidney Phillips and other European writers, speak of this form of relapse as a recrudescence. After the period of high temperature has passed and the patient appears to be well on the way to recovery the temperature again rises to a high point and all the symptoms of the fastigium reappear, continue for a week or more, and then gradually fade away. The course of this form of re-infection may be very severe and protracted. The frequent occurrence of relapse seems to indicate that immunity to typhoid infection is acquired slowly and is not fully established until some weeks after the end of the febrile period.

Second Attack.—One attack of typhoid fever usually gives immunity that continues through life. Immunity may, however, be abridged, and a second attack occasionally occurs at an interval of months or years after the first.

During the last year the author (Jennings) observed a boy of 15 in the height of a typhoid attack who had passed through an equally typical attack under the same attending physician eight months before. As the diagnosis in both attacks was made by clinical findings alone one of the infections may have been a paratyphoid. Infection by different

strains of the typhoid group of bacilli may explain many if not all cases of second attacks.

DIAGNOSIS

The modern diagnosis of typhoid fever rests upon (1) the analysis of the clinical history and symptoms presented by the patient, and (2), the demonstration by laboratory methods of the typhoid bacillus in the body and the specific reactions that it there produces.

Because of the high morbidity from typhoid fever in rural communities, remote from hospital and laboratory facilities, the diagnosis of the disease at the present time, in a large proportion of the cases, is based upon clinical data alone. The establishment in the last few years of public and private clinical laboratories extensively throughout the country is rapidly bringing laboratory facilities for diagnosis within the reach of all.

Bedside diagnosis by experienced clinicians can usually be made with precision, and few cases running anything like the average course escape detection, although the diagnosis is often delayed until late in the course of the disease when a retrospective analysis of the symptom-complex can be made and other pathological conditions excluded by the course of events. However, the disease presents such a variability in symptomatology, it simulates so closely other febrile diseases, and so many mild and atypical cases occur in which distinctive symptoms are missing, that diagnosis without laboratory aid may be very difficult; indeed, it is often impossible.

The laboratory is the short cut to a positive diagnosis. Its aid when available should always be sought, but it should not take the place of careful clinical observation and study. A presumptive clinical diagnosis should first be made and then checked up by laboratory examinations. Too great dependence upon the laboratory conduces to carelessness in bedside observation and tends to develop a feeble faith in clinical deductions.

In the final analysis, however, it must be admitted that no positive diagnosis of typhoid fever can be asserted without the confirmation of laboratory tests. As Gay correctly says, "If repeated and complete laboratory tests for typhoid fever, properly performed, result negatively, no definite positive diagnosis of typhoid fever should be made on the basis of the clinical examination alone."

Depending upon the period in the clinical history in which a case first comes under observation, or in which the question of typhoid infection first arises, the problem of the diagnosis of typhoid fever presents itself practically at the bedside in three phases:

First, the diagnosis in the first week of the disease.

Second, the diagnosis in the period of continuous high temperature, from the second to the fourth week.

Third, the diagnosis in cases of prolonged pyrexia in which typhoid infection is suspected.

Diagnosis in the First Week

Typhoid fever should be considered as a possibility in the diagnosis of every acute febrile illness, regardless of the mode of onset or the age of the patient. A provisional or positive diagnosis at the earliest possible time is important both to the welfare of the patient and for the protection of the community. With this disease in mind the physician will so direct his clinical and laboratory investigations that an early solution of the problem is made possible. The differential diagnosis of typhoid fever in the first week from the many diseases that resemble it is peculiarly the problem for the family practitioner. The symptoms are rarely so urgent as to suggest consultation or hospital care. The family practitioner should be an expert in this field of differential diagnosis.

General Diagnosis.—Clinical Data.—From the clinical data alone only a provisional diagnosis of typhoid fever is possible in the first week. There are no characteristic individual symptoms of onset, but a careful study of the group of phenomena present will usually lead to a suspicion strong enough to be a guide to personal and preventive therapeutics.

The clinical data of the first week that determine the provisional diagnosis are:

(1) *Mode of Onset.*—This is usually gradual, and is often preceded by a few days of vague symptoms that are ascribed to a cold, digestive disturbances, or to some other minor ailment. Chilliness, or less frequently a distinct chill, may usher in the invasion period.

(2) *Temperature.*—The gradual steplike ascent of the temperature is a symptom of significance when observation begins on the first or second day. Opportunity for this early observation comes frequently to the family practitioner. Unfortunately the habit of the routine administration of an antipyretic in the early days of acute febrile diseases too often hides the suggestive curve. Such treatment is unwise when the diagnosis of a developing infection is in doubt. No variety of temperature curve, however, should exclude typhoid; exceptions to the rule of gradual rise are very frequent.

(3) *Pulse-rate.*—The pulse-rate, which is remarkably slow in relation to the height of temperature, quickly arrests the attention of the careful clinician. With a temperature of 102° or 103°F. (38.9° or 39.4°C.) a pulse rate below 100 is often noted. This lack of harmony is quite peculiar to typhoid fever and is a valuable suggestive symptom. The character of the pulse is full, soft, and shows dicrotism quite early. Associated with the slow rate, the dicrotism has much significance.

(4) *Headache.*—Headache is often the most emphatic symptom of invasion, and while common to other acute diseases it should always direct attention to typhoid fever. It may be severe and persistent. It is quite significant in patients previously free from headaches.

(5) *Tenderness and Gurgling.*—These symptoms can be demonstrated in the right lower quadrant of the abdomen during the first

week, in quite a percentage of the cases. Abdominal pain, general or localized, is also frequent.

(6) *Diarrhea.*—Diarrhea at the onset is very unusual in other acute febrile diseases. It is present early in from 20 to 30 per cent. of typhoid cases.

(7) *Epistaxis.*—Epistaxis from the second to fourth day occurs often enough to be an important suggestive symptom.

(8) *Prostration and Mental Dullness.*—In early typhoid these symptoms are quite out of proportion to the other manifestations, and should direct attention to this disease.

(9) *Cough.*—Cough is present in a large percentage of cases. Associated with a rising temperature and with other symptoms disproportionate to the findings in the chest, it should suggest further examination for the presence of typhoid infection.

The foregoing group of symptoms, more or less complete, persisting over a period of a week and not manifestly due to some other infection, justifies a provisional diagnosis of typhoid fever. The prevalence of typhoid fever in the locality, the history of a recent visit to an infected community, or the possibility of personal contact with a typhoid patient, may be incidents of distinct aid in establishing the diagnosis.

Laboratory Data.—A positive diagnosis of typhoid fever by laboratory tests can be made in the first week of the disease in from seventy to eighty per cent. of the cases. This certainty, as compared with the vagueness of clinical deductions, emphasizes the importance of resorting to laboratory methods of diagnosis in every case of acute febrile disease which is ushered in by symptoms suggestive of typhoid fever. Laboratory methods are considered in detail under a separate heading.

(1) *Blood Culture.*—A positive blood culture is the most convincing evidence of typhoid fever. It is the most important single factor in the early diagnosis of the disease. Fortunately the percentage of positive cultures is highest in the first week. Any physician should be able to master the simple technic necessary to withdraw blood aseptically from a vein and to inoculate a flask of sterile boullion. The culture can then be sent to a bacteriological laboratory for incubation and study. This simple procedure will usually cut short the many days of embarrassing doubt that must intervene if one waits for the development of convincing clinical data.

(2) *Agglutination Test or Widal Reaction.*—A positive agglutination reaction can be obtained in about 90 per cent. of all cases of typhoid fever, at some period of the disease. It is a late symptom, rarely appearing before the eighth day. It is, therefore, of comparatively little assistance in making a diagnosis in the first week. While a positive result is highly presumptive of typhoid, a negative finding has no significance. As noted elsewhere, subjects vaccinated against typhoid fever give a positive agglutination test for several months following vaccination.

(3) *Leukocyte Count.*—Uncomplicated typhoid fever gives a low white-cell count, manifested early and continuing throughout the dis-

ease. At the onset the count is often normal or slightly increased. By the middle of the first week the number of white-cells falls to from 2,000 to 5,000 per cu. mm. The differential count shows the polymorphonuclear cells and eosinophils to be decreased, and the mononuclear cells increased. Increased leukocyte count is common to most diseases that may simulate typhoid fever in the first week. This simple laboratory procedure, therefore, is of great value in early diagnosis. A leukocytosis rules out uncomplicated typhoid, while a leukopenia is strongly suggestive of it.

Differential Diagnosis.—All of the acute febrile diseases must be passed in review in the differentiation of typhoid fever in the first week. In most of these diseases the appearance of distinctive clinical symptoms within two or three days eliminates the possibility of typhoid; in a certain number of cases careful matching of symptoms for several days, and an early resort to laboratory aid, are necessary to reach a conclusion.

THE ACUTE EXANTHEMATA.—The symptoms of the eruptive fevers before the appearance of the rash may give rise to the suspicion of the onset of typhoid fever. Sudden onset with vomiting, rapidly rising temperature, quick pulse, peculiar tongue and red, sore throat are characteristic of *scarlatina*. The eruption, appearing in from twenty-four to thirty-six hours, quickly determines the diagnosis. In rare cases a scarlatiniform erythema in the first week of typhoid may be confusing. In *variola* the longer period of invasion and the severe headache may suggest typhoid. In variola vomiting is common and the intense backache is very characteristic. The eruption comes on the third day. *Measles* may be more confusing. The invasion is more gradual and the distinctive catarrhal symptoms are frequently delayed for three or four days. The cough may resemble the early cough of typhoid, and the drowsiness may suggest the typhoid stupor. The conjunctivitis and coryza are almost never seen in typhoid. Koplik's spots are positively diagnostic of measles. The rash comes on the fourth day. In the exceptional cases in which the eruption is delayed until the fifth or sixth day typhoid fever may be strongly suspected.

IN INFLUENZA the onset is usually sudden. In the recent epidemic, however, many cases developed gradually, with steplike rise of temperature, abdominal tenderness and relaxed bowel movements. This was followed by mild catarrhal symptoms, relatively slow pulse, low white blood-cell count, headache and nose-bleed,—a symptom-complex impossible to distinguish from typhoid fever. The critical drop in temperature about the end of the week would determine the diagnosis of influenza, except that it might mark the end of an abortive attack of typhoid fever. A positive diagnosis is possible only by blood culture. Persistence of the continued fever through the second week renders typhoid probable, although the pyrexia of influenza may persist for two weeks or longer. Recently a hospital patient under the author's (Jennings') care, convalescent from typhoid, surrounded by influenza, developed fever two weeks after defervescence. The question arose: was the fever due to

influenza or to a typhoid relapse? A positive blood culture on the fifth day made typhoid relapse fairly certain, as the typhoid bacillus is rarely found in the circulating blood so long after the end of the fever. The subsequent typical course of the relapse confirmed the laboratory diagnosis.

PNEUMONIA may simulate typhoid fever in the invasion period. The physical signs of pneumonia in children and in the aged are often masked and the disease will run along for several days with only the symptoms of fever, a slight cough and almost no physical signs. Central pneumonia at any age may give the same confusing clinical history. In contradistinction to typhoid fever the onset of pneumonia is abrupt, usually with a chill. The temperature quickly rises to a moderate height and persists. Increased frequency of respiration is almost always present from the beginning, and is a symptom of such great significance that it should call attention immediately to pulmonary disease. Pleuritic pain may be absent or, what is more confusing, if present it may be referred to the abdomen. The expected rusty sputum may not appear for several days. Herpes, practically never seen in the first week of typhoid, is a frequent pneumonia symptom. Repeated physical examination of the chest, carefully made, searching for signs at the apex, the base and in the axillary region, will rarely fail to unmask a pneumonia after two or three days. The leukocyte count, high in pneumonia, low in typhoid, is a great diagnostic aid. Blood culture with a positive finding is conclusive. Typhoid fever with pneumonia-like onset, pneumo-typhoid, giving the symptoms and the physical signs of pneumonia, is a rare condition, which the author has never observed. It would deceive the elect. Only the late history of the case will suggest the possibility of typhoid fever, and a positive diagnosis can be made only by laboratory methods.

SEPTICEMIAS AND LOCAL INFECTIONS.—The septicemias and local infections by the streptococcus, staphylococcus, gonococcus, colon bacillus and other organisms, often present the problem of differentiation from typhoid fever. The *septicemias* develop rapidly and without premonitory symptoms. The first days are marked by chills and by an erratic temperature, irregularly remittent or intermittent in type. After the initial chill the temperature may rise to a high point and persist as a continued fever. Profuse sweats are common. The pulse is rapid, quite distinct from the slow, dicrotic pulse of typhoid. The spleen enlarges early and may be a confusing symptom, although early enlargement is but rarely seen in typhoid. A portal of entry of the infection can often be demonstrated. With its usual symptoms of onset, typhoid fever would rarely be confused with a septicemia, but the early clinical history of both conditions is so variable and may be so similar that in many cases certainty in diagnosis in the first week may be obtained only by laboratory methods. A high leukocyte count with a high percentage of polymorphonuclears is characteristic of septicemia. A blood culture with positive findings would certainly differentiate the two diseases.

The fever attending hidden *local infections* by the various pyogenic organisms may be mistaken for typhoid fever before local symptoms of pus infection are pronounced. Infections of the throat, middle ears and of the accessory sinuses of the nose, particularly in the case of children, may pursue their course for several days, with fever as the only symptom, and would suggest the onset of typhoid fever. Subdiaphragmatic abscess, cholecystitis, pylephlebitis, hepatic abscess and perinephritis in the upper abdomen; salpingitis, prostatic or perirectal abscess in the lower abdomen, may begin with fever and indefinite or no localizing symptoms. The urinary septicemia of old men with prostatic disease, manifested by fever, dry, brown tongue, nervous symptoms and prostration, may arouse the suspicion of typhoid. Pyelitis in children and pregnant women causes a fever with no distinctive subjective or objective symptoms, and if a routine urinary analysis be neglected the disease may easily be mistaken for typhoid. Osteomyelitis in children has been mistaken for typhoid fever. General infection by the gonococcus may cause confusion when the local infection is concealed.

The distinction of these various infections from typhoid fever depends, *first*, upon a searching and complete physical examination—every region and organ should be examined for localizing signs—*second*, upon the results of the white blood-cell count and blood culture. A high leukocyte count fixes the attention upon a pus infection and stimulates further search for the focus. It may in itself be conclusive. A blood culture is of decisive assistance.

Puerperal Septicemia.—The obstetrician occasionally is reluctant to acknowledge puerperal infection and seeks to explain a postpartum fever by the presence of an intercurrent infection like typhoid fever or malaria. The problem of differential diagnosis is the same here as in septicemia of other etiology. The fact of the puerperal state, however, is of the highest significance. It is strong presumptive evidence of a septicemia, and only the positive results of laboratory tests should be taken as proof of an intercurrent typhoid. Typhoid fever may occur in the pregnant woman and cause abortion or premature delivery. The fever persists after delivery and a differential diagnosis from septic infection may be impossible without laboratory assistance.

Appendicitis.—Appendicitis begins suddenly with sharp abdominal pain, circumscribed tenderness in the right lower quadrant, and muscular rigidity. Irregular fever, slight or of moderate degree, is present; the pulse is rapid; nausea or vomiting and constipation are usual. The abdominal symptoms of typhoid fever are very rarely as pronounced as in appendicitis, and an error in diagnosis should not occur. Although there may be pain and tenderness, rigidity is not present in typhoid. The leucocyte count is of great value. It is quite uniformly high in appendicitis. We have known eager young surgeons impressed with the necessity of immediate operation in appendicitis to open the abdomen in typhoid, expecting to find a diseased appendix. Typhoid fever with an early complicating appendicitis would present unusual difficulties. In recent army experience, anti-typhoid vaccination has

occasionally been followed by fever, acute abdominal pain and vomiting. Such cases have been mistaken for and treated as appendicitis.

ACUTE ENTERITIS.—Acute enteritis with fever, abdominal pain, distention and tenderness, and diarrhea suggests the onset of typhoid fever. The severe forms of enteritis begin with stormy symptoms. The fever rises abruptly and all the symptoms reach their height in from twenty-four to forty-eight hours and then as a rule begin to subside. Should the fever persist longer distinction by clinical evidence alone is impossible until the presence of the rash, the enlarged spleen, and the steady temperature curve of the second week of typhoid fever clears the diagnosis. Milder forms of gastro-enteritis are frequently met with, particularly in children, and are more difficult to differentiate. The fever is moderate; distention, gurgling, pain and tenderness in the right lower quadrant are frequently seen. Anorexia, coated tongue and headache may be added and complete a clinical picture identical with that of the first few days of typhoid fever. Such symptoms usually promptly respond to low diet and cathartic medication, but when rebellious to such treatment laboratory aid to exclude typhoid fever may be required.

EPHEMERAL FEVER, FEBRICULA, SIMPLE CONTINUED FEVER.—These terms are used to designate short, febrile attacks of undetermined etiology. Such fevers may resemble typhoid fever during the period of onset. Complete laboratory study of these cases shows that many of them are examples of mild typhoid or paratyphoid infection. Others are symptomatic of hidden local infections or due to toxic causes. A final diagnosis of febricula, which is a confession of ignorance, is justified only when thorough investigation by clinical and laboratory methods fails to reveal a definite etiology.

PARATYPHOID FEVER, A AND B.—Paratyphoid fever cannot certainly be distinguished by clinical methods from typhoid fever. Either variety of paratyphoid may pursue a course identical with that of typhoid fever and present all the symptoms and complications of this disease. Practically a positive differential diagnosis is of minor importance. The therapeutics of the two diseases is identical and the measures to be adopted for the prevention of their extension in the community are the same.

The recent studies of groups of paratyphoid infections by observers with the armies in France have shown, however, that there are certain clinical differences between the paratyphoid and typhoid fevers which, while they are not sufficiently marked to distinguish with any certainty individual cases, may be adequate in group observation for provisional differential diagnosis. Wiltshire states that as his experience increased he found that it was possible to give a fairly sound opinion on the differential diagnosis of the two diseases, "though never with such certainty that bacteriological examination could be excluded."

In general, the paratyphoid fevers pursue a milder and shorter course than does typhoid. The onset of paratyphoid is more frequently abrupt, and the duration of the period of invasion is shorter—from three

to four days. The initial symptoms are very similar to those of typhoid. Anorexia, nausea, headache, epistaxis and insomnia are usual. Vomiting and chills are much more frequently noted than in typhoid. The temperature rises more sharply and reaches the usual maximum of about 103°F. (39.4°C.) in three or four days. The fastigium and the period of decline are both shorter than in typhoid, and the total duration of the pyrexial period is usually not more than two weeks. Early and marked remissions of the fever are the rule. The pulse is slow, as in typhoid, but dicrotism is less frequent. The tongue is more apt to be moist and is not so heavily coated as in typhoid. Gastro-intestinal symptoms are often more severe but of shorter duration. The stools are darker in color. The liver is frequently palpable below the rib line, and jaundice, very unusual in typhoid, is a frequent symptom. The spleen, although enlarged, is rarely palpable. The rose rash is present in about 60 per cent. of the cases and appears rather later in the disease than in typhoid. Wiltshire gives the average date of appearance as the thirteenth day. The spots may not be distinguishable from the typhoid roseola. In about 50 per cent. of the cases the rash is of the "paratyphoid type" (Wiltshire). Each individual spot is larger than the rose spot of typhoid fever, much more raised, and frequently lenticular in outline. The spots are darker in color and do not completely disappear on pressure. Pigmentation and desquamation are usual. This peculiar type of eruption is quite striking in appearance and is of considerable importance in differential diagnosis. Herpes, very rare in typhoid fever, is quite frequent in paratyphoid and when present should always suggest this disease. Perspiration is frequent, both at the onset and during the course of the disease, and is often profuse. Nervous symptoms are less frequent and less severe than in typhoid, and the typhoid state is unusual. Meningeal involvement is stated to be more frequent than in typhoid. Severe occipital pain is common.

While the foregoing group of differential symptoms may be sufficient for a presumptive diagnosis, especially when viewed in retrospect, or observed in a group of cases, positive differentiation of paratyphoid from typhoid fever can be made only by the isolation of the paratyphoid bacillus from the blood, urine or feces and its identification by cultural methods, or by the Widal agglutination reaction.

Malaria.—The intermittent types of malarial fever bear no resemblance to typhoid fever. The onset of the remittent and the estivo-autumnal types, however, may closely resemble the onset of typhoid fever. Chills may be absent and a fever with slight remissions and increasing in severity may mark the first few days. Malaise, prostration, headache, coated tongue and diarrhea are common. There is a low leukocyte count and an early enlargement of the spleen. Differentiation can be made only by blood culture to isolate the typhoid bacillus and by the examination of the stained smear for the plasmodium. The estivo-autumnal parasite may not be found in the circulating blood for several days.

There is no such clinical entity as typhomalarial fever. The careful

studies of Osler in Baltimore, where both diseases prevail, have conclusively proven that such a mixed infection does not occur. In very rare cases the two infections may be concurrent and produce a confused clinical picture.

If laboratory aid is not available for diagnosis **quinin** in full doses may be given as a therapeutic test. Quinin has practically no effect upon the course of typhoid fever. It promptly arrests the fever of malaria.

TYPHUS FEVER—BRILL'S DISEASE.—The confusion of typhoid with typhus fever until the middle of the last century shows how closely these two diseases may resemble each other. Typhus fever is very rare in this country and occurs only under conditions which arouse suspicion of its possible presence. Typhus begins suddenly with chills, high fever, rapid pulse, great prostration, vomiting, severe headache and pain in the back and legs. The temperature rises rapidly and reaches its maximum in four or five days. Delirium and severe nervous symptoms begin early. The eruption appears from the third to the fifth day, is very abundant, darker in color than the rose spots of typhoid, and quickly becomes hemorrhagic. Mild cases, such as those described by Brill, may show a clinical course much less distinctive than the above. Differentiation from typhoid by clinical data alone may be impossible. Early laboratory tests should always be made.

RELAPSING FEVER.—Relapsing fever is a tropical disease, rare in the United States. It is distinguished from typhoid fever by the sudden onset with chill, high fever, nausea and vomiting, pain in the back and frequently jaundice. In from five to six days the temperature falls to normal with profuse perspiration. After an intermission of from a week to ten days there is a sudden relapse with a repetition of the symptoms of the first paroxysm. Positive diagnosis is made by the demonstration of the spirochetes in the blood.

CEREBROSPINAL FEVER.—Some cases of this disease with gradual onset may be mistaken for typhoid fever. The temperature rises slowly but irregularly. Headache is severe, vomiting is frequent and constipation marked. By the third or fifth day distinctively meningeal symptoms—rigidity of the neck, a positive Kernig's sign, and hyperesthesia—appear. A rash, appearing first on the abdomen, occurs in some cases on the third or fourth day. It is petechial in character, and quite distinct from the rose rash of typhoid. On the other hand, certain cases of typhoid fever with meningeal symptoms, *meningotyphoid,* may be mistaken for one of the forms of meningitis. Cases of true typhoid meningitis with invasion of the meninges by the typhoid bacillus have been reported. In doubtful cases the diagnosis must be made by laboratory tests. In cerebrospinal fever there is always a high polymorphonuclear leukocytosis, from 15,000 to 30,000 per cubic millimeter. In the presence of symptoms indicating the possible onset of cerebrospinal fever an early lumbar puncture is imperative for curative serum treatment, as well as for diagnosis. In cerebrospinal fever the spinal fluid is cloudy with polymorphonuclear cells containing the *Diplococcus*

intracellularis. In typhoid fever the fluid is clear. In the rare cases of typhoid meningitis Eberth's bacillus may be demonstrated in the fluid. In unusually doubtful cases a blood culture may be decisive.

TUBERCULOUS MENINGITIS.—Tuberculous meningitis, with its premonitory stage of vague symptoms and its slow onset, may present a still more difficult problem. The white-cell count is low as in typhoid. The spinal fluid in both diseases is clear and the tubercle bacillus is difficult to demonstrate. If a blood culture is available an early positive diagnosis may be made. In certain cases with a negative blood culture and with other confusing laboratory data, a differential diagnosis must be made from the clinical findings. In tuberculous meningitis the fever is very irregular in its course and not high. The pulse is often slow and arrhythmic. Vomiting, repeated several times during the first few days of the illness, is present in practically every case. It is often of the explosive type and comes at irregular intervals without adequate exciting cause. It is one of the most significant symptoms of the onset of the disease. There are present obstinate constipation and retraction of the abdomen, alternate flushing and paling of the face or extremities, rigidity of the neck, positive Kernig and Babinski signs, irregular pupils and local palsies. Stupor and coma develop comparatively early, without high fever or toxemia. As these distinctive symptoms are often of tardy development a diagnosis may not be possible in the first week.

Meningitis due to the pneumococcus, streptococcus, etc., is recognized by the demonstration of these organisms in the spinal fluid.

TRICHINIASIS.—Outbreaks of trichiniasis have been considered at first to be outbreaks of typhoid fever. In isolated cases mistakes are even more likely to occur. Trichiniasis is rather rare in this country and the possibility of the disease does not at once come to the mind of the average practitioner in the diagnosis of an acute febrile malady. Cases may readily be mistaken for typhoid fever. The onset, however, is sudden in trichiniasis. The fever is irregular in type. Usually it is remittent or intermittent; occasionally it is continuous. There are severe muscular and joint pains. The muscles are very tender, swollen and indurated, and the skin over them often edematous. Edema of the face, particularly of the eyelids, appears early. Abdominal pain and diarrhea are common. A white blood-cell count will determine the diagnosis. As first shown by Thomas K. Brown, of Baltimore, there is in trichiniasis a leukocytosis, 10,000 to 25,000 white blood-cells per cubic millimeter, with the remarkable finding of from 20 to 30 per cent eosinophils. A history of the ingestion of uncooked pork can usually be obtained.

DIAGNOSIS OF TYPHOID FEVER IN THE SECOND AND THIRD WEEKS

This problem is most frequently presented to the hospital attendant and the consultant. The hospital attendant rarely sees typhoid fever in the first week. The disease is usually well under way before the patient is admitted. The consultant also is not often called until the seri-

ous symptoms of the fastigium cause anxiety, or the absence of distinctive clinical signs has raised a doubt as to the diagnosis of typhoid.

In the second week the characteristic clinical signs of typhoid fever appear. The rose rash comes out from the 8th to the 12th day, and the enlarged spleen can be demonstrated about the same time. These two phenomena, with the history of gradual onset, continued fever with slow pulse, right iliac tenderness, diarrhea and nervous symptoms are, with rarely an exception, conclusive.

Cases entering the hospital seriously ill, unable to give a history of the previous course of the disease, with symptoms atypical in character or masked by complications, are often very puzzling and require complete clinical and laboratory investigation for their differential diagnosis.

The Widal reaction, the leukocyte count and the blood culture all are available at this period and a positive diagnosis by these methods can quickly be made, with only an occasional exception.

Differential Diagnosis.—Most of the diseases that must be considered in the early diagnosis of typhoid are eliminated by the second week of the fever. Diseases which earlier presented symptoms suggestive of typhoid either end or become distinctly differentiated before this time. The diseases most frequently confused with typhoid fever at this period are the septicemias and hidden localized pus infections, malarial, typhus and relapsing fevers, miliary tuberculosis and tuberculous peritonitis, malignant endocarditis, and syphilis.

Acute Miliary Tuberculosis.—The differentiation of this disease from typhoid fever may be very difficult. Either disease may continue for an indefinite time with high fever, a general toxemia, and no well-defined localizing symptoms. Tuberculosis is rarely recognized or even suspected in the first week. Cases usually come up for differentiation in the second or third week of the disease, or even later, with a presumptive diagnosis of typhoid fever made from clinical data. Some irregularity in the course of the disease or some delay in the appearance of the expected characteristic signs of typhoid fever raises a doubt in the mind of the attending physician as to the correctness of the diagnosis and calls for a review of the diagnostic data.

Acute tuberculosis may show the same gradual onset as typhoid fever, with chilliness, malaise, general muscular pains, headache, nosebleed, cough, occasional vomiting and diarrhea. In miliary tuberculosis the temperature is more often irregular and shows wide oscillations. The pulse is rapid, not dicrotic, and follows the temperature curve closely. The respiration is rapid—a symptom of great significance that should always direct attention to the respiratory organs.

Anorexia is not so marked as in typhoid fever and the tongue remains moist for a longer time. The abdomen is flat, gurgling and tenderness are absent. Diarrhea is not frequent and the peculiar typhoid stools are wanting. There is no rose rash. The spleen may be palpable as in typhoid. Pulmonary hemorrhage is distinctive of tuberculosis; intestinal hemorrhage distinctive of typhoid.

Repeated and careful physical examination of the chest may reveal the signs of early pulmonary disease. An *x*-ray may be of value. Complete laboratory tests should settle the diagnosis. A low white blood-cell count is found in both diseases. Tubercle bacilli in the sputum clinch the diagnosis of tuberculosis. A positive Widal reaction and a positive blood culture distinguish typhoid fever.

TUBERCULOUS PERITONITIS.—This disease pursues a long, febrile course with abdominal symptoms, and may closely resemble typhoid fever. The fever is usually not high and is remittent or intermittent in character. The pulse is rapid. Abdominal pain and tenderness, distention and diarrhea may be present in tuberculous peritonitis. The severe toxemia and the nervous symptoms distinctive of typhoid fever are not seen in peritonitis, except possibly very late in the disease. Sooner or later masses in the abdomen, or ascites, reveal the nature of the disease. The Widal reaction and blood culture are positive methods of differentiation; the tuberculin test may be of additional value.

MALIGNANT ENDOCARDITIS.—The typhoidal type of malignant endocarditis is a close counterfeit of typhoid fever. It is characterized by high fever of a remittent or continuous type with few or no definite localizing symptoms. The toxemia is severe and the patient soon falls into the typhoid state with dry tongue, delirium and picking of the bed clothes. Confusion with typhoid fever is increased by the frequent enlargement of the spleen, by the presence of petechiæ, and of a mild bronchitis. The abdominal symptoms of typhoid may be simulated by a complicating colitis with distention.

The cardiac signs in endocarditis may be vague, or a systolic murmur may be attributed to an old valvular lesion. A systolic apex murmur is not infrequently found in the late stage of typhoid. A tachycardia is always found in endocarditis but is only suggestive, as it is not uncommon in the late period of typhoid fever.

A diagnosis without laboratory data is usually impossible. Leukocytosis is suggestive but does not rule out typhoid. A positive Widal is strongly presumptive of typhoid. Blood culture gives the only decisive evidence. Either the typhoid bacillus or the organism of the endocarditis may be found.

SYPHILIS.—The pyrexia of syphilis may be mistaken for typhoid fever. A period of continued fever, mild or severe, without localizing symptoms, may occur in any stage of syphilis and in the absence of a history of luetic infection may prove very puzzling. The author recalls two cases observed before the Widal and Wassermann reactions were known, which were thought to be typhoid, until the distinctive signs of syphilis appeared. General adenopathy is very suggestive of syphilis. Involvement of the postcervical and epitrochlear glands is of particular significance. The history of nose-bleed, diarrhea with abdominal symptoms, the scattered rose spots on the chest and abdomen and enlarged spleen, point to typhoid. The laboratory findings will positively differentiate the two diseases. The positive findings in syphilis are leukocy-

tosis and a positive Wassermann reaction. In typhoid the leukopenia, the positive Widal and the recovery of the typhoid bacillus by blood culture are decisive.

Diagnosis in Cases of Prolonged Pyrexia in Which Typhoid Fever is Suspected

Occasionally the practitioner is confronted with the problem of the differential diagnosis of a prolonged pyrexia that has been classified as typhoid fever from clinical findings; or, during the course of such a pyrexia otherwise classified, the question arises, Is this a case of typhoid fever? The problem may be very difficult of solution, especially in the absence of a clear history of the onset and course of the disease. Late in typhoid distinctive clinical signs may disappear, or may be overshadowed by the symptoms of complications. The rose spots, so important in bedside diagnosis, usually fade in the third week. The enlargement of the spleen often subsides and the diarrhea and abdominal symptoms may disappear. A rapid, small pulse takes the place of the slow dicrotic pulse of the first and second weeks. The temperature curve loses its continued type, and sharp rises or intermissions occur. The nervous symptoms and the great prostration and wasting are common to all pyrexias of long duration. The laboratory findings, also, may be uncertain. Late in typhoid a leukocytosis due to various complications is quite frequent. The percentage of positive blood cultures is reduced. The agglutination reaction, on the other hand, is usually positive, but the frequency of antityphoid vaccination at the present time takes away some of the value of this sign. The isolation of the typhoid bacillus from the urine and feces is of distinct practical value if the possibility of a chronic carrier can be excluded.

Influenza, tuberculosis, malignant endocarditis, septicemia from hidden foci of suppuration, malaria and syphilis are the common infections which may cause a prolonged pyrexia mistakable for typhoid fever. The differential diagnosis of these conditions from typhoid has been fully considered.

Pernicious anemia, leukemia and Hodgkin's disease, carcinoma and sarcoma of different organs, and cirrhosis of the liver may be marked during their progress by periods of pyrexia that may bring to mind the possibility of typhoid fever. The prolonged pyrexia of indefinite etiology that is not infrequent in children may bring up the same question. The mere mention of these causes of pyrexia will suggest the lines of investigation to be followed. A painstaking review of the history of the onset and course of the disease, a searching physical examination and a careful analysis of laboratory findings will rarely fail to lead to a definite conclusion.

In all of these conditions the isolation of the typhoid bacillus from the blood, urine or feces may be the only deciding evidence.

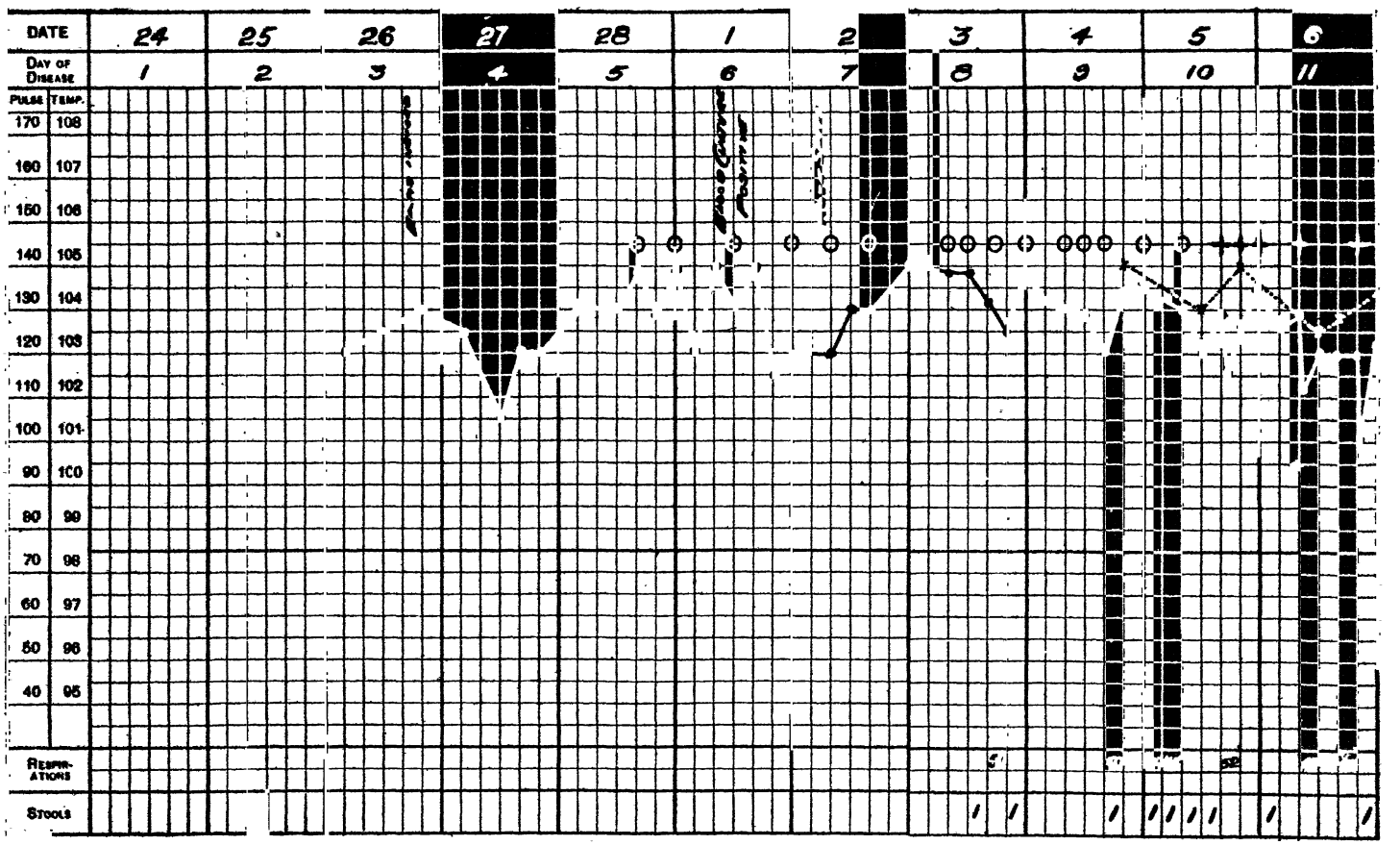


FIG. 8.—CHART IN MODERATELY SEVERE INFANTILE TYPHOID FEVER.

Temperature curve modified by baths. O, sponge baths; ×, tub baths. Patient aged 9 months. (Personal observation.)

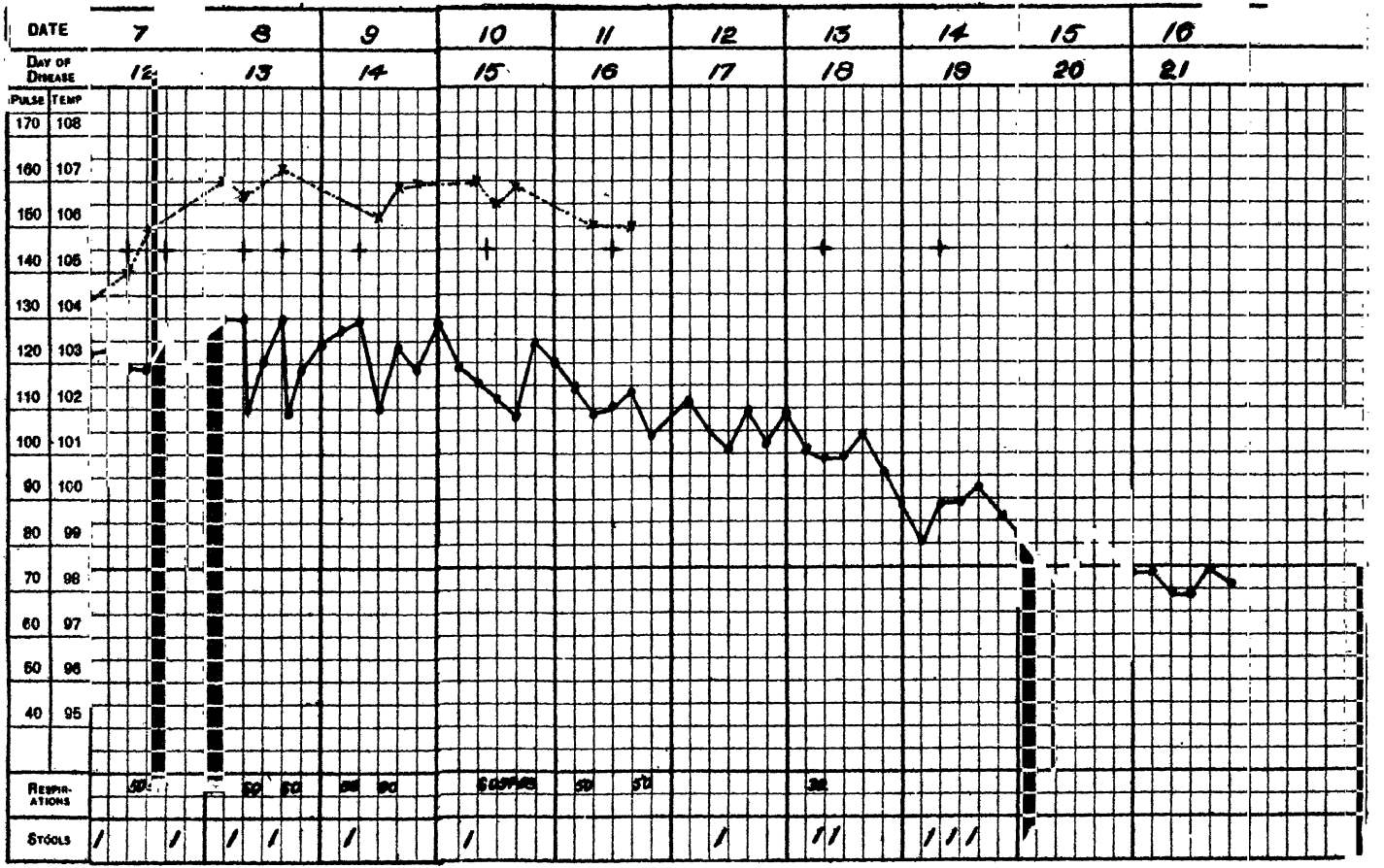


FIG. 8.—CONTINUED

Diagnosis of Typhoid Fever in Infancy

Typhoid fever is so rare in infancy that it is usually the last disease considered in the diagnosis of an acute febrile disease. It should be borne in mind that infants often have temperature of a few days' duration without the distinctive or localizing symptoms that make a diagnosis possible. Under such circumstances the possibility of typhoid fever should always be considered. Only by careful analysis and exclusion and the early resort to laboratory aids can the cause of such a fever be determined.

The diseases of infancy which typhoid fever may simulate are the eruptive fevers, particularly measles or smallpox; acute indigestion with fever; pneumonia; meningitis; otitis media; pyelitis; acute tuberculosis; malaria and influenza.

The usual problem presented by an infant with typhoid is to explain a persistent high fever with no distinctive or localizing associated symptoms.

In the *eruptive fevers* the appearance of the rash serves to clear up the diagnosis. The first few days of the onset of typhoid fever may closely simulate the fever of an acute digestive disturbance. The moderate fever, loss of appetite, occasional vomiting and one or two abnormal stools a day with abdominal pain and tenderness make a close counterfeit of an attack of *indigestion*. This condition is so common, particularly in artificially fed infants, that it is usually the explanation first considered. Typhoid fever should be suspected if the symptoms persist after the administration of an efficient cathartic and reduction in the food intake. An actual increase in the fever and other symptoms is not infrequently noted in typhoid fever after a brisk cathartic. A blood culture is the only method of making a positive diagnosis in the first week. In the case illustrated in Fig. 8, a positive diagnosis was made on the fifth day by blood culture. A white blood-cell count of 5,000 or 6,000 would strongly indicate typhoid. The characteristic rash on the seventh and eighth day should be carefully sought. When present it clinches the diagnosis. A positive Widal is equally distinctive, but unfortunately is rarely present before the second week of the disease. In the absence of these positive findings the persistence of the fever and other symptoms beyond a week render the diagnosis of typhoid almost a certainty.

Primary pneumococcus *pneumonia* may closely resemble typhoid. Pneumonia in the infant is usually preceded by an upper respiratory tract infection with trifling or no rise of temperature. The invasion of the lung is marked by a sharp rise of temperature, rapid respiration, short, suppressed, painful cough, prostration and somnolence. The leukocyte count is uniformly high—15,000 to 25,000. The physical signs of impending or actual consolidation should be manifest in two or three days. The referred abdominal pain and tenderness often noted in pneumonia in the young patient may be a very confusing symptom. With

the respiratory type of typhoid only a blood culture would make an early differential diagnosis possible.

Malarial infection is common in infants in malarial districts and will be distinguished from typhoid fever by the temperature curve. The persistent high temperature of typhoid is rarely seen in malaria. Marked daily remissions or an irregular curve with the temperature reaching normal at some time during the twenty-four hours is distinctive of malaria. The demonstration of the plasmodium in the blood is final. In the absence of this positive laboratory finding the administration of full doses of quinin is a therapeutic test of great value. The course of typhoid is uninfluenced by the drug; malarial fever promptly yields to it.

Otitis media is a frequent complication of typhoid fever in infants, even in the first week, and when the drums are found injected in the routine examination for diagnosis this may be thought to be the primary disease. Incision may be followed by temporary abatement of the fever, but it quickly regains its former height.

As in the adult, general *tuberculosis* of the infant may show a course which renders a differentiation from typhoid fever on the basis of symptoms alone impossible before the appearance of physical signs in the lungs, peritoneum or other organs. Only the demonstration of typhoid bacilli in the blood or excreta, or a positive Widal, will clear up the doubt. The tubercle bacillus may be demonstrated in the secretion from low in the pharynx, and is conclusive. A positive von Pirquet skin reaction is strongly suggestive of tuberculosis.

The onset of typhoid fever may be marked by nervous symptoms suggesting meningism or *meningitis.* These symptoms are usually atypical, and a close analysis will show only an imperfect picture of meningitis. The retracted abdomen, rigid neck, positive Kernig sign, slow arrhythmic pulse, irregular respiration and coma of meningitis are practically never seen in typhoid. An early lumbar puncture is essential to the definite diagnosis and proper treatment of meningitis and should be made on the appearance of the first symptom suggesting meningeal infection. This, with the routine laboratory tests for typhoid fever, should settle the question of diagnosis.

During an epidemic of *influenza,* typhoid fever might be mistaken for this disease. Persistence of symptoms beyond the usual time for defervescence of influenza should arouse suspicion and suggest laboratory aid. Leukopenia is a characteristic of both diseases. Blood culture and the agglutination test may be the only certain means of differentiation in the absence of rose spots, enlargement of the spleen and abdominal symptoms.

Pyelitis in infancy causes a continued fever with no localizing symptoms and may be mistaken for typhoid fever if the routine examination of the urine is neglected. The demonstration of pus in the urine will clear up the diagnosis.

It should be emphasized that a diagnosis of typhoid fever in the infant is not justified, regardless of the course of the fever, unless the

positive clinical signs of rose spots, splenic enlargement and abdominal symptoms, or a positive blood culture or agglutination test are present. On the other hand it is believed by many pediatricians that many febrile attacks of short duration in the young would be proven to be mild or abortive typhoid fever if laboratory methods of diagnosis were more frequently employed.

Laboratory Diagnosis

The diagnosis of typhoid fever in the hospital is usually a laboratory matter and is accomplished earlier than would be possible on the basis of a study of the symptom-complex. Unless the clinician resorts to the laboratory, he must wait until well along into the third week of the disease before he is able to say positively that he is dealing with even a typical case of typhoid fever. This is true even when a good history is obtainable—which is often impossible. When we consider the great variation in symptoms and signs which the *Bacillus typhosus* produces we can say without fear of being too dogmatic that no diagnosis of typhoid fever should be made on purely unsupported clinical evidence. The diagnostic laboratory methods in typhoid fever may be grouped in the order of their importance and usefulness under five heads:

1. The blood culture.
2. The Widal reaction.
3. The blood examination.
4. The isolation of the bacillus from the stool.
5. The diazo-reaction, and other urinary findings.

Blood Culture.—The technic of making the blood culture is described in detail in the section on Bacteriology of Typhoid Fever (p. 472). It should be borne in mind that the earlier in the disease the blood culture is taken the greater is the chance of success, and that if two or three trials are made on those cases which are at first negative, the percentage of successes is very high. If strict attention is paid to the important details such as the use of a sufficient amount (10 c.c.) of blood, well diluted in bile-broth, the great majority of cases will be positive at the first trial during the course of the first week. Blood cultures obtained in paratyphoidal infections are somewhat more uncertain, the bacteria apparently existing in the peripheral circulation for a shorter period in the course of the disease. The typhoid bacillus may be isolated from a blood-clot, and if no material for making a culture is at hand a positive result may be obtained by drawing a small amount of blood in a well-boiled syringe and delivering it into a small, well-boiled test-tube tightly corked with a sterile cork. The test-tube may then be mailed to a distant laboratory and there examined. The vacuum tubes furnished by clinical and public health laboratories for collecting blood for the Wassermann reaction may be used for this purpose. In small children the drawing of blood for culture under aseptic conditions is often difficult and sometimes impossible. The jugular vein can usually be made large enough to enter by compressing the space above the clavicle with a gauze-

pad and getting the child to cry. Sometimes the vein at the internal malleolus can be used. These failing, probably the next best method is careful sterilization of the skin of the ear or great toe and, after a puncture wound with a sterile instrument, the withdrawal of 1 or 2 c.c. of blood into a sterile Wright capsule, and the subsequent isolation of the bacillus from the clot. Failure to enter the vein of an adult is extremely rare, and one should not cut down upon an arm vein for the purpose of a diagnostic blood culture, as the bacillus may be isolated from the urine or stool by the second or third week with a little care and trouble. Krumbhaar and Smith state that in vaccinated individuals the chance of obtaining a blood culture is lessened by about 50 per cent. This disadvantage is of course offset by the fact that vaccinated persons rarely contract typhoid fever.

The Widal Reaction.—The agglutination test for typhoid fever is very specific when properly done. Its most frequent real source of error is the occurrence of a positive result in an individual recently vaccinated against typhoid fever. In actual practice the most frequent source of error in the Widal reaction is to be referred to the use of the microscopical method by inexperienced clinicians. Positive reactions are frequently reported in this way where they are really nonexistent.

There are two methods for accomplishing the Widal test. The first, which the authors recommend, is the macroscopical or test-tube method. They employ the technic given by Gay, using a killed suspension of typhoid bacilli. Typhoid bacilli from a fresh agar slant are washed off the slant with 0.85 per cent. sodium chlorid solution and diluted to make a heavy suspension. The best density is easily determined by a trial. The one which the authors use contains approximately one billion bacilli per c.c. To this enough formalin is added to make a 0.1 per cent. solution. This suspension will keep indefinitely and is always ready for use. The serum is drawn from the arm-vein with a syringe and allowed to clot in a small test-tube, or it is obtained by pricking the finger or ear, and drawn off in a Wright capsule. After the serum has separated, two drops are delivered from a capillary pipet into the first of a row of small sedimentation tubes. Any small test-tube may be used. A test-tube 55 x 8 mm., tapered at the lower end like a centrifuge tube, is convenient. Eighteen drops of saline are added to the first tube and the whole mixed thoroughly, making a serum dilution of 1:10. Ten drops from this tube are placed in the second tube and ten drops of saline added and the contents mixed. This operation is repeated in the third and fourth tubes successively, ten drops being thrown away from tube number four after mixing. In the fifth tube ten drops of saline are placed for a control. We now have serum dilutions of 1-10, 1-20, 1-40 and 1-80. To each tube are now added ten drops of killed typhoid suspension made as directed above, and the tubes are well shaken. The final dilutions of serum represented by the successive tubes are 1-20, 1-40, 1-80 and 1-160, the fifth tube containing the same concentration of killed suspension as the others, but no serum. The rack is set aside in the incubator for

two hours and then in the icebox over night. The positive reactions by this method are very clear-cut. The positive tubes are water-clear, with a feathery white precipitate collected at the bottom of the tube. When the reaction first appears only the first tube may be positive, but as the disease progresses the 1:80 dilution always becomes positive, and usually much greater dilutions also give complete agglutination. By this method partial and false agglutinations do not confuse the observer. A clear-cut reaction in a dilution of 1-20 is of great value.

Interpretation of the Widal in vaccinated individuals is subject to much uncertainty at present. It is well known that after vaccination with a triple vaccine the blood contains agglutinins for a period varying from six months to two years or even longer. It has been assumed that a rise in agglutinin content in vaccinated individuals during the course of a fever pointed to typhoid, and that such a phenomenon might be regarded as suggestive. Krumbhaar and Smith believe several agglutinin determinations in the course of a fever, interpreted in the light of the history and the time elapsed since vaccination, to be of value. Fennel basing his opinion upon intercurrent infections occurring in vaccinated men and officers at the Army Medical School, believes that fluctuations either way in the agglutinin content may be sudden and without apparent cause and may occur in healthy individuals, as well as in those sick of diseases other than typhoid. It is necessary to state that, at the present stage of our knowledge, the use of the Widal reaction as a diagnostic aid in vaccinated individuals has lost much of its value. Whatever may be discovered in the future regarding the use of the Widal in the diagnosis of typhoid in vaccinated persons, it is probable that the great simplicity of the test, on which has rested its strongest claim to usefulness in the past, will be destroyed, and a more highly technical method requiring standardized cultures and several applications in the course of the disease will have to be applied. The authors believe that an often repeated Widal reaching its maximum between the sixteenth and twenty-first day and then gradually diminishing, in a vaccinated individual, is of distinct positive value. On the other hand, it must be remembered that infection as well as revaccination often retards and even suppresses the formation of agglutinins, making for a negative finding or an irregular curve of no negative significance. Usually a standard strain of a typical *Bacillus typhosus* is all that is necessary, but occasionally the serum of a patient will react to one strain and not to another. It is advisable to have as many different strains as possible at hand so that several may be tested in the event that one gives negative results. Cultures recently isolated from typhoid fever cases are apt to be inagglutinable. Gay and Claypole have shown that cultivation on special media may render a strain inagglutinable, but that if animals are immunized to these inagglutinable strains their serum acquires the power to agglutinate these bacteria readily. Bull and Prictchett have been unable to duplicate Gay and Claypole's results.

Another method in more general use but in the authors' opinion less reliable in any but expert hands is the microscopical method. Serum

dilutions are prepared as for the macroscopical method, usually of only one strength (1-20), and a platinum loopful of the serum dilution mixed with a loopful of bacillary suspension on a coverglass. This is inverted over a hanging-drop chamber and the edge brought into focus with the low power under the microscope, using artificial light for illumination. The high power is then switched on and the hanging-drop carefully inspected. There should be a uniform distribution of many actively motile bacilli in the field. In one hour clumping should be complete, in a positive serum, with all the bacteria collected into large masses and the rest of the drop entirely free of bacilli. Care must be exercised in the preparation of the bacillary suspension when using the microscopical method. The formalized culture may be used, but the authors prefer a young (12 to 18 hour) agar culture of *Bacillus typhosus.* A loopful of culture is rubbed up carefully with a little salt-solution in a small test-tube, the wire being rubbed against the side of the tube above the level of the fluid and rinsed down by tipping the tube, to prevent the presence of clumps. The suspension for the microscopical method, mixed with an equal quantity of saline, should be placed in a second hanging-drop chamber as a control at the time the examination is made, and examined side by side with the serum dilution preparation. At the end of an hour the bacteria in the control should be actively motile and uniformly distributed throughout the field, as at the beginning.

There is some difference of opinion regarding the value of the Widal reaction as a diagnostic test in the paratyphoid fevers. The following facts analyzed by Gay should be borne in mind:

1. As to Typhoid Fever.—If a serum agglutinates the *Bacillus typhosus* better than it does either the paratyphoid A or paratyphoid B organisms the disease is not paratyphoid but typhoid fever. If either of the paratyphoid organisms is agglutinated in a higher dilution than the *Bacillus typhosus,* the disease may still be typhoid fever. From eight to ten per cent. of typhoid cases agglutinate one or both of the paratyphoid organisms to a greater or lesser extent. Group agglutinins are more likely to be present in typhoid fever than in paratyphoid fever. For this reason a typhoid serum may agglutinate a paratyphoid organism even better than the typhoid bacillus. Vaccination against typhoid fever is said to produce a positive reaction to the typhoid bacillus more often than to the para organisms. Therefore, in vaccinated individuals, a positive reaction to para organisms is of more value than a positive reaction to the typhoid bacillus.

2. As to Paratyphoid Fever A.—Para A is less agglutinable than para B. A positive reaction to para A at ordinary dilutions is of more significance than a positive to para B. Agglutination in a dilution as low as 1-40 is of significance in para A infections but is of no value in para B. Para A serum may agglutinate the typhoid bacillus and *Bacillus paratyphosus B*—the former more frequently.

3. As to Paratyphoid Fever B.—*Bacillus paratyphosus B* is easily agglutinated, and low dilutions are of no significance. To be of

diagnostic value dilutions of serum for para B agglutination should be high, 1-1000 or even higher. The serum of para B cases less frequently gives group agglutinins for *Bacillus typhosus*, and for *Bacillus paratyphosus A*. Therefore a positive para B reaction in high dilution is of considerable value in diagnosis. On account of the ready agglutinability of para B a negative reaction in ordinary dilutions (1-80) is presumptive evidence against para B infection.

These statements should be regarded merely as representing an average opinion and should not be applied too strictly as criteria upon which to decide a particular result.

Blood-count and Differential.—Typhoid fever produces a rapid and rather marked anemia. There is evidence, ascertained at autopsy, of red-cell destruction. Usually the hemoglobin per cent. and the red-cell count fall, but often a severe diarrhea causes the apparent cell-count to remain constant on account of loss of fluid. There is not a profound hemolysis as in streptococcus infections, with the development of hemolytic icterus, but a more gradually progressive anemia throughout the disease. Added to the red-cell destruction, as evidenced by the intense pigmentation of the spleen found at autopsy, there is undoubtedly a defective formation of blood-cells due to the bone-marrow injury.

The most characteristic findings are the leukopenia and absence of eosinophils manifested as soon as the disease is well established. For the first few days we may have a mild leukocytosis up to 12,000, but very soon the total white-cell count drops to 5,000 or less, with a relatively great diminution of the polymorphonuclears and a relative increase in the number of large lymphocytes. This sudden marked diminution of leukocytes in a febrile affection is restricted to typhoid, miliary tuberculosis, tuberculous peritonitis, malaria and influenza; but it is more regularly of value as a diagnostic aid in typhoid than in any of the other diseases. This phenomenon is very valuable in differential diagnosis. Cases of typhoid fever often have an onset strongly suggestive of acute inflammatory conditions in the abdomen, such as cholecystitis and appendicitis, and the blood-count here is of great assistance. The condition which resembles typhoid fever more closely than any other, perhaps, is miliary tuberculosis with beginning meningeal involvement. In this disease a moderate leukocytosis is the rule. Army experience has shown that typhoid vaccination gives rise at times to acute abdominal pain and vomiting, closely simulating appendicitis, clinically, and here again the blood-count prevents many unnecessary operations. On the other hand, the tendency of typhoid vaccination to light up slumbering infections is well known, and some of these cases following typhoid vaccination are true appendicitis and need prompt surgical intervention. The blood-count usually decides this point, but it should be remembered that a sharp rise in the number of leukocytes may appear as a result of the vaccine injection. J. Wheeler Smith, Jr., showed that an average leukocytosis of from 11,000 to 12,000 was the rule within twenty-four hours of an antityphoid vaccination.

The blood-count may also be valuable in giving warning of inter-

current pneumonia due to other organisms than the typhoid bacillus, although the response is usually not as decisive as in primary pneumonia. Perforation usually does not stimulate a leukocytosis in typhoid fever proportionate to the severity of the peritonitis, and the leukocyte increase following hemorrhage is feeble.

The depression of the leukocyte count in typhoid fever is probably due to the involvement of the bone-marrow with multiple focal necroses first described by Longcope.

Examination of the Stool.—The stool in typhoid fever is usually of the thin, watery variety. Sometimes considerable free fat is recognizable, due to the diarrhea accompanying a diet containing a large proportion of milk. After the diagnosis of typhoid fever has been made, the stools should be examined daily for the presence of occult blood. A strong occult blood reaction gives warning of bleeding from the bases of the intestinal ulcerations, and measures may be instituted to ward off more serious hemorrhage. The daily occult blood test of typhoid stools should be routine, at least in hospital practice. There are several good methods of procedure. One of the simplest of the reliable methods is the modification of the benzidin test as described by Warren Vaughan.

A quantity of stool equal to about ½ gram is placed on a white card, as, for instance, a calling-card, and to this a few drops of equal parts of freshly prepared glacial acetic acid solution of benzidin and hydrogen peroxid is added. A strong reaction shows a brilliant blue, fading off to pale green shades for smaller traces of blood. This method is quick of execution, and there is no glassware to be cleaned up afterwards, because the white card is thrown away and incinerated. If one is not certain of a fresh, active hydrogen peroxid reagent a more certain test is the benzidin perborate test of Dudley Roberts, furnished in tablet form ready for use by Squibb & Sons. The tablets contain benzidin and sodium perborate. The tablet is moistened with the specimen to be examined and a drop of glacial acetic acid added. The tablet turns blue or green in the presence of blood.

The bacteriological examination of the stool in typhoid may have either of two purposes. First, it may be used as a method of finally clinching the diagnosis in a case where attempts at blood culture have been made too late in the course of the fever. Second, and most important, is the application of the bacteriological examination of the stool in convalescent cases, to determine when it is safe to discharge patients and to allow them to mingle freely with the population at large. Nothing is plainer from the point of view of public health than that negative stools should be required before discharging a typhoid patient, just as negative throat cultures are required in diphtheria. If this practice were efficiently carried out the importance of protecting the water supplies would be correspondingly lessened.

The methods for the detection of *Bacillus typhosus* in stools are fully detailed in the section on Bacteriology. They are not difficult, with a little experience, but require a fairly well equipped laboratory. In pri-

vate practice the stool samples may be collected in screw-capped sputum bottles, such as are used for mailing sputum samples, and sent to distant laboratories for examination. Teague and Clurman have pointed out that while the typhoid bacillus tends to be overgrown and to disappear from old samples of stool which are not examined promptly after being passed, the addition of 30 per cent. glycerin to the sample preserves the typhoid bacillus and allows the examination of the specimen after several days. One part of stool is thoroughly mixed with 2 parts of 30 per cent. glycerin, prepared by adding glycerin to sterile 0.6 per cent. sodium chlorid solution. As already mentioned, the chance of isolating the *Bacillus typhosus* from the stool is greatest in the third week of the disease, except that Krumwiede reports that in paratyphoid A infections the successes are greatest during the first week. It should be remembered that paratyphoid A has a greater resistance to brilliant green than the other members of the series, and Krumwiede reports the examination of a regiment for paratyphoid carriers where the brilliant green agar was directly standardized against the known offending strain, thus greatly lessening the labor of several hundred examinations.

Urinary Findings.—There are no characteristic findings in the urine in typhoid fever. Albuminuria is occasionally present, usually associated with a typhoid bacilluria. Indicanuria is common. Bile in the urine is rare. Polyuria is occasionally present in convalescence. The significance and importance of typhoid bacilluria, and the method of detecting typhoid bacilli in the urine have already been discussed.

The most important urinary finding in typhoid fever is the diazo-reaction. The exact substances which give the diazo-reaction are not known, but in several diseases abnormal aromatic bodies are eliminated in the urine, which react with diazo-compounds to give a characteristic color reaction. The opinions regarding the value of the diazo-reaction in the diagnosis of typhoid fever differ widely. It is necessary to keep in mind several limitations to which the test is subject. The diazo-reaction is found occasionally in several diseases, in diphtheria, erysipelas, pneumonia, scarlet fever, typhus, cachectic states such as cancer, cirrhosis, syphilis, malaria and grave anemias. It occurs also as a result of poisoning from certain drugs such as chrysarobin, guaiacol, phenol and opium. The reaction is obtained quite constantly in typhoid, severe tuberculosis, and in measles. The following analysis as given by Todd covers the subject well. The reaction is obtained in practically all cases of typhoid fever in the appropriate stage of the disease, usually between the fourth and fourteenth day. It thus appears earlier than the Widal and tends to disappear about the end of the second week. It is more frequently positive in diluted urines in typhoid than in any other of the diseases which occasionally show it. According to Todd it may be present in typhoid in a dilution as great as 1 to 50. It reappears during a relapse, thereby helping to distinguish a relapse from a complication. Certain drugs often given in typhoid interfere with or prevent the reaction, namely: creosote, tannic acid and its compounds, opium and

its alkaloids, salol, phenol and the iodids. The test is accomplished as follows:

(1)	Sulphanilic acid	1.0 gram	(15.5 grains)
	Concentrated HCl	10.0 c.c.	(2.71 fl. drams)
	Water .....200.0 c.c.		(6.76 fl. ounces)
(2)	(Must be freshly prepared.)		
	Sodium nitrite	0.5 gram	(7.716 grains)
	Water .....100.0 c.c.		(3.38 fl. ounces)
(3)	Strong ammonia		

Mix 100 parts of (1) with one part of (2). Place equal parts of this mixture and of urine in a test-tube, and pour 2 c.c. (33 minims) of ammonia on the surface. A pink or red foam on shaking denotes a positive reaction.

It would seem that this test has a certain value if considered as a symptom in conjunction with clinical findings. If the time limits of its appearance are remembered—fourth to fourteenth day—the liability of its being present in diluted urine, the appearance of the test about four or five days after the onset, and its disappearance after the second week, are valuable scraps of evidence favoring a diagnosis of typhoid. Unfortunately the one condition often most difficult to separate from typhoid, namely miliary tuberculosis, often gives a diazo-reaction, which seriously lessens the value of the test.

Weis has offered a substitute for the diazo-reaction which is claimed to be more sensitive and of the same significance. This test depends upon an increased urochromogen content in the urine. It is subject to the same criticism and sources of error as the diazo-reaction. The urochromogen test is performed by adding 3 drops of 1-1,000 potassium permanganate to 6 c.c. (1.6 fluid drams) of urine diluted 1-3. The appearance of a canary yellow color denotes a positive reaction.

Another substitute for the diazo-test is Russo's methylene-blue test. Five drops of 1-100 aqueous methylene blue are added to 5 c.c. of urine in a test-tube. A grass-green without a trace of yellow is interpreted as positive reaction. In the author's experience the test is of no value. Highly colored febrile urines in general react positively.

COMPLICATIONS AND SEQUELÆ

Typhoid fever is remarkable for the number, variety and gravity of its complications. Practically every organ and tissue in the body may be the seat of secondary pathological processes that tend to increase the severity of the illness, prolong its course and add to its danger. Complications, mild or severe, occur in from 25 to 30 per cent. of all cases, and are responsible for from 60 to 75 per cent. of all fatalities from the disease. Many of the conditions described as complications may develop late in the convalescent period or at varying times after

recovery from the primary infection appears to be complete. When developing in this way these conditions may properly be classed as sequelæ. To save repetition complications and sequelæ have been considered together.

Among the important diseases which may develop as sequelæ to typhoid fever are thrombophlebitis, arterial thrombosis, chronic myocarditis, arterial sclerosis and arterial hypertension; pulmonary tuberculosis and pulmonary gangrene; perichondritis, osteoperiostitis and osteomyelitis; peripheral neuritis, hemiplegia and the posttyphoid psychoses; chronic derangements of digestion, prolonged or permanent impairment of nutrition and anemia.

The Skin

The specific eruption of typhoid fever has been described in the section on symptomatology. A number of cutaneous lesions may complicate the disease.

Erythema.—A scarlatiniform erythema is occasionally seen in the first week, preceding the eruption of the rose rash. It is of special interest at this stage, because of the possibility of mistaking it for the rash of scarlatina. It appears as a delicate scarlet rash limited to the flexor surfaces, or spread over the entire skin. The eruption fades in a day or two and may be followed by a fine desquamation. In severe toxic cases a diffuse erythema may appear in the third week and, as Phillips has shown, a large number of the reported cases showing this symptom have terminated fatally. Phillips saw one case of erythema multiforme, and Osler has reported a case of erythema nodosum appearing on the fifteenth day. A case with a morbilliform rash without the catarrhal symptoms was seen by Beevor on the third day and another by Newman in the third week.

Desquamation.—Desquamation of the skin is rather frequent. It may follow an erythema or sudamina, or it may result from trophic changes in cases with high fever. Some remarkable cases of peeling of extensive areas of the skin without apparent cause have been reported.

Sudamina.—Retention of minute drops of perspiration in the epithelial layer of the skin is common in the third and fifth week in cases with profuse perspiration. The eruption is most marked over the chest and abdomen. The skin appears to be covered with a multitude of droplets of water. Desquamation follows. The experience of Phillips confirms the observation of De Lacaze that the appearance of sudamina in the third week ushers in the period of convalescence.

Herpes.—Herpes is a rare skin manifestation in typhoid, in marked contrast to the frequency of the lesion in pneumonia and malaria. Different observers have noted it in the first week in 1 or 2 per cent. of cases. Herpes is characteristically present in typhoid complicated by meningitis. *Urticaria* is also a rare condition dependent in some cases upon drug administration. A pemphigoid eruption of several small or large blebs is occasionally seen.

Purpura.—In the third or fourth week, in severe cases, purpuric spots may develop over the abdomen or lower extremities, sometimes following intestinal or other hemorrhage. Superficial sloughing of the skin over the hemorrhagic area has been reported. More extensive *gangrene* may occur in the case of greatly debilitated individuals.

Erysipelas.—Erysipelas is a rare complication of the period of decline. It runs the usual course, and is not necessarily a serious complication. The typhoid bacillus has been found in the affected skin.

Pus Infections.—Pus infections of the skin are quite common in the period of decline and in early convalescence. Impetigo, furunculosis, carbuncles, onychia and superficial abscess are the usual forms. Furunculosis is the most frequent. The lesions are very painful and troublesome and are often the cause of recrudescence of the pyrexia. They develop most frequently on the back and buttocks. Edsall observed a limited outbreak in the Pennsylvania Hospital, apparently due to bed-pan contagion. The streptococcus and the staphylococcus are the usual infecting organisms.

Lineæ Atrophicæ.—In young subjects particularly, lines of atrophy similar to those seen on the abdomen after pregnancy are occasionally seen. They occur over the abdomen, on the outer aspect of the thighs, around the ankles and above and below the patella. Phillips and others have described this condition under the term "striæ patellans." The lesions involve the true skin and leave permanent scars.

Bed-sores.—Modern care of fever patients has made bed-sores infrequent. They occur, however, in hospitals where good nursing is the rule in about 1 per cent. of the cases. A certain number result from neglect before admission. The usual cause is unrelieved pressure upon the tissues over a bony prominence. Development of the lesion is favored by soiled skin and clothing. The enforced quiet following a severe hemorrhage may be a determining factor. The common bed-sore is therefore usually preventible by cleanliness and proper nursing technic. Sores occur as a late complication in severe cases with great emaciation. They are most frequently seen in the sacral and gluteal regions where pressure is greatest and most continuous and where the skin is soiled by the excretions. The elbows, heels and the scapular region are less frequent sites. The sore begins with a persistent area of circumscribed redness over the most prominent points of the sacral region. Unless it is promptly arrested the epidermis is eroded, the deeper layers of the skin are exposed, and a superficial slough forms, with a line of demarcation. In the more severe cases the process continues, and extensive destruction of soft tissue and bone may result. In severely toxic cases with profound disturbance of nutrition the subcutaneous type of bed-sore, as it is termed by Curschmann, may develop, even with the most scrupulous care of the patient. In this author's experience it usually occurs in the lower sacral region in the depth of the anal fold. The process is a subcutaneous necrosis with suppurative softening of the connective tissue. It may go on to quite an extent before it is revealed to the attendant by alterations in the appearance of the skin.

Perspiration.—Perspiration is unusual during the period of high fever. In the period of decline and in convalescence it is quite common. In the second or third week paroxysms of chill, fever and perspiration may occur and arouse suspicion of malaria or sepsis. Hemorrhage and other complications of this period may be attended by profuse perspiration.

The Hair.—A temporary alopecia occurs after all attacks of severity, and the nails show ridges after convalescence, due to impaired nutrition. Very rarely is the baldness permanent.

The Digestive System

Mouth.—The salivary secretion is diminished and the tongue and mouth become dry in proportion to the height of the fever and the intensity of the toxemia. Without scrupulous care the tongue, lips and gums become covered with dry, brown masses of sordes. Painful cracks and fissures may form on the tongue and lips. In neglected cases flakes of thrush or a thin pseudomembrane may form on the mucous surfaces. The septic mouth may be the center for the extension of secondary infections to the parotid glands, pharynx or middle ears. Stomatitis with superficial ulceration is not infrequent under these circumstances. A circumscribed gangrene has been observed. An acute glossitis occurred at the onset of a relapse in one of Osler's series.

Parotid Gland.—Parotitis is an occasional complication in the third or fourth week or a sequel in severe protracted cases. It is due to an ascending infection from an oral sepsis to the glands through Steno's duct. In 12,173 cases collected by McCrae, parotitis occurred in 0.7 per cent. The staphylococcus is the most common infecting organism. The typhoid bacillus in pure culture was isolated from a parotid abscess by Schudnot and Blachos. The inflammation is usually unilateral, although both parotids may be infected. The infection may be mild in character or of intense virulence. The gland rapidly becomes swollen, tense and painful. A chill with a sharp increase of fever may mark the onset. Resolution without suppuration takes place in a majority of the cases. Suppuration, when it occurs, begins at the proximal end of Steno's duct and extends peripherally. The abscess may point on the face or in the external auditory canal or it may open into the mouth by way of the duct. It may burrow to the pharynx or along the great vessels of the neck into the mediastinum. Necrosis of part of the gland may occur. If suppuration impends an early incision is necessary. Parotitis is a serious complication of typhoid chiefly because it is a complication of the severe toxic cases. Reported cases show a mortality of about 30 per cent.

Pharynx.—Occasionally pharyngitis and tonsillitis dominate the clinical picture of the onset of typhoid fever and conceal the true nature of the infection. Patches of thin pseudomembrane may appear on the mucous surface, and in rare cases small, superficial ulcers have been noted on the pillars and tonsils. The typhoid bacillus has been recovered

from these lesions. Pharyngitis with the same manifestations may complicate the later stage of the disease. Ouskow, cited by Hare, found evidence of pharyngitis in a majority of 439 cases coming to autopsy. Rarely invasion of the cervical lymph-nodes and connective tissue by a secondary infection may occur, with great swelling and induration of the neck. It may terminate in resolution or in suppuration.

Esophagus.—Inflammatory lesions similar to those in the pharynx may be found in the esophagus. Louis and other early writers found ulceration of the esophagus of frequent occurrence. Modern observers have found it rare. Packard reviewed 5,000 cases, none of which showed ulceration. More recent literature contains descriptions of a number of cases. Baer cites 10 cases in a collection of 83 cases of typhoid with ulceration in unusual sites. In 59 autopsies in Johns Hopkins Hospital esophageal ulceration occurred in one case. In one fatal case observed by the author (Jennings), showing persistent hiccough for several days before death, an ulcer 2 cm. in diameter was found in the esophagus, 4 cm. above the cardiac orifice. Streptococci and staphylococci are the organisms found associated with the ulceration. The typhoid bacillus has not been demonstrated. It seems probable that esophageal lesions are late results of oral sepsis.

Ulceration of the esophagus causes no symptoms that make it recognizable during life. Dysphagia, hiccough, possibly hematemesis are suggestive.

Stricture of the esophagus is a very rare complication or sequela of typhoid. James F. Mitchell describes one case in Osler's series and quotes two others; one reported by Packard and the other by Summers, of Omaha.

Stomach.—Anorexia is the rule in typhoid fever. The secretory and motor functions of the stomach are greatly reduced. The digestive ferments are present in reduced amount and free hydrochloric acid is either absent or the percentage is reduced. Vomiting is decidedly the exception, both at the onset and during the course. Severe and persistent vomiting is an occasional complication of the first week. Vomiting may take place after the period of onset from indigestion or over-feeding, but it is so unusual that it should always suggest the possibility of some complication. Nephritis, appendicitis or perforation may be announced by vomiting. Hiccough is rare. The author (J. C. Jennings) has noted it in one severe case, in which it was apparently a symptom of an ulcer in the esophagus at the cardiac end. It is also a symptom of perforation. Hematemesis, usually from a gastric ulcer, is a rare complication. The stomach may be involved in cases with severe meteorism.

Intestines.—Diarrhea, one of the characteristic symptoms of typhoid fever, may attain such severity as to constitute a complication. In the local outbreaks from water infection before mentioned, all of the 56 cases were complicated during the period of incubation and onset by severe gastro-enteritis. In many of the cases the diarrhea was replaced by constipation after a few days of fever. In others it persisted throughout the whole febrile period. Two, at most three, loose movements a day

are the limit for a normal course of typhoid. From four to ten or even a larger number may take place in severe cases. This excessive diarrhea may be due only to the specific ulceration in the ileum. An ileocolitis is the usual condition underlying a severe diarrhea.

HEMORRHAGE.—In 829 cases of typhoid fever reported by Osler from Johns Hopkins Hospital there were 50 cases with intestinal hemorrhage, representing 6 per cent. McCrae's later report from the same hospital gives 1500 cases in which 118 cases of hemorrhage occurred, or 7.8 per cent. In 23,271 cases collected by McCrae, hemorrhage occurred in 7 per cent. Typhoid fever developing in vaccinated subjects shows a remarkable reduction in the incidence of hemorrhage, as of other complications. In the series reported by Lieut. Col. Webb-Johnson of the British Army, hemorrhage occurred in but 10 out of 821 vaccinated cases, representing 1.21 per cent., and in 40 out of 297 unvaccinated cases, or 13.46 per cent. The percentage incidence is much lower in children and up to the thirtieth year, and reaches a maximum from the forty-fifth to the fifty-fifth year. Insignificant bleedings manifestly due to hemorrhoids or fissures should not be classed with the hemorrhage which has its origin in the specific bowel lesions of typhoid fever.

The complication occurs most frequently in the second and third weeks of the disease, rarely before the seventh day. Approximately 20 per cent. occur in the fourth, and ten per cent. in the fifth week. After this time hemorrhage is very unusual. It is a rare complication of relapse. The incidence of hemorrhage bears no relation to the severity of the disease. It occurs as often in the mild as in the severe cases. In the mild ambulatory cases it may be the first symptom to warn the patient that he has a serious illness. The hemorrhage may be single or several attacks may occur at varying intervals. The amount of blood in the discharge varies from a few cubic centimeters to a liter or more. In small hemorrhages the blood is mixed with the feces and is dark red or black in color, the characteristic tarry stool of an upper intestinal hemorrhage. With a profuse hemorrhage, quickly expelled, bright red blood may be passed in the fluid state or in clots. When a considerable interval elapses between the bleeding and the expulsion of the blood from the bowel the blood appears in dark, altered clots.

The blood in small hemorrhages and in the early stage of the disease may come from intensely congested Peyer's patches and from other areas in the intestines. In later hemorrhages the necrotic and ulcerated Peyer's patch is the source of the bleeding. Gay believes that the peculiar anatomical arrangement of the blood-vessels supplying Peyer's patches, as demonstrated by Professor Evans, of Berkeley, accounts for the profuse hemorrhage that may come from an ulcerated Peyer's patch. Straight, unbranched arterioles radiate from all sides into the patch, and an erosion near the margin may open up simultaneously a large number of these vessels. Hemorrhage has been attributed to a variety of exciting causes. Injudicious feeding with solid food, tympanites, or physical exertion would quite probably precipitate an impending hemorrhage. It

has sometimes followed immediately after the administration of a bath or an enema.

A small hemorrhage causes no subjective symptoms. A single large hemorrhage, or a succession of small hemorrhages quickly repeated, is indicated by the usual symptoms of a sudden large loss of blood. The patient feels faint, the face pales, the skin becomes cool and moist, the pulse rapid, small and weak, and the temperature suddenly falls. Vomiting may occur. The drop in temperature may be from two to six degrees or more. The author (Jennings) has seen it fall from 105° to 96° F. (40.6° to 35.6° C.) and remain at this low point for several hours. Occasionally abdominal pain precedes the bleeding. These symptoms may be present for some little time before the blood is passed from the bowel. The systolic blood-pressure falls to 80 or 90 mm. Hg or lower. McCrae observed the very low pressure of 55 mm. Hg in one case. The hemoglobin content and red-cell count of the blood are low in proportion to the severity of the hemorrhage. A leukocytosis often follows the hemorrhage. From a detailed study of this condition Thayer concludes that "intestinal hemorrhage in typhoid may exercise little or no apparent influence on the number of leukocytes in the peripheral circulation. Often, however, there is a tendency toward a leukocytosis which begins immediately after the hemorrhage, reaching its maximum in from twelve to twenty-four hours. In from one or two days to a week, the number of leukocytes generally returns to the normal number for the period of the disease."

The effect of the hemorrhage upon the course of the disease will depend upon the amount of blood lost and upon the condition of the patient at the time of the hemorrhage. Strong, robust patients endure the loss of blood well. Indeed, some observers believe that a moderate bleeding may have a beneficial influence upon the subsequent course of the disease. Gay has suggested that the hyperleukocytosis mentioned above may account for the improvement.

In patients otherwise seriously ill the effect of severe hemorrhage is bad, and is often the determining factor in a rapidly fatal issue. In cases which recover, the severe anemia predisposes to a complicated and tedious convalescence.

Hemorrhage is a serious complication and always causes apprehension. The statistics from various sources give a mortality rate varying all the way from 10 to 30 per cent. Without accurate data the cases in the author's personal experience have shown a percentage very near the low figure.

PERFORATION.—The incidence of perforation in several series of cases reported by observers in this country and Europe varies from 2 to 6 per cent. In a total of 34,916 cases summed up by McCrae perforation occurred in 3.1 per cent. Antityphoid vaccination markedly reduces the percentage. In Webb-Johnson's series of 821 vaccinated cases perforation occurred in only 0.36 per cent., while in the 297 unvaccinated cases it occurred in 2.02 per cent. It is more frequently seen in men than in women. In 661 cases in which sex incidence was noted, 471, or 71

per cent., occurred in men. It is unusual in patients over forty years of age. The complication is generally spoken of as rare in children, although among 1,550 cases of typhoid fever in children collected by Adams there were 17 cases of perforation, representing 3.09 per cent. Of 1,028 cases compiled by Holt 12 cases of perforation were found, or 1.1 per cent.

Cases with severe general symptoms give the highest percentage, although in mild and moderately severe cases it is almost as great. In 444 cases collected by Fitz, 200 were mild or moderately severe and 14 cases belonged to the ambulatory type.

Statistics from England, Canada and the United States show that perforation is responsible for one-third of all the deaths from typhoid fever.

Due to the same underlying cause, perforation, like hemorrhage, is a complication of the later weeks of the disease. It is very unusual before the tenth day. Accurate figures by Fitz of 193 cases show, first week, 4 cases; second week, 32 cases; third week, 48 cases; fourth week, 42 cases; fifth week, 27 cases; sixth week, 21 cases; seventh week, 5 cases; eighth week, 3 cases; ninth week, 2 cases; tenth week, 4 cases; eleventh week, 3 cases; twelfth and sixteenth weeks, 1 case each.

The immediate cause of the perforation is the ulceration and necrosis of the intestine. It cannot be foretold or prevented. The final break in the bowel wall, however, may be precipitated by excessive tympanites, an attack of indigestion, vomiting, or physical exertion. These accessory causes are more or less under control.

Symptoms of Perforation.—The possibility of perforation should be constantly in the mind of the physician during the stage of intestinal ulceration. Careful inspection of the abdomen should be a part of the daily routine examination, and the attendants should be instructed to be on the alert for symptoms suggestive of rupture.

While the onset is usually without premonitory symptoms, certain objective and subjective symptoms may be forerunners of the accident. Hemorrage, unusual abdominal pain and tenderness, distention or vomiting may have significance, and should put the physician on his guard. In certain cases a localized peritonitis at the site of an underlying ulcer sometimes causes pain, tenderness and leukocytosis, which may continue for two or three days before the bowel perforates. This condition has been termed by Harvey Cushing the "preperforative stage of ulceration." As in a case reported by him, these symptoms may disguise a perforation when it actually occurs and lead to unfortunate delay in diagnosis.

(*a*) *Sudden Onset.*—Sudden, severe pain in the abdomen, tenderness, rigidity, vomiting, collapse and rapid pulse are the initial symptoms. In a few hours general peritonitis develops. The abdomen becomes more distended, pain and tenderness become general over the abdomen, the temperature rises, the pulse becomes small and very rapid, respiration increased and thoracic in character. A cold, clammy perspiration covers

the surface, the face is pale and pinched and the patient rapidly sinks. Consciousness may be retained to the end.

(*b*) *Insidious Onset.*—The symptoms of perforation may develop gradually. The perforation may be small and the escape of the intestinal contents slow. There may be but little pain and the symptoms of general peritonitis may be latent or absent. In 76 cases mentioned by Fitz the onset in 15 was gradual or latent, and in 5 cases there were no signs of perforation. Dieulafoy's experience led him to state that peritonitis from perforation very rarely announces itself acutely with pain and marked constitutional symptoms. In severely toxic cases with severe diarrhea, abdominal distention and profound nervous symptoms, perforation may occur and be revealed only at autopsy.

The relative frequency of the so-called characteristic symptoms of perforation is noted by Finney in 112 operated cases. "Sudden and severe abdominal pain was present in 58 cases; collapse, more or less severe, in 15 cases; nausea and vomiting in 26 cases; a marked fall in temperature in 14. In 9 of the cases the symptoms denoting perforation were not marked and came on gradually. In 5 of the cases only, was the absence of liver-dullness noted."

The pain is continuous or may be intermittent or colicky in character. It is usually referred to the right lower quadrant of the abdomen as general peritonitis develops. Or, like the pain of appendicitis, it may be general at first and then localized in the right lower quadrant. A referred pain in the left lower quadrant has been noted. The pain may be most intense about the navel. During the paroxysms the pain may be referred to the pubis, and with it there may be vesical irritability.

Tenderness and rigidity are emphatic symptoms, and in the first few hours are most marked in the right lower quadrant. As general peritonitis develops, the whole abdomen becomes tense and tender. More or less abdominal distention quickly follows and the liver dullness may be obliterated. Occasionally the abdomen becomes retracted, with rigid walls. Rectal examination should always be made.

Nausea and vomiting are quite constant symptoms immediately following the perforation. Vomiting is so rare during the perforation period of typhoid fever that it should always arouse the suspicion of this accident. *Hiccough* may be present at this time, but it is more frequent and persistent later.

The pulse quickly changes with the onset of the pain. It becomes rapid and small, and this quality persists regardless of fluctuations in the temperature. In exceptional cases the pulse-rate is unchanged until the onset of general peritonitis. A rise of *blood-pressure* often follows the perforation. In obscure cases this finding may be of value in the differentiation from hemorrhage. *Respiration* is quickened, shallow and thoracic in character.

A sudden, marked drop in the *temperature* is often a striking feature of perforation. The fall in temperature may immediately follow the perforation, or it may come later after an initial rise of one or two degrees. The collapse noted at the onset, with cold, moist skin, may be

associated with a rise of the central temperature. A chill is a not infrequent initial phenomenon. With the development of general peritonitis the temperature shows the usual variability observed in this condition from any cause.

The *leukocyte count* is of great interest and may be of conclusive importance in diagnosis. A knowledge of the leukocyte content of the blood previous to perforation is necessary for a proper evaluation of the findings. With this knowledge even a moderate leukocytosis is of great significance. Usually an increased count follows the perforation. The number of leukocytes rises, rapidly reaching from 10,000 to 15,000 or higher in a few hours. With the development of general peritonitis a sharp fall often takes place, due to the great outpour of leukocytes into the peritoneal cavity. This fall may take place within three or four hours after the perforation, a fact which emphasizes the necessity of hourly counts when perforation is suspected. In some cases no change in the leukocyte count takes place.

Diagnosis of Perforation.—The diagnosis of perforation in typhoid fever may be very easy or extremely difficult. With a large perforation and copious extravasation into the peritoneal cavity the signs and symptoms of an acute abdomen are emphatic and unmistakable. With small perforations, and especially in the case of patients whose sensations are blunted by profound typhoid toxemia, the symptoms may be vague and misleading. Prompt recognition of the condition is so imperative that in doubtful cases every aid to diagnosis must immediately be sought. A few hours' hesitation may remove even the moderate hope which early surgical interference offers. The two most valuable symptoms for diagnosis are pain and rigidity. The less sudden the pain is in its development and the less severe it is, the greater the difficulty in diagnosis.

A number of abdominal conditions may simulate perforation. *Hemorrhage* may resemble it very closely. The sudden fall in blood-pressure and the anemia are distinctive of hemorrhage; abdominal pain, tenderness and rigidity are not as marked as in perforation. The coincident occurrence of hemorrhage and perforation presents a most difficult situation.

Iliac phlebitis may be recognized by tenderness along the course of the veins extending down the thigh and accompanied by swelling.

Appendicitis gives the same clinical picture as perforation and cannot be certainly differentiated. Practically this is of little importance as the surgical indication is the same in both conditions. *Acute intestinal obstruction* from any cause may be very difficult to differentiate.

The various conditions previously mentioned which excite abdominal pain may arouse the suspicion of perforation. A small localized peritonitis may be especially puzzling. These conditions demand careful study. The absence of pulse and temperature changes and grave general symptoms of perforation are of diagnostic importance. Except in the cases of local peritonitis a low white blood-cell count is a valuable sign. The great difficulty in diagnosis in these cases is clearly shown by the fact that in suspected perforation the abdomen has been opened in our

best hospitals, after careful study by the ablest clinicians, and no adequate cause for the symptoms found. Such exploration, in doubtful cases and after full consideration, is justified.

Peritonitis not the result of perforation is a rare complication, usually occurring during the third week of the disease. It may result from the rupture of a softened mesenteric gland or of an abscess in any of the abdominal or pelvic organs. Migration of organisms through the intestinal wall without gross lesions seems to be the only explanation in a number of reported cases. Sudden onset with pain, tenderness, rigidity and distention is the rule. Differentiation from peritonitis due to intestinal perforation is impossible. Without operation the result is uniformly fatal.

Results of Perforation.—A number of cases of recovery following the characteristic symptoms of perforation have been reported. In how many of these cases perforation actually took place must remain in doubt. The question is well answered by Fitz. "Since perforation of the intestine in typhoid fever may take place without any suggestive symptoms, and since suggestive, even so-called characteristic, symptoms may occur without any perforation having taken place, it must be admitted that recovery from such symptoms is not satisfactory evidence of recovery from perforation." Still, recovery from perforation without abscess formation must be admitted as possible. Several such cases have been verified by subsequent operation or autopsy findings.

In rare cases the peritonitis is localized and an abscess forms similar to the localized abscess which follows perforative appendicitis. Recovery may follow surgical drainage, or the abscess may discharge externally or into one of the hollow viscera. This is most likely to occur if the perforation involves a relatively quiet sector of the abdomen like the appendix region.

In the great majority of cases, general peritonitis follows perforation and, unless relieved by laparotomy, proves rapidly fatal. Death occurs, according to Fitz, in over 37 per cent. on the first day following perforation, in over 29 per cent. on the second day and in over 83 per cent. of all cases during the first week. Even with prompt surgical interference the outlook is grave. Only about 20 per cent. recover. This is a high mortality, but with the prospect of an almost certain fatal result without laparotomy, operation is not only justified, but imperative.

Liver and Gall-bladder.—The typhoid bacillus has a peculiar affinity for the liver and gall-bladder. The organism is present in the gall-bladder from the onset of the infection in practically every case of typhoid fever and, as in the case of certain healthy carriers, it may be found in the gall-bladder of individuals who give no history of clinical typhoid infection. It is, therefore, remarkable that hepatic and gall-bladder complications do not occur with greater frequency.

JAUNDICE.—Jaundice is extremely rare. Liebermeister found 26 cases in 1,420 cases of typhoid. Recent German statistics, however, give a higher incidence. Posselt found icterus reported as present in from 0.14 to 7.14 per cent. of the individual cases in various groups. It ap-

pears to be rarer in this country. Apart from abscess and cholecystitis it was noted in only 8 of McCrae's series of 1,500 cases. Of 52 cases of jaundice analyzed by Da Costa, 4 were catarrhal and 24 toxic. The jaundice was a symptom of pylephlebitis in 3 cases, of cholangitis in 5 cases, of abscess in 5 cases and of acute yellow atrophy in 5 cases.

Catarrhal jaundice is usually a late complication, although it has been noted in the period of onset. Coleman reports a case in the prodromal period. This complication may be mild and transient and cause no aggravation of the symptoms of the primary disease. In the more severe form the jaundice may be quite intense and accompanied by nausea and vomiting, chill and an increase in the pyrexia. Enlargement of the liver, pain and tenderness in the hepatic region are not usually present. Bile is usually absent from the stools. *Toxic jaundice* is a late complication of severe typhoid. It may be distinguished from the catarrhal form by the gravity of the symptoms and by the continued presence of bile in the feces.

Hepatic Abscess.—Hepatic abscess, solitary or multiple, is a very rare complication or sequel of typhoid fever. Da Costa collected 22 cases. The solitary abscess may be the result of an infection ascending from the ulcerative lesions in the bowel, or it may be part of a pyemia with abscesses in other parts of the body. Cases following parotid abscess and necrosis of bone have been reported. Multiple abscesses may be due to a septic pylephebitis having its origin in suppuration or gangrene in the intestine or in the mesenteric glands, or to suppurative cholangitis. The colon bacillus, the staphylococcus, the streptococcus and the typhoid bacillus have been recovered from the pus. The prognosis is very grave. Cases of solitary abscess have been successfully drained.

Cholecystitis.—In typhoid fever, as stated above, the gall-bladder is a constant metastatic focus of lodgment and multiplication of the typhoid bacillus. It is generally believed and has been experimentally demonstrated that the organism reaches the gall-bladder through the circulating blood by a descending infection. As a rule the presence of the organism in the gall-bladder and its passage through the biliary tract to the intestine causes no inflammatory reaction. It is quite probable, however, that a mild cholecystitis not infrequently occurs and runs its course without symptoms severe enough to attract attention. In a small percentage of the cases the inflammation is of sufficient severity to cause definite symptoms. Gall-stones of ancient or recent formation may be a predisposing etiological factor. In Webb-Johnson's series of 2,500 cases of typhoid and paratyphoid fever, there were 15 cases with more or less definite symptoms of cholecystitis. The diagnosis was made in 19 of McCrae's 1,500 cases, representing 1.2 per cent. The complication is announced by chill, rise of temperature, pain in the right upper quadrant, and usually by vomiting. The pulse and respiration rate are increased. Tenderness and rigidity are present over the gall-bladder area, and occasionally the enlarged gall-bladder may be palpated. Jaundice may develop. There is a moderate leukocytosis, from 10,000 to

15,000. The disease usually terminates by resolution in a few days; or, in rare cases, ulceration and perforation of the gall-bladder, followed by general peritonitis, may result. In only one of the 15 cases reported by Webb-Johnson was surgical interference necessary. A mild, chronic cholecystitis may result from the acute attack and be the immediate cause of the development of gall-stones. In 30.9 per cent. of Curschmann's cases followed over long periods, symptoms of gall-stone disease were found. The infection may persist in the gall-bladder without causing inflammatory reaction and may produce a temporary or permanent carrier state.

Spleen.—Perisplenitis, infarct and spontaneous rupture are rare complications of typhoid fever. One of these conditions may be suspected if pain, tenderness and rigidity in the left upper quadrant develop in the second or third week of the disease. A positive diagnosis is impossible. Abscess of the spleen may result from a failure to eliminate the typhoid bacilli from the spleen to the liver. The Mayos have operated on several cases of single or multiple abscess containing pure cultures of the typhoid bacillus. In 800 cases of typhoid fever with surgical complications collected by Keen there were 9 cases of splenic abscess.

Circulatory System

Blood.—The anemia following typhoid fever is very moderate in degree, rarely exceeding a 20 per cent. loss of red-cells and hemoglobin. Very exceptionally posttyphoid anemia may be severe and constitute a serious complication. In 2,000 fatal cases reported by Hölscher from the Gaieme Hospital in Munich, 54 cases, or 2.7 per cent., showed severe anemia. Thayer carefully studied two cases. In one the number of red-cells fell to 1,352,000 and the hemoglobin to 27.5 per cent. on the thirty-fifth day of the disease. In the other the red-cells numbered 1,996,000 on the thirty-second day. Both patients made very slow recoveries.

Heart.—The symptoms of *myocardial insufficiency* may appear as a complication in the latter weeks of the pyrexial period of typhoid fever or as a sequel early or late in the convalescent period. From the studies of Romberg, Hayem, and more recently of Hamman, it has been shown that the anatomical basis of the symptoms may be an interstitial myocarditis or granular or fatty degeneration of the muscle-fibers. Grave and fatal cardiac insufficiency appearing in the height of the disease may depend primarily upon vasomotor paralysis, the changes in the myocardium being of secondary importance. Romberg asserted that circulatory failure during the height of an infection depends entirely upon vasomotor paralysis.

Symptoms of cardiac weakness of more or less severity usually begin in the third week of the pyrexia, sometimes earlier, without a corresponding rise in temperature. The pulse increases in frequency, loses its dicrotic character and becomes small, soft and compressible. In the average case of typhoid this pulse frequently continues into convales-

cence and gradually subsides, with no further evidence of myocardial weakness. In cases with more serious myocardial degeneration the symptoms increase in severity. The pulse may be intermittent or irregular in rhythm and force. Instead of a tachycardia, a bradycardia may be the first symptom of a failing myocardium. General prostration may be profound, with paleness of the skin and perspiration. Vomiting is not infrequent. Physical examination shows a feeble or diffuse apex impulse with the left border of the heart displaced to the nipple line or still further to the left. The heart-sounds are feeble, or the first sound may be feeble and the pulmonary second accentuated; gallop rhythm or embryocardia may be present. A soft systolic murmur may be heard at the apex or in the third interspace, due to a relative mitral insufficiency. Dilatation is usually confined to the left side of the heart.

Although often a cause of much anxiety, myocardial degeneration in typhoid fever is rarely a direct cause of death. The symptoms usually subside gradually and the physical signs of dilatation disappear with the decline of the pyrexia. Sudden collapse, more or less severe, may occur from exertion or emotion, and some cases of sudden death during the period of decline and in convalescence are unquestionably due to acute myocardial degeneration. The above symptoms may first appear during convalescence, when the patient is beginning to be about. Instability and irritability of the heart, with subjective symptoms, may persist for several weeks or months after recovery.

Endocarditis and *pericarditis* are very rare complications of typhoid. Occasionally at autopsy recent vegetations are found on the valves. Considering the frequency of secondary infections in the declining period of typhoid fever, the immunity of the endocardium and pericardium from invasion is rather remarkable. It is only rarely that a chronic valvular lesion can be traced to an attack of typhoid fever.

Arteries.—Arteritis is rare, but it occurs more frequently as a complication of typhoid fever than of the other acute infections. The disease is apparently due to the direct invasion of the arterial wall by the typhoid bacillus. Vincent and Muratet found the arteries of the right leg to be most frequently affected. The posterior tibial, femoral, popliteal, anterior tibial and dorsalis pedis were affected in the order named. More rarely the arteries of the upper extremities or of the brain were involved. In 4 cases in Osler's series 2 were in the femoral artery, 1 in the middle cerebral and 1 in the brachial. Thrombosis of the cerebral arteries may cause the sudden development of convulsions, coma or hemiplegia. Typhoid arteritis occurs as early as the third week and as late as the eighth week, when convalescence has apparently been fully established. It appears to be as frequent in mild as in severe cases.

The onset of the complication is sudden, with pain along the course of the affected vessel, or involving more extensive areas or even the entire limb. The pain is increased by movement and pressure. Paresthesias over the affected areas are common, and tenderness is marked over the inflamed artery. Thrombus formation brings out the vessel as

a hard, painful cord. Below the obstructed vessel the limb is pale or blue, swollen and cool. Pulsation in the artery is diminished or lost. The circulation may be slowly restored by the development of an adequate collateral circulation or by the formation of channels through the thrombus; or the obstruction may be complete and the process terminate in dry gangrene of the extremity.

Thayer studied the late cardiovascular condition of 183 typhoid patients treated in the wards of Johns Hopkins Hospital. From one month to thirteen years had elapsed between the attack of fever and the examination. The date of the examination was less than one year after the attack in 48 cases, between one and five years in 93 cases and between five and thirteen years in 42 cases. The results show that arterial hypertension, palpable radial arteries, cardiac enlargement and chronic valvular disease were found with much greater frequency than in individuals who gave no history of typhoid fever. He concludes that typhoid fever is an important factor in the etiology of arteriosclerosis and cardiovascular disease.

Veins.—THROMBOPHLEBITIS.—**The** studies **of** Conner have brought forward phlebitis as one of the common and very important complications of typhoid fever, responsible for many of the irregularities in the course of the pyrexia and the underlying cause of many complicating conditions hitherto not satisfactorily explained. In general literature phlebitis is stated to occur in about 2 per cent. of the cases of typhoid. Thayer found venous thrombosis in 39, or 2.6 per cent., of 1,463 cases. Da Costa reports 16 cases of milk leg in 135 soldiers treated for typhoid in the Pennsylvania Hospital, representing 12 per cent. In Webb-Johnson's series of 297 cases of typhoid fever in British soldiers not protected by antityphoid vaccination, 3.36 per cent. were complicated by phlebitis. Conner analyzed 1,540 cases treated in the New York Hospital, in which there were 78 cases, or 5 per cent., of undoubted thrombosis. He believes that with more accurate diagnosis an incidence of from 10 to 15 per cent. in all cases of typhoid will be shown.

Phlebitis is a late complication, rarely appearing before the third week of the disease. Nearly one-half of the cases develop in the third or fourth week, and about an equal number during the convalscent period.

The veins of the left leg are most frequently affected. The left femoral is the favorite site. The iliac, popliteal, internal saphenous veins, and those of the calf of the leg, may be affected primarily or by extension from the femoral. The veins of both legs are affected in about 30 per cent. of the cases. Quite rarely the process is confined to the pulmonary vein or to the veins of one arm, usually the left.

Autopsy findings often show thrombosis extending far beyond the site of the local symptoms as observed during life.

The onset of thrombophlebitis is often latent and insidious, and the early localizing symptoms may be absent or so mild as to escape recognition. As Aschoff has shown in his studies on thrombosis, the primary white thrombus is built up gradually, layer upon layer, from the blood-

platelets while the blood is still circulating. The local symptoms by which the condition is recognized develop only when complete occlusion of the vein has taken place. During this latent period, which may last for a number of days, as Conner has shown, thrombophlebitis may be manifested only by symptoms remote from the seat of thrombus formation. Small fragments may be detached from the growing, friable clot and cause pulmonary embolism and infarction. In the absence of the local symptoms of phlebitis the real nature of these small infarcts may not be suspected. Conner believes that most of the late pulmonary and pleural complications of typhoid fever have this etiology. The puzzling chills and the unaccountable irregularities in the course of the pyrexia so frequently seen in the declining period of the fever are very often due to a thrombophlebitis which has not yet shown itself by local symptoms.

The characteristic symptoms of fully developed thrombophlebitis are fever, pain, tenderness, swelling, edema and induration along the course of the thrombosed vein. Fever is present in approximately 90 per cent. of the cases. Should the complication occur before defervescence the regular typhoid temperature curve is interrupted by a rise, which may be sustained for a number of days, or may persist with various irregularities, and indefinitely prolong the pyrexial period. The increase of fever usually begins with the local signs of thrombosis of a large vein. In exceptional cases the rise may precede or follow the local symptoms by several days. During the convalescent period the onset of phlebitis may cause either a sharp transient rise of temperature or a longer period of pyrexia, showing violent remissions and exacerbations; or it may cause a prolonged, mild febrile movement. In the absence of coincident, frank, local symptoms these periods of fever may be confused with recrudescence from various other causes, or with true relapse.

The evidence advanced by Conner is very strong that many post-typhoid disturbances of temperature without other apparent cause are due to a latent phlebitis. Chills, either at the onset or during the course of the complication, were noted by Thayer in 28 per cent. of his cases. The relation of phlebitis to the multiple chills of the later period of typhoid has previously been considered.

Leukocytosis with moderate increase of the polymorphonuclear cells usually accompanies the complication. In all of Thayer's cases the count was above 6,000; in 54.5 per cent., it was from 10,000 to 20,000. In exceptional cases the typhoid leukopenia may persist for some time after the appearance of the phlebitis.

Thrombophlebitis is a distressing and sometimes a dangerous complication of typhoid fever. Death may result directly from pulmonary embolism, or from extensive thrombosis into the abdominal veins, or indirectly, from exhaustion or complications following and dependent upon the phlebitis. It may cause much suffering and greatly prolong the period of convalescence. Some permanent disability may be left from occlusion of the large vein. Persistent swelling of the leg after exer-

cise, varicose veins below the occlusion, and ulceration may result. Cramps in the calves of the legs are common. Gangrene is very rare.

Respiratory System

Larynx.—Routine laryngoscopic examinations during the course of typhoid show that laryngeal inflammation of greater or less severity occurs as a complication in a majority of the cases running a severe course. Jackson, of Pittsburg, carefully studied the condition of the larynx in 360 hospital cases. He classified the lesions under (1) subacute laryngitis, (2) ulcerative laryngitis, (3) perichondritis. He found subacute laryngitis in 227 cases, or 63 per cent.; ulcerative laryngitis in 68 cases, or 18.9 per cent.; and perichondritis with or without necrosis in 17 cases, or 4.7 per cent.

No satisfactory records of the frequency of laryngeal complications in private practice are available. They are probably much less frequent than in hospital experience. However, laryngoscopic examination of the larynx is rarely made during the course of typhoid fever, and it seems quite certain that mild laryngeal complications are rarely recognized and that only the severe lesions with emphatic symptoms have received consideration in medical literature.

Catarrhal Laryngitis.—The mucous membrane of the larynx participates in the catarrhal state common to the various mucous surfaces. The symptoms do not differ from those of the disease occurring as a primary affection. Jackson noted that the mucous membrane was continuously covered with a secretion, which appeared to come from the trachea and bronchi. Catarrhal laryngitis is important because of the possibility of its influence in the development of ulceration, edema or other serious conditions. Laryngeal symptoms, however mild, occurring during the course of typhoid fever, should put the physician on his guard and lead to careful laryngoscopic exploration for the presence of the more severe forms of laryngeal disease.

Ulceration of the Larynx.—Autopsy findings show that ulceration of the larynx occurs in about 10 per cent. of all fatal cases. Only a small percentage of this number is recognized during life. Jackson's studies indicate that systematic examination of the larynx would reveal a much higher incidence. The high mortality rate of the cases collected by Keen and others as compared with the mortality rate of Jackson's series seems to prove that only those cases presenting serious symptoms of laryngeal obstruction are included in these reports.

The nutritional changes in the mucous membrane of the larynx, the result of the typhoid toxemia, are the important predisposing factors in the etiology of ulceration. A large majority of the cases occur in severe typhoid with high fever and intense toxemia. Immediate exciting causes are:

(1) Traumatism by friction and irritation in phonation, coughing and deglutition.

(2) Injudicious exposure to cold and draughts.

(3) Arterial or venous thrombosis. Suddenness of onset in certain cases points to vascular occlusion as the determining factor in the ulceration. Arterial thrombosis is possible, but from Conner's studies it appears more probable that thrombosis of the small veins is the condition present.

(4) Infection. The typhoid bacillus has been recovered from the ulceration in a few cases. Infection by this organism is by the blood stream. Secondary infection by pyogenic cocci is the principal factor in the immediate etiology of the complication. Drainage into the larynx of infected secretions, and food remnants from a septic mouth and pharynx, and retention through lessened cough reflex keep the mucous membrane bathed with infected material. Loss of tissue-immunity determines the invasion of the mucous membrane by the organisms. A few cases have followed suppuration in the ears, or abscesses in the parotid gland and other contiguous structures. The Klebs-Löffler bacillus is rarely the infecting organism.

Laryngeal ulceration is a late complication. Sixty-seven of Jackson's sixty-eight cases and over 70 per cent. of the cases collected by Keen and Rieser occurred after the third week. The site of the ulceration in about 60 per cent. of the cases was the posterior laryngeal wall at the insertion of the vocal cords. The location in the remaining cases was the arytenoid cartilages and interspace, the aryteno-epiglottidean folds, the epiglottis and the thyroid cartilage, in the order named.

The onset of the complication is insidious, and the well-known symptoms of laryngeal inflammation may be absent, or so mild as to escape notice. Apathy, diminished sensibility or delirium may conceal the symptoms until a paroxysm of laryngeal dyspnea announces the formidable complication that is present. In Jackson's carefully observed cases, the average day of onset of the ulceration was the twenty-second; the average day of onset of symptoms was the thirty-first day.

Hoarseness, croupy cough and aphonia are the symptoms usually first noted. Pain, tenderness, dysphagia and dysphonia are present in patients whose sensibility is not too blunted. The symptoms of an apparently mild laryngitis may suddenly be followed by an alarming attack of dyspnea, or the dyspnea may be the first symptom to announce the laryngeal complication. The obstruction may be from acute edema, from an abscess in the laryngeal wall, from occlusion of the glottis by a sloughing mass, or from abductor paralysis of the vocal cords. When obstruction occurs after the period of profound toxemia the well-known violent symptoms of asphyxia are present. In the profoundly toxic patient the symptoms may be masked by the stupor, and death may take place without the attendant suspecting the gravity of the situation. A bronchopneumonia from aspiration of the laryngeal secretions may occur. The diagnosis of laryngeal ulceration is easy if the possibility of the condition is suspected and a laryngoscopic examination made. Unless particularly looked for, the complication may progress to a fatal termination without recognition.

Perichondritis and chondritis result from the extension of the ul-

ceration into the deeper structures of the larynx. More or less extensive necrosis of the cartilages of the larynx frequently takes place. Keen, basing his opinion upon his study of the reported cases of laryngeal disease complicating typhoid, states that necrosis of the cartilages is the most common lesion. It seems quite certain, however, that Jackson's personal experience represents more accurately the relative incidence of the various lesions. The milder forms of infection are not usually recognized and do not seriously affect the ordinary course of the primary disease.

Abscess of the larynx, ulceration of the trachea and perforation with subcutaneous emphysema are occasional results of ulcerative laryngitis.

The prognosis of the severe forms of laryngeal disease complicating typhoid fever is very grave. Of the 243 cases collected, 158, or 65 per cent., died.

The influence of the early recognition and treatment upon prognosis is shown by Jackson's experience. Of his 68 cases of ulceration, which included all the cases of the serious form of laryngeal invasion, only 4 died, representing 5.8 per cent., all of them from causes remote from the larynx. Of the 8 patients upon whom tracheotomy was performed for the relief of asphyxia, one died from toxemia. Jackson believes that with proper local treatment the prognosis depends upon the severity of the typhoid toxemia rather than upon the local condition. Permanent deformity, impairment or loss of voice, or stenosis requiring prolonged treatment may result from the destructive lesions.

Bronchi.—Bronchitis.—A mild bronchitis with cough, scant expectoration and a few râles scattered over the chest is quite a constant manifestation of typhoid, beginning in the first and continuing into the second week or throughout the febrile period. It usually causes but little discomfort. A severe bronchitis may complicate the onset and mask the primary disease, or it may develop at any time in the course. Occasionally the cough is severe and distressing. Like the bronchitis of measles it is a local manifestation of the general infection. The typhoid bacillus may be demonstrated in the sputum. Secondary infection by the pneumococcus, streptococcus or other organism may occur in severe septic cases. Bronchitis is rarely an important factor in a fatal issue. Osler cites one fatal case. Collapse of the lung with bronchopneumonia may result.

Lungs.—Bronchopneumonia.—Extension of the infection from the bronchi to the lung occurs in a small percentage of cases. It is often a late event in serious cases. The lesions of bronchopneumonia are found in about one-third of the fatal cases at autopsy. The typhoid bacillus, the pneumococcus, or more commonly the pyogenic cocci, are the infecting organisms. The onset is usually insidious, and is masked by the toxic state. Occasionally the complication begins with a chill. Rapid respiration, increased pulse-rate and cyanosis are significant symptoms. Areas of partial or complete consolidation can be demonstrated in the interscapular and subscapular regions. The complication adds greatly to

the gravity of a case. Rarely, in grave cases with myocardial weakness, edema of the lungs may result.

HYPOSTATIC CONGESTION.—Hypostatic congestion of the lower lobes of the lungs is a frequent complication of the latter half of the febrile period. In debilitated patients with severe toxemia it may occur in the first or second week. The development of the condition is favored by myocardial weakness and by the influence of prolonged dorsal decubitus. The condition causes no distinctive symptoms. There is no pain and no increase in the fever, cough or respiratory rate. The complication can be recognized only by a physical examination of the chest and will be overlooked in the absence of routine auscultation of the lungs in the back. Slightly tympanitic or impaired resonance over one or both lower lobes, absent or diminished respiration, prolonged expiration and bronchial voice and many fine râles are the physical signs which distinguish the condition.

Secondary infection of the congested area determines the development of *hypostatic pneumonia,* with the signs of complete consolidation. Elevation of temperature, rapid pulse and increased respiration are then present. With the decline of the fever and the improvement in the general condition of the patient, the consolidated area slowly undergoes resolution. The complication is grave. It was present in 121 of 1,830 cases observed by Curschmann, with 65 deaths. Careful nursing, with frequent change of the patient from side to side, tends to prevent stasis. The **bath treatment** is the most important preventive measure.

LOBAR PNEUMONIA.—In 1,420 cases of typhoid fever Liebermeister found lobar pneumonia in 52 cases, or 3.7 per cent. In Osler's series it occurred in 15 of the 829 cases, or 1.8 per cent. It is not a frequent complication. It may occur as a complication of the period of onset, of the fastigium, or of the period of decline. Typhoid fever may begin suddenly with the symptoms of a frank pneumonia and the characteristic physical signs of this disease. This is the "pneumotyphoid" of the French writers. The disease runs a course similar to that of primary lobar pneumonia for a number of days, and there is nothing in the clinical history to indicate the presence of a complicating or associated disease. Persistence of the pyrexia beyond the usual period and the appearance of rose spots, splenic enlargement, and intestinal symptoms will uncover the underlying typhoid infection. The pulmonary lesion may be a local manifestation of the typhoid bacteriemia, a typhoid bacillus pneumonia, or it may be due to a complicating infection by the pneumococcus or by one of the rarer pneumonia-producing organisms. Bacteriological studies have, up to this time, been too meager to permit a statement as to the relative frequency of the various infections.

Lobar pneumonia, complicating the latter stages of typhoid, occurs most frequently in the second and third weeks. The usual stormy onset of pneumonia is obscured by the apathy and diminished sensibility of the patient. The symptoms at this time are few and infrequent. Cough may not be increased and rusty sputum may not appear. The white-cell count may or may not be increased. Increased

respiration, cyanosis, rapid pulse and sharp disturbance in the temperature curve are the most important diagnostic symptoms. Physical examination of the chest will determine the nature of the complication. Curschmann states that the height of the consolidation of the lung is reached more slowly and that resolution is more often delayed than in primary pneumonia. Many cases do not advance beyond the symptoms of congestion. Lobar pneumonia is a grave complication. Of Liebermeister's 52 cases, 29 died. Marignac, cited by Hare, reported 13 cases with 10 deaths.

PULMONARY EMBOLISM AND INFARCTION.—Pulmonary embolism presents itself in two clinical forms:

(1) The severe form, with suddenly developing severe thoracic pain, dyspnea, cyanosis and collapse, usually rapidly terminating in death. This form is very rare. It is caused by a large embolus detached from a cardiac or venous thrombus occluding one of the large branches of the pulmonary artery.

(2) The mild form, giving rise to obscure and atypical signs of pleurisy or pneumonia. This form is relatively common. In Conner's study of 1,540 cases of typhoid fever there were 88 of pulmonary and pleural complications exclusive of bronchitis. In 63 of this number the character of the thoracic symptoms made it probable that most of them were due to pulmonary embolism. As shown above, the embolism has its origin in a thrombophlebitis.

The pulmonary symptoms may be the first evidence of a developing phlebitis. It may appear several days before the local signs of the complication, and the etiological relation between the two phenomena may be entirely overlooked. Thoracic pain is present in practically all of the cases; usually it is the first symptom. It is sudden, sharp, and may be very severe. It is usually referred to the lower axillary region, occasionally to the hypogastrium or shoulder. Cough is usual and may begin with the onset of pain or after two or three days. Bloody sputum is seen in about one half of the cases. It appears first in small, bright red clots or as a blood-streaked mucus, the color becoming dark later. Dyspnea and thoracic oppression occur in the severe cases. A chill is occasionally noted at the onset. Rapid breathing, increased pulse-rate and fluctuation in temperature are usual. The leukocyte count is usually increased. Rigidity and tenderness are occasionally observed in the upper abdomen, just below the ribs.

Physical Signs.—Conner classified the cases according to the physical signs into three groups: (1) Those with friction rubs or crepitant râles over a small area and lasting only two or three days; (2) cases with signs of a small circumscribed pneumonia, usually in one of the lower lobes, the consolidation disappearing in three or four days; (3) cases with extensive plastic pleurisy or pleural effusion.

PLEURISY.—Pleurisy is not a frequent complication. It has been observed at the onset as a localization of the typhoid infection. The thoracic symptoms may dominate the clinical picture, and the underlying typhoid infection may not be suspected until it is unmasked by

the subsequent decline of local signs and the continuance of the pyrexia, with the appearance of the characteristic rose spots and splenic enlargement. More frequently it is a late complication. In patients dull with typhoid toxemia the complication may develop with few symptoms and escape recognition.

The pleurisy may be of the dry plastic variety or show effusion. The exudate may be serous, purulent or hemorrhagic. The typhoid bacillus has been found in both the serous effusion and in the empyemas. Empyema is usually due to a secondary infection by the pneumococcus or one of the pyogenic organisms. The hemorrhagic effusions are often due to tuberculosis. Small pulmonary infarctions may give the symptoms and physical signs of pleurisy. A mild complicating pleurisy does not add much to the gravity of an attack of typhoid fever. Empyema and hemorrhagic effusion are more serious.

TUBERCULOSIS.—Typhoid fever may activate a latent pulmonary tuberculosis, and the pulmonary condition may appear as a complication either during the late period of the course of the fever or as a sequel at any time after convalescence is established. The evidence is not convincing that typhoid infection predisposes to infection by the tubercle bacillus.

ABSCESS AND GANGRENE.—Abscess and gangrene are among the rarest pulmonary complications. Either of these conditions may result from one of the pneumonias or from general sepsis. In profoundly toxic patients aspiration of septic material from the larynx during the course of ulcerative laryngitis, or of food particles from the pharynx, may be the immediate cause.

RENAL SYSTEM

Retention of Urine.—This is a common and annoying condition. In the early days of the fever it may be due to the difficulty many patients experience in voiding in the recumbent position. Later it is the result of the obtunded sensibility of the typhoid state. The patient may not make a definite complaint, but will indicate his distress by restlessness or by an increase in the delirium. Physical examination will reveal a bladder-tumor in the hypogastrium. Constant dribbling of urine is a suggestive symptom. Incontinence is occasionally seen in stuporous patients.

Polyuria.—Sollmann and Hofmann have shown that the eliminating capacity of the kidney for salt and water is not impaired in typhoid fever. The therapeutic use of a large water intake proportionally increases the urinary output. The urine may be increased to five liters or more. One of Osler's patients passed 23 liters in one day. Polyuria without excessive intake of fluid is occasionally seen in the second or third week of typhoid, and is a common phenomenon at the beginning of convalescence. It has been spoken of as a urinary crisis. The condition passes away with convalescence.

Febrile Albuminuria.—In typhoid fever the kidneys are not, as a rule, seriously affected. The slight albuminuria which is characteristic of

all acute infections with fever and due to a mild parenchymatous degeneration of the epithelial cells of the tubules is common. It occurs in about 60 per cent. of the cases. This febrile albuminura should be sharply distinguished from acute glomerulonephritis. It is not of serious import and disappears in a few days or with the decline of the fever. It does not impair the functional efficiency of the kidney. The albumin rarely amounts to more than a trace. A few casts, hyaline or finely granular, are usually found. In McCrae's series casts were present in 37.8 per cent. of the cases.

Nephritis.—Acute glomerulonephritis is not a common complication. Curschmann gives the incidence as about 1 per cent. Talley's series of 18,000 cases shows 3 per cent. Typhoid fever may be complicated with nephritis at the onset, constituting the nephrotyphoid or renal typhoid. More commonly the nephritis is a complication of the late febrile period; or it may appear during convalescence. It may begin suddenly with edema and uremic symptoms and a scant, highly albuminous urine, containing also blood and numerous casts. The onset may be insidious, without marked edema or uremic phenomena. The complication may be overlooked in the absence of routine urinary examinations, its symptoms being obscured by those of the typhoid fever.

Nephritis at the beginning of typhoid fever is a serious complication. Cases which develop late in the disease usually recover. The condition rarely terminates in chronic nephritis.

Infections of the Upper Urinary Tract.—Bacilluria.—From the third week on, typhoid bacilli are present in the urine in about one-third of the cases. The infection is usually mild, and no symptoms are present. The urine may be turbid from the presence of the bacilli, without other evidence of infection. It is generally thought that the bacilli pass through the kidney from the circulating blood in small numbers and multiply in the bladder urine. Mild local lesions in the bladder and prostate may produce the conditions favorable to the multiplication of the organisms. Bacilluria may persist for an indefinite period after recovery from the typhoid, and the host thus become a chronic typhoid carrier. Mild cases may remain latent for a number of years and then give rise to acute and severe symptoms. The colon bacillus or other organisms may be associated with the typhoid bacillus.

Pyuria.—Pus in small amount may be found in the urine without other symptoms. It may have its source in gonorrhea or in a mild catarrh of some part of the urinary tract.

Pyelitis.—Infection of the pelvis of the kidney may take place at the height of the disease or during convalescence. The complication is ushered in by an increase of temperature or, in the convalescent period, by a recrudescence of the fever preceded, perhaps, by a chill. Pus and, in the first days, blood are found in the urine. There is often a sudden leukocytosis. Bimanual palpation of the kidney will often elicit tenderness. The typhoid bacillus may be the infecting organism. Colon bacillus infection is also frequent.

The complication usually runs a course of a few days and ends with

recovery; or it may persist for considerable time and be the cause of a prolonged posttyphoid febrile state. Pyelonephritis may result. Perinephritis is quite rare and is practically always due to a secondary infection by one of the pyogenic cocci.

Cystitis.—The typhoid bacillus not infrequently causes a cystitis, mild or severe. The colon bacillus and the staphylococcus are also common infecting organisms. The usual symptoms of bladder irritation are present, with fever and leukocytosis. The typhoid infections are more amenable to treatment. Chronic cystitis may result. Hugh Young reported a case of seven years' duration.

Nervous System

Meninges.—Symptoms of meningitis or meningeal irritation may develop suddenly any time during the course of typhoid fever. Cases are recorded in which the symptoms appeared in the prodromal period. In some epidemics, particularly in those coincident with the prevalence of cerebrospinal fever, the incidence may be very high. During a milk infection epidemic, Curschmann observed five hospital nurses who were attacked in quick succession by typhoid fever, in all of whom meningitis symptoms predominated in the first week. Nervous symptoms of typhoid fever occurring with the onset may dominate the clinical picture and completely conceal the underlying typhoid infection. These cases have been designated as meningotyphoid by French writers.

Cole studied the meningeal complications of typhoid fever and, from pathologic findings, divided the cases into three groups: (1) meningism, (2) serous meningitis, (3) purulent meningitis. Lumbar puncture is the only means of differentiating these conditions.

Meningism.—Symptoms of mild, transient, meningeal irritation may occur with negative spinal fluid and insignificant autopsy findings. Curschmann and others have called attention to the condition. Wolf published twelve cases from Curschmann's clinic. In three fatal cases coming to autopsy there were no lesions of the brain or cord, and cultures from the central nervous system were negative. Such cases may be explained as due to the action of a soluble toxin upon the cortical neurons. Schultze, however, found that in certain cases, although no gross anatomical alterations could be demonstrated, small-cell infiltration was present along the course of the vessels of the meninges, and that there were similar microscopic foci in the substance of the brain and cord. Meningism has been most frequently observed in the typhoid fever of children. When the condition occurs at the onset of an attack of typhoid fever the symptoms often fade away in a few days and give place to the usual symptoms of the primary disease. When occurring later, meningism indicates a serious toxemia and is of graver significance. From our personal experience it would appear that this mild form of meningeal complication is more frequent than the reported cases indicate.

Meningitis.—Both serous and purulent meningitis may be produced

by the typhoid bacillus. Cole's studies show that *serous meningitis* is particularly a manifestation of the localization of the typhoid organism in the central nervous system. He considers it to be caused by toxins liberated from the typhoid bacilli localized in the spinal canal. Cole reported 13 cases, 8 from the literature and 5 from the wards of Johns Hopkins Hospital. In 1917 Bayne-Jones collected 17 cases reported subsequent to Cole's communication. Serous meningitis may subside, especially after lumbar puncture, or it may continue and prove to be the early stage of a purulent meningitis. Of 13 cases reported by Claret and Lyon-Caen 8 recovered and 5 died.

Purulent meningitis complicating typhoid may be produced by the Eberth bacillus, or it may be a secondary infection by the meningococcus, pneumococcus or one of the common pyogenic organisms. Mixed infection with one of these organisms and the typhoid bacillus may occur. In rare cases developing in the convalescent period the bacillus of tuberculosis is the infecting agent. The identification of the infecting organism is made by lumbar puncture and examination of the spinal fluid. Lumbar puncture should be a routine diagnostic procedure in all cases presenting meningeal symptoms. Cole reported 15 cases and Bayne-Jones collected 18 additional cases. According to these data purulent meningitis may occur at any time in the course of typhoid fever. It is an exceedingly fatal complication. All reported cases have died, usually within three days of the onset of the meningeal symptoms.

The symptoms of meningeal invasion by the typhoid bacillus are those of acute cerebrospinal meningitis, and they do not differ in essential particulars in the two forms of the disease, serous and purulent. The symptoms are severe headache, photophobia, vertigo, pain in the spinal region with rigidity and retraction of the head. There are also cutaneous hyperesthesia, pain and tenderness in the muscles with muscular twitching and occasionally convulsions. The deep and superficial reflexes are usually increased. Kernig's sign is generally present. The onset may be with chills and facial herpes, the latter being very rarely seen in typhoid fever without meningeal symptoms.

Meningitis, serous or purulent, whether due to the typhoid bacillus or to some other organism, is a very grave complication. Most cases die. As has been noted, mild cases of the serous form occasionally recover, particularly after repeated spinal puncture.

Hemiplegia.—Hemiplegia is one of the rare complications of typhoid. It may occur at any time from the third week until well into the period of convalescence. Age does not appear to have an important influence on the incidence. Of 42 cases collected by Smithies 9 were in children under ten years of age. In about two-thirds of the cases the paralysis is right-sided, with aphasia. The cerebral lesion may be thrombosis, hemorrhage, embolism or a meningo-encephalitis. In very rare cases the lesion is a meningeal hemorrhage. According to autopsy records thrombosis appears to be the most common lesion. The clinical history of hemiplegia complicating typhoid presents no distinctive features. 6 of the 42 cases reported by Smithies were fatal. Aphasia without

hemiplegia and terminating in recovery at the end of a few days has been reported a number of times. Hutenel stated that this form of aphasia always occurs in children, more frequently in boys. The author observed two cases, one a male adult, in the recent Alpena outbreak. Among the very unusual complications that have been recorded are paraplegia, monoplegia, bulbar paralysis and myelitis.

Convulsions.—Convulsions have been observed with extreme rarity. Convulsions may occur (1), as one of the phenomena of a sudden and stormy onset, especially in the typhoid of infancy or childhood; (2), during the height of the fever and toxemia; and (3), as a symptom of a vascular cerebral accident, as thrombosis or hemorrhage. Of the 42 cases of hemiplegia collected by Smithies, 10 were preceded by convulsions. As in the other acute infections, convulsions occurring at onset are not of such grave import as when they occur late in the disease as a result of serious toxemia or organic brain mischief.

Peripheral Neuritis.—Peripheral neuritis sometimes occurs as a late complication. The nerves of the lower extremities are involved more often than are those of the trunk and arms. The disease may manifest itself as a multiple neuritis involving both the lower or all four extremities, or it may be restricted to a single nerve. Pain, tenderness, paresthesia, motor and sensory paresis and trophic disturbances may result.

Neuralgia and painful areas in the muscles and skin are often seen without other evidence of organic changes in the nerves. As Conner has shown, these painful conditions are often due to phlebitis.

Tender Toes.—In early convalescence the plantar surfaces of the toes and sometimes more extensive areas of the feet become painful and tender. Contact with the bed-clothes or with any object may be exceedingly painful. This condition has been described as a peripheral neuritis. Conner believes it is due to a thrombophlebitis. Recovery takes place in a few days.

Psychoses.—Kraepelin's classification of the typhoid psychoses, which has been quite generally adopted, is the following: (1), the initial delirium, the psychoses of the period of incubation or the period of onset; (2), the febrile psychoses, developing during the height of the fever and toxemia; and (3), the asthenic or posttyphoid psychoses.

Initial Delirium.—In the initial stage, the mental derangement manifests itself as an acute delirium or a state of mental depression. The acute delirium is characterized by profound mental obtusion with hallucinations. The patient may wander from home and conceal himself in his effort to escape fancied persecution. There may be impulses to acts of violence. The condition may closely simulate alcoholic delirium. In two such cases recently seen in the wards under the author's observation, a diagnosis of delirium tremens was made on admission.

The form in which mental depression is the leading feature is rare. As the mental state may be the only outspoken symptom of the general infection, the true nature of the malady may not be suspected and the patient may be treated for a primary mental disease.

FEBRILE PSYCHOSES.—The mental derangements of the period of high fever are exaggerations of the ordinary fever delirium or stupor so frequently present in severe cases. The delirium may be of the expansive type and the stupor may assume the character of a coma-vigil. In the case of a boy of fourteen years under the author's (Jennings') observation, a few days of active delirium at the end of the febrile period were followed by a state of coma-vigil which continued for ten days after defervescence.

ASTHENIC PSYCHOSES.—The posttyphoid insanities may develop as a continuation of the febrile delirium, or they may appear at various times during the convalescent period. Dercum recognizes the following forms: (1), acute delirium; (2), confusional insanity, stuporous insanity; (3), cerebral asthenia, pseudodementia, pseudoparesis; (4), insanity with systematized delusions resembling paranoia; (5), true mania or true melancholia. Age is not an important factor in the etiology. Many cases are observed in children.

The prognosis of the typhoid insanities, considered as a class, may be said to be good. The severe delirium of the prodromal or initial period is of grave import. About one-third of the cases terminate fatally. The delirium and stupor of the febrile period usually decline with the pyrexia, and complete recovery is the rule. The prognosis of the posttyphoid psychoses is also favorable for ultimate recovery. It is true that of the cases committed to asylums only about 50 per cent. recover. These figures, however, do not represent the real situation. A large percentage of the milder cases which recover do not come under hospital care.

General Neuroses.—Various functional diseases of the nervous system may complicate the late state of the disease. Hysteria is not uncommon, and it may assume any of the well-known counterfeit manifestations of disease. Chorea, tremor, tetany, paralysis agitans and diabetes insipidus have been observed.

ORGANS OF THE SPECIAL SENSES

The Eye.—The ocular complications of typhoid have been fully studied by Geo. E. de Schweinitz. Paresis of accommodation, as a part of the postfebrile asthenia, is frequently seen. Conjunctivitis, catarrhal and phlyctenular, are among the most common ocular complications. Ulcerative and suppurative keratitis are more rare. Affections of the uveal tract are occasionally met with in the convalescent period. Iritis was seen by Sorel once in 871 cases of typhoid. Cataract may follow inflammation of the uveal tract, or it may result from nutritional disturbances without antecedent inflammation. Retinal hemorrhage is not very rare during the height of the febrile state. Embolism of the central artery of the retina has been noted. Optic neuritis with optic nerve atrophy, either partial or complete, may occur. De Schweinitz mentions amblyopia as a possible result of excessive quinin medication. Optic nerve atrophy may be caused by severe intestinal hemorrhage or epistax-

is. Transient amblyopia without ophthalmoscopic changes has been reported. Thrombosis of the orbital veins, panophthalmia and paralysis of extra-ocular muscles are very rare complications.

The Ear.—Otitis media occurs in from 2 to 3 per cent. of the cases. It is particularly frequent in the typhoid of childhood and infancy. It is usually a secondary infection by one of the common pyogenic organisms originating in the nasopharynx. Mastoid disease and sinus-thrombosis are far less frequent than in other acute infections. The impairment of hearing and the subjective sensations of sound so characteristic of the febrile state of typhoid are apparently due to the action of the typhoid toxin on the structures of the middle and internal ear. These symptoms usually disappear with convalescence. From 1 to 2 per cent. of all cases of impairment of hearing can be traced to a previous attack of typhoid fever.

Glandular System

Derangements of the Lymphatic Glands.—In addition to the enlargement of the mesenteric glands which is uniformly present, a general enlargement of all the lymph-nodes may occur. It is not of importance and subsides with the decline of the fever.

Mastitis.—Mastitis is a rare complication of typhoid fever, usually appearing in females. Osler saw 4 cases in his series. It occurs late, and is usually a secondary infection. The typhoid bacillus has been isolated from the pus in a few cases. It involves one or both breasts with about equal frequency. Half of the cases terminate in suppuration.

Orchitis.—Orchitis is occasionally met with, as in other infectious diseases. The epididymis is usually implicated. The disease presents no special characteristics. Chills, and fever with severe local pain and swelling, are the symptoms. The right testicle is most frequently affected, and only rarely are both involved. It runs a course of about two weeks' duration and terminates in suppuration in a minority of the cases. Atrophy of the testicle is an occasional result.

Thyroiditis.—The thyroid gland, under normal conditions, is peculiarly resistant to bacterial invasion. Bacterial thyroiditis is therefore a rare complication of typhoid, and requires for its production a very virulent infection or a greatly diminished resistance in the gland itself. Liebermeister and Hoffman found 15 cases of thyroiditis, 6 cases resulting in abscess, among 1,700 cases of typhoid. The complication appears to be more frequent in districts where goiter is common. Infection may be by the typhoid bacillus or by one of the pyogenic organisms. The disease may pursue its course as a non-purulent inflammation and terminate in resolution, or it may result in abscess formation. It appears late in the febrile period or in convalescence. Galli has reported a thyroid abscess with pure culture of the typhoid bacillus occurring twenty-one years after the primary typhoid infection.

The symptoms are pain, tenderness and swelling of part or of the whole gland. Dysphagia and other pressure symptoms may occur.

Without abscess formation the complication is not very serious. Of 41 cases of suppurative thyroiditis from all causes collected by Richardson, 9 were fatal. Crotte remarks that good surgery should reduce this mortality. Exophthalmic goiter is a possible sequela.

Locomotor System

Muscles.—Myositis.—The changes in the muscles in typhoid fever are degenerative rather than inflammatory. In convalescence, groups of muscles may become tender and painful on manipulation or with contraction. The symptoms suggest a myositis, although there is not at present satisfactory evidence that infection is the cause. The symptoms gradually disappear. *Rupture* of groups of fibers or of whole muscles may take place when degeneration is advanced, either from severe or very slight exertion. Hemorrhage at the site of rupture takes place with the development of a hematoma. The contents of the tumor may be infected and suppuration result. The typhoid bacillus has been recovered from both the blood and the pus. The muscles of the abdominal wall and of the thigh are most frequently the site of rupture. The diaphragm may be involved, with respiratory embarrassment. Sudden acute pain is the important symptom of rupture. In profoundly stuporous patients with severely degenerated and friable muscles the accident may pass unnoticed.

Joints.—Arthritis.—Webb-Johnson divides the joint affections of typhoid fever into (1), acute arthritis, serous or suppurative; (2), subacute arthritis, usually serous, but which may go on to suppuration.

Acute serous arthritis complicates the first stage of typhoid. It is polyarticular, involving the knees, elbows and other joints, and closely simulates acute rheumatic arthritis, for which it may be mistaken. As a rule the affection lasts a few days only, and ends in complete recovery. In exceptional cases some restriction of motion may result, or very rarely suppuration may take place. This form is similar in its clinical course to the more common and familiar arthritis of scarlatina. Salicylates have no effect upon it. It is a local manifestation of the typhoid bacteriemia.

Acute suppurative arthritis may result from an acute serous arthritis or from a subacute arthritis. More frequently it is a secondary infection of the joints by the streptococcus, staphylococcus or other pyogenic organism, absorbed from various skin and mucous membrane infections of the late period of the typhoid. When due to secondary infection it does not differ from the septic arthritis complicating other infections. The typhoid bacillus alone may produce the suppuration, or it may be due to a mixed infection. Suppurative arthritis is a highly dangerous, often fatal complication.

Subacute serous arthritis occurs about as frequently as acute arthritis. This form is a complication of the late febrile or convalescent period. It is almost always monarticular and affects by preference the large joints of the lower extremities, especially the hip joint. The onset is

insidious and the symptoms are mild. In apathetic patients it is easily overlooked, particularly when it involves a deeply-seated joint like the hip. The course of the disease is often mild, and terminates in resolution with complete restoration of joint function. It may be more severe and persistent and end in ankylosis or, rarely, in suppuration. Spontaneous dislocation is a frequent accident, due to great distention of the joint by serous effusion into the synovial sac. Dislocation is especially frequent in the subacute arthritis of the hip joint in children. In 84 cases of this type of arthritis collected by Keen spontaneous dislocation of the hip occurred in 40 cases, dislocation of the shoulder in 2 cases, and dislocation of the knee in 1 case. Subacute arthritis is undoubtedly due to invasion of the joint by the typhoid bacillus. Fluid from the joint has been found to be sterile in some instances, in others to contain the typhoid bacillus.

Bones.—The typhoid bacillus uniformly localizes and multiplies in the bone-marrow, which may harbor the organism for an indefinite period after recovery. The bacillus has been recovered from bone lesions, in one case thirteen years, in another twenty-three years after an attack of typhoid. In spite of the uniform infection of the bone-marrow, bone lesions are rare, occurring in less than 1 per cent. of the cases. Appearing chiefly in convalescence or long after recovery, they are sequelæ rather than complications. Adults are most frequently affected. The two essential forms of bone disease are (1), *osteoperiostitis* and (2), *osteomyelitis*. Osteoperiostitis is the common lesion. *Necrosis* and *caries* may result from either of the conditions. Of Keen's 237 collected cases, 110 were periostitis, 85 necrosis and 13 caries. The bones most frequently affected are, in order, the tibia, ribs, femur, ulna and humerus. Other bones may be involved. A solitary lesion is the rule. Multiple lesions may affect a single bone.

The disease begins with a tender, localized or diffused swelling over a superficial bone. There are practically no constitutional symptoms. The nodule may persist for a short or for a long time and then subside, or it may end in suppuration. Recurrence with or without suppuration is sometimes noted. The pus almost always yields the typhoid bacillus. Secondary infections with streptococcus staphylococcus, etc., occasionally occur.

The pure typhoid lesions do not often cause serious damage to the bone. The secondary infections are much more serious and may endanger life. The *x*-ray is of great value in determining the character of the lesion and the extent of bone involvement.

Spine.—SPONDYLITIS.—Gibney in 1889 described a group of four cases occurring in the convalescent period of typhoid fever under the term "Typhoid Spine" in which there were pain, tenderness and rigidity of the lower spine, which he regarded as due to a perispondylitis. Carnett, writing in 1915, states that over 100 cases have been reported since Gibney's paper was published. *X*-ray examinations of the more recent cases support the view that an organic lesion, usually a periostitis, is the foundation of the symptoms. "The skiagrams show periostitis with

effusion under the periosteum, changes in the intervertebral discs, and new formation of bone. Commonly only two adjacent vertebræ are involved, although rarely several may be. In rare instances with septic infection there may be suppuration, when caries and necrosis may occur'' (Webb-Johnson). Neuroses simulating this condition possibly occur, but they should be excluded from the list of true typhoid spine cases.

The disease as a rule involves the lumbar vertebræ, either alone or together with the immediately adjacent dorsal or sacral vertebræ. The disease occurs as a late complication or as a sequela, two or three months often intervening between defervescence and the onset of the spondylitis. One case occurred four years after recovery from the primary infection. The affection occurs in both mild and severe cases and more frequently in young men, from twenty to twenty-five years of age.

The onset of symptoms is usually gradual, but may be abrupt and severe. Pain over the lumbar spine is the most constant and positive symptom. It may be very severe. It may be restricted to the lumbar area or referred along the course of the lumbar or sacral nerves. The pain is aggravated by movement. Tenderness and rigidity are present in almost all cases, and occasionally there is swelling. Some rise of temperature is usually seen. In one of our cases developing six weeks after convalescence, the temperature ranged from 101° to 104° F. (38.3° to 40° C.) during six days at the height of the disease. Sensory disturbances, muscular paresis and atrophy and changed reflexes are occasionally observed from involvement of the spinal nerve-roots.

The disease usually ends in recovery in two or three weeks. It may be prolonged for several weeks. Severe cases with necrosis and caries are of course more serious.

The Carrier State

Bacteriological recovery from typhoid fever may not be coincident with clinical recovery. With the beginning of the stage of decline the bacilli in the circulating blood diminish in number, and as a rule they disappear from the blood stream several days before convalescence begins. The bacilli, however, persist in the gall-bladder, intestine and other residual foci, for varying periods after they have left the blood stream. In favorable cases the blood and tissues are free from bacilli within a few days after the temperature becomes normal. In a certain percentage of all cases residual foci persist for months or years, in which the bacilli live and multiply and from which they are continuously or intermittently excreted. This sequela of typhoid fever is termed *the carrier state,* and an individual thus harboring typhoid bacilli in his body is termed a *typhoid carrier.*

According to the channels of elimination of the typhoid bacilli, typhoid carriers are classified as: (1) intestinal or fecal carriers; (2) urinary carriers, and (3) pus carriers.

Intestinal carriers are in large majority. The gall-bladder is the

focus of vegetation of the bacilli, and elimination is through the feces. The pelvis of the kidney is the most common focus in the urinary carriers. A chronic cystitis or a spermovesiculitis is the focus in rare instances. Pus carriers are rare and of relative unimportance as sources of infection. A chronic abscess, otitis media, or periostitis may harbor the bacilli. Of 314 cases of the carrier state collected by Prigge, 291, or 93 per cent., were fecal and 23, or 7 per cent., were urinary carriers.

Sacquépél divides all carriers according to their relation to an attack of typhoid fever into the following groups:

Group 1.—Precocious or *incubation carriers,* who discharge bacilli before the onset of clinical symptoms of typhoid fever.

Group 2.—Recovered carriers: (*a*) *Convalescent carriers,* who discharge bacilli up to three months after clinical recovery. (*b*) *Chronic carriers,* who discharge bacilli longer than three months after clinical recovery.

Group 3.—Healthy carriers, giving no history of typhoid fever.

Individuals of groups 1 and 2 have been designated *active carriers* and those of group 3, *passive carriers.*

The number of typhoid carriers among the general population has been estimated at 3 carriers for every 1,000 people. Of 993 persons examined in Washington by Rosenau, 3 per cent. were found to be carriers. Approximately the same percentage was found in a large number of examinations made in Germany.

The duration of the carrier state is variable. A majority of the individuals are convalescent or temporary carriers, and they cease to discharge bacilli before the end of the third month. Of 400 cases analyzed by Lentz, 6 exceeded the three months' period and subsequently made a bacteriological recovery at periods ranging from three and one-half to nine months; 15, or 3.75 per cent., became permanent carriers.

The carrier state is most frequent in women and children: 60 per cent. of the convalescent carriers and 82 per cent. of the chronic carriers are women; 35 per cent. of the convalescent carriers and 4 per cent. of the chronic carriers are children (Simon).

The etiological relation of typhoid fever and gall-stones has been demonstrated by many observers. The calculi may contain typhoid bacilli. Subjects of gall-stone disease are, therefore, typhoid carrier suspects.

The number of organisms discharged in the feces by a carrier varies from time to time. During the fever, and early in convalescence, the discharge is often intermittent. Later it tends to become continuous, and while this is the rule for chronic carriers, fluctuations in the discharge are frequently noted and intervals of varying duration occur when bacilli are absent from the discharge. A single negative examination is not, therefore, conclusive evidence of the absence of the carrier state.

Precocious Carriers.—Conradi, in 1907, recorded two cases of precocious carriers. G. Mayer had already demonstrated the presence of typhoid bacilli in the stools of a patient eight days before the onset of symptoms. Battlehner has reported 4 precocious carriers who dis-

charged bacilli in the feces for from twenty-one to one hundred and seventeen days before the onset of fever. Typhoid bacilli in any numbers are not present in the feces until general infection and gall-bladder localization have taken place. "It seems necessary to assume in the case of incubation carriers that the evolution of the disease symptoms has simply been delayed beyond the usual period following general invasion of the typhoid bacillus" (Gay). Considering the prolonged duration of the precocious carrier state as demonstrated in the above cases it seems not improbable, in the present state of our knowledge, that precocious carriers are in fact healthy carriers whose resistance to auto-infection has finally broken down.

Recovered Carriers.—We are largely indebted to German investigators working along the lines recommended by Koch in 1902 for the demonstration of the incidence of the carrier state as a sequela of typhoid fever. In a total of 2,714 persons convalescent from typhoid fever reported by nine German, English and American writers, an average of 4.1 per cent. were found to be carriers for three months or longer. One group of 86 cases very thoroughly studied by Semple and Greig in India gave the exceptionally high incidence of 11.6 per cent. From these statistics, therefore, it is demonstrated that from 4 to 5 per cent. of all persons who suffer from typhoid fever become chronic carriers.

Healthy Carriers.—Among 431 cases of typhoid carriers collected by Klinger, 44 individuals, or 20 per cent., were found who gave no history of a previous attack of typhoid fever. Although undoubtedly there were included in this number many mild and unrecognized cases of the disease, it seems conclusively proven that many persons become typhoid carriers without having passed through clinical typhoid fever.

The diagnosis of the carrier state is made by bacteriological examinations of the feces and urine and of the pus from suspected foci. The persistence of the Widal reaction for many years after an attack of typhoid is a suspicious circumstance and calls for complete bacteriological investigation.

Pregnancy

Typhoid fever is rare in pregnant women. Authorities differ on the question of the relative immunity of the pregnant woman. In any large collection from 1 to 3 per cent. of the cases of typhoid fever complicate pregnancy. The condition is one to cause anxiety. It leads to abortion or premature labor in from 40 to 60 per cent. of the cases. Of 233 cases collected by Sacquin pregnancy was interrupted in 150 cases; 37 of the patients died.

Abortion or premature labor usually occurs at the height of the fever and toxemia. When abortion occurs in the early months severe hemorrhage is common. Delivery at term usually takes place normally and at times a healthy child may be born. Fetal death is the result of typhoid bacteriemia. The organism has been repeatedly demonstrated in the blood and tissues of the fetus.

ASSOCIATION WITH OTHER DISEASES

Acute Diseases.—Typhoid fever is preëminently a disease of early life. Any of the acute diseases common to this period may be accidentally associated with typhoid infection, although as a matter of fact such coincidence is not frequent. Furnier collected 75 cases of *scarlet fever* associated with typhoid fever. Usually typhoid is the first infection and the scarlatina follows, probably from exposure to a passive carrier. *Measles,* a more common infection, is not readily carried and is very rarely seen. *Small-pox, chicken-pox, whooping-cough* and *diphtheria* have been rarely observed. *Influenza* may be an accidental associate, but it certainly does not predispose to typhoid fever. In fact there was an exceptionally low incidence of typhoid fever in this city and state during the prevalence of the recent epidemic of influenza. In the late period of typhoid, when complicating pyogenic infections of the skin are frequent, *erysipelas* may develop. Water-borne infections like *cholera, dysentery* and other diarrheal diseases may develop with typhoid. The ingestion of highly polluted and typhoid-infected water may cause a quickly appearing *gastro-enteritis,* and this may be followed by typhoid fever after the usual incubation period.

Before the discovery of the specific organism of typhoid fever clinicians of this country, following the lead of Woodward, concealed their uncertainty in diagnosis and lack of definite etiological knowledge in the term *"typho-malarial fever,"* assuming the existence of a hybrid infection. This term is less ominous than typhoid fever and was widely used to designate any continued fever of doubtful etiology. Bacteriological study has shown that there is no such pathological entity, and the name in this sense should disappear from medical literature. The term is also given to severe continued *malarial fever* with adynamic symptoms. In French literature it is used to designate cases infected coincidentally with the typhoid and malarial organisms. In malarial districts this combined infection is occasionally seen. McCrae met with only 3 cases in his series. Chills and distortion of the temperature curve may excite suspicion of the malarial complication. Only the demonstration of the plasmodium will identify the intruding infection.

Chronic Diseases.—The association of *tuberculosis* with typhoid fever is of interest. The evidence is not convincing that either infection predisposes to the other. Both are diseases particularly incident to early life, and it would indeed be remarkable if an occasional tubercular subject did not contract typhoid fever. The frequency of the association is not great enough to suggest anything but an accidental relation. In the author's experience the association is certainly rare. McCrae found only 6 cases of active clinical tuberculosis in his series. It is a noteworthy fact that in recent years there has been about an equal rate of decline in the mortality from typhoid fever and from tuberculosis. This decline may be attributed, the author believes, rather to the effect

of modern sanitation, which affects the incidence of both diseases about equally, than to the influence of a direct etiological relation between the two. Typhoid, like any acute debilitating disease, may activate a latent tuberculosis. Only in this sense can typhoid predispose to tuberculosis. A high percentage of consumptives give a history of one or more attacks of fever which have been thought to be typhoid, and for this reason typhoid fever has been considered to be a predisposing cause of tuberculosis. A history of a previous attack of typhoid fever in a consumptive patient should be received with suspicion. Periods of fever in cases of latent tuberculosis are very common and may closely simulate typhoid. Only laboratory evidence should be accepted as conclusive.

Association of typhoid fever with other chronic infections and with metabolic and degenerative diseases is rarely seen. The association with *syphilis* is uncommon. Before the days of antityphoid vaccination it was a particularly frequent coincidence in military medicine. *Diabetic* patients may develop an intercurrent typhoid infection. Severe cases run their course with a low temperature, although this in itself is not of unfavorable significance.

Chronic *alcoholics* are bad subjects for typhoid. Curschmann observed a mortality of 34 per cent. among drunkards in Hamburg. Although the temperature generally runs low, signs of myocardial weakness develop early. Severe intestinal and other hemorrhages are frequent. Delirium, stupor and profound adynamia are frequent and grave manifestations. *Nephritis* with renal insufficiency and uremia may hasten a fatal issue.

CLINICAL VARIETIES

Mild Typhoid Fever.—Occasionally in hospital wards, quite frequently in private practice, cases of continued fever of short duration are seen which, from clinical signs alone, are difficult or impossible to classify. They have been described under the vague terms: febricula, ephemeral fever, gastric fever, simple continued fever, etc. That a certain or large percentage of such cases are examples of mild typhoid infection is the conviction of many careful and experienced observers. Louis mentions a mild case with perforation that came to autopsy. Gresinger, 1864, described a form of typhoid fever in which the symptoms were mild and the duration of the disease was from eight to fourteen days. Murchison, Liebermeister and others of this period also mention a mild form of the disease. As these observations were made before the knowledge of bacteriological diagnosis, the question was an open one. In mild cases the more positive clinical signs, the rose rash and the splenic enlargement, may not appear at all, or at least until the case has passed from observation. In fact the diagnosis of mild and atypical cases of typhoid fever by clinical means alone was, and still remains, notoriously unreliable. Laboratory aids now give certainty, and many continued fevers classified under various names have been

identified as belonging to the typhoid group. French observers obtained positive serum reactions from cases of *embarras gastrique febrile.* In a typhoid epidemic in Saarbrücken in 1904 Koch and his co-workers determined that many mild febrile cases of indefinite clinical character were typhoid infections. J. P. Bates, in 1909, studied 68 cases of typhoid fever in Panama. Of these, 21 were of the short duration variety, in all of which a positive diagnosis was made by blood culture or serum reaction. Warren Coleman studied 24 cases of short duration typhoid fever in the second medical division of Bellevue Hospital. They constituted 10 per cent. of all the typhoid cases admitted to the division in five years. The diagnosis in 20 of the cases was made by blood culture or serum reaction; in the remaining 4 cases, by clinical evidence alone.

The typhoid fever commission of the Spanish-American War concluded from their studies that because of their mild character a large percentage of the cases of this disease, both in civil and military practice, were not recognized as typhoid fever.

From the foregoing it seems proven that mild cases of typhoid fever of short duration are common, and in the interest of both the patient and of the public health they should be recognized and treated as such. Bacteriological and serological study should be made of every continued fever of more than two or three days' duration for which an adequate cause cannot be found.

The clinical history of mild typhoid shows many variations from the typical course. The fastigium of the disease is shortened and the temperature curve may exhibit many irregularities. Only exceptionally does it rise above 103° F. (39.4° C.) (Fig. 3). The stage of decline is equally variable. It may be short, or it may continue for a full week or longer, the temperature showing sharp remissions or irregularities. The symptoms are slight throughout the whole course of the disease. Diarrhea is mild or absent. Prostration is not great, and important nervous symptoms are absent. The typhoid rash is present in a majority of the cases that continue into the second week. The spleen is palpable only in a small percentage of the cases. Complications are unusual, wasting is not marked and convalescence is usually rapid.

Abortive Typhoid Fever.—In the abortive form of mild typhoid the disease begins sharply, and all of the symptoms of an attack of moderate severity progress in the usual sequence. At the end of a week or ten days defervescence unexpectedly begins; the temperature rapidly declines, all the symptoms abate and convalescence is establishd in from ten to fourteen days from the onset.

Afebrile Typhoid Fever.—A form of mild typhoid fever running its course with characteristic typhoid symptoms and without a febrile temperature is described by various authors. Diagnosis in the reported cases has usually been made from the clinical history and has apparently been confirmed in a few cases by autopsy. As elevation of temperature is an essential fact in the clinical conception of typhoid infection, a period of vague ill health without temperature above the normal would rarely arouse suspicion of typhoid fever and lead to its identification

by laboratory methods. Only an occasional case has been reported by American writers. In the present state of our knowledge a diagnosis of afebrile typhoid fever demands verification by positive pathological or bacteriological evidence.

Ambulatory or Walking Typhoid.—It not infrequently happens that the subjective symptoms of the initial period of typhoid fever are not of the usual severity, and a patient may continue his ordinary activities until the disease is well advanced, when an overwhelming prostration or a serious complication like hemorrhage or perforation compels him to seek medical advice.

These cases fall into two groups. Cases of the first group are observed most frequently in men of the lower classes who are not mindful of bodily discomfort and who resist the illness to the last moment. Eventually such a patient consults the physician in his office, or walks into the hospital, where he is found to be well along in the second or third week of the disease. Intelligent devotees of the various forms of mental therapeutics are also found in this group. The subsequent course of the disease in these cases is often severe and fatal.

In the second group are included the cases of mild typhoid which escape recognition as such and are thought to be cases of influenza, cold, acute intestinal catarrh or other unimportant infection. Patients of this group may pass through the disease without taking to their beds.

Malignant Typhoid Fever.—A profound toxemia characterizes this form of the disease. The onset may be sudden, with high fever, frequent and persistent vomiting, quick and feeble pulse and a rapidly developing and fatal asthenia. In other cases, after a violent onset, early adynamic symptoms develop. There is abundant diarrhea, great prostration, feeble heart action, low delirium or profund stupor. The patient is overwhelmed by the intensity of the infection and succumbs in the second week of the disease.

Subcutaneous and internal hemorrhages are occasionally seen, and constitute what is known as *hemorrhagic typhoid fever*. This form is very rare. In Osler's studies at Johns Hopkins Hospital only 1 case was observed. This was reported in detail by Hamburger. Hamburger cites Uskow's series of 6,513 cases of typhoid fever with 4 of the hemorrhagic form. Liebermeister observed 3 cases of this form among 1,900 cases of typhoid.

Typhoid Fever in Children.—Children are just as susceptible to typhoid fever as adults. They are more resistant to the typhoid toxemia, and the general course of the disease is as a rule milder. Short duration typhoid and the abortive types are frequently seen, and the individual stages of the disease are shortened. Septic and protracted cases are infrequent.

Some of the individual symptoms show variation from the adult type. The slow pulse of adult typhoid is not observed. From the onset the pulse is rapid, especially in very young children. Vomiting more often occurs at the onset and diarrhea is more constant than in the adult. Pain and abdominal distention are more pronounced. Hemorrhage and

perforation are rare accidents up to six years of age. After this the incidence of these accidents increases with the age of the patient and about equals the adult percentage by the end of childhood.

In the severe cases nervous symptoms and complications are apt to occur. Convulsions at the onset and meningeal symptoms during the course are not rare. Transitory aphasia is a complication seen more commonly in children.

Recrudescence and relapse occur with greater frequency than in adult typhoid. The mortality rate is low. The Hamburg statistics show a rate of 4 per cent. between the ages of two and five years and of 6.4 per cent. between five and ten years.

Typhoid Fever in Infancy.—Infants enjoy a relative immunity to typhoid fever, as they do to some of the other acute infectious fevers. The disease is comparatively rare under the age of two years, and decidedly rare under one year. The occurrence of the disease in very early life has been doubted by many clinicians, but the positive findings of modern laboratory diagnosis and the accurately recorded cases of many pediatricians have demonstrated that typhoid fever is one of the diseases that must always be given consideration in the differentiation of the acute febrile diseases of infancy.

Holt states that but 11 cases of typhoid fever in infants under two years of age were observed in the Babies' Hospital in New York during a period of thirteen years. Five were under one year of age. Griffith, of Philadelphia, who has repeatedly called attention to the occurrence of typhoid fever in the young, observed 45 cases in the Children's Hospital in infants under two years of age. Nine were in infants under one year, the youngest being three months old. Cases in the newly born have been recorded. Jacobi reports a case developing on the sixteenth day after birth.

Of 145 cases of typhoid fever in children reported by A. Hand, Jr., 2 were under two years of age. In a study of 337 cases of typhoid fever in children by Adams, of Washington, 13 were in infants two years of age and in 1 case one year of age. Of 200 cases in the experience of Abt, of Chicago, 4 patients were two years of age and 2 were under one year. In the various discussions on the subject in the American Pediatric Society it has been brought out that members who have had a large experience in the care of children have all met with a few cases of infantile typhoid. During an extended personal experience with diseases of children in a city with a large typhoid fever incidence, the author (Jennings) observed only 2 cases occurring in infants under one year of age. One at nine months gave a positive blood culture on the fifth day. Statistics from European sources show about the same incidence. In 3,686 cases treated in the Hamburg general hospital in 1886 and 1887, 7 were under two years of age. In the Jacobspital of Leipzig, from 1880 to 1893, there were 1,626 cases of typhoid, including 5 under two years of age. The mortality statistics of Paris from 1880 to 1889 give 36 cases under the age of one year, out of 16,036 deaths from typhoid fever.

SYMPTOMS.—The onset of the disease in infants is more apt to be abrupt and without prodromic malaise. The infant is severely ill from the beginning. Anorexia, vomiting, diarrhea and abdominal pain are frequently noted in the first day or two. In rare cases convulsions mark the onset of the disease, or they may occur in the fastigium and are then, as in other severe infections, of grave import. The temperature curve (Fig. 7) shows variations from the usual adult type. It rises to a moderate height on the first day and attains in two or three days the high level that in adult cases is not reached until the end of the first week. The remittent character of the fever in the fastigium is less marked. During this period the range of the temperature is apt to be higher than in adult cases of the same general severity. The pulse is rapid and more in harmony with the temperature, and is not often dicrotic. Diarrhea is present in about the same general proportion of cases as in adult typhoid. The dejecta, however, have more the appearance of the ordinary diarrheal stool in infancy than of the peculiar typhoid stool of adult cases. Tympanites is not severe and gurgling and tenderness are infrequent. The grave intestinal accidents, hemorrhage and perforation, are decidedly rare.

The eruption appears somewhat earlier than in the adult, but is not so constantly seen. Hand noted it in 70 per cent. of his cases, an unusually high percentage. The spots are fewer in number and not so distinctive in appearance.

The normal leukocyte count in infancy varies from 9,000 to 18,000; in childhood from 8,000 to 12,000. The low leukocyte count of adult typhoid fever, so valuable in diagnosis, is not found in the very young. Only rarely is the count below 5,000, and it varies all the way to 16,000 in uncomplicated cases. The blood-count in infancy is, therefore, of comparatively little value in diagnosis; a count below 6,000, however, would be strongly suggestive of typhoid fever.

The typhoid of infancy does not show the multiplicity of complications and sequelæ that are so marked a feature of adult typhoid. Some cases succumb to the toxemia in the second or third week of the disease, and the milder cases recover completely.

Typhoid Fever in the Aged.—Typhoid is decidedly rare in the latter part of life. Of 5,306 cases observed by Curschmann 60 were in patients over fifty years of age. The course of the disease is severe and the prognosis unfavorable. The mortality is from 30 to 40 per cent.

The onset and evolution of the symptoms are gradual. Chill is very rare. Repeated chilly sensations are usual the first few days of the febrile period. Resistance to the toxemia is feeble. Prostration is manifested early and soon becomes profound. Stupor and coma are early symptoms. Tremor, subsultus and muttering delirium are almost always present. In the patients who recover these adynamic symptoms are marked throughout the entire course of the disease.

The temperature is in harmony with the sluggish reaction to the infection. The curve holds at a low maximum, rarely rising above [illegible] F. (38.9°C.); it is erratic, with marked remissions or intermissions.

The characteristic typical curve of typhoid is almost never seen. Afebrile cases occur most frequently in the aged.

Cardiac asthenia appears early. The pulse is rapid from the beginning, and becomes irregular and feeble as prostration increases. It does not show the dicrotic character of typhoid in earlier life.

Bronchitis is apt to be severe, and the feeble right heart favors the development of hypostatic pulmonary congestion and pneumonia.

Hemorrhage and perforation are of average frequency. Hemorrhage is a severe complication, even small losses of blood adding greatly to the gravity of a case. Diagnosis by clinical means is difficult. The rose spots are few, less brilliant and disappear quickly. The spleen is seldom palpable. The general picture of the disease is misleading, and laboratory aid is essential to prompt and positive diagnosis.

The disease is often long drawn out, convalescence is tedious, and the former state of health is rarely regained.

TREATMENT.

General Prophylaxis

Typhoid fever is a preventable disease. The elimination of typhoid as an important factor in the death rate from disease in the United States Army during the recent war is convincing evidence that with equally efficient administration in civil communities, of the prophylactic measures now known to sanitary science, typhoid fever would practically disappear from mortality statistics. In the present state of society, eradication of the disease is not to be expected. Under the best civil sanitary administration now possible, living bacilli will occasionally escape the protective barriers thrown out against them and reach the alimentary canal of unprotected individuals. Typhoid fever, like smallpox, should be only a rare visitor in any community.

The prevention of typhoid fever may be accomplished by (1) the destruction of the bacillus at its source; (2) the prevention of the transmission of the bacillus from the excreta of the typhoid patient or carrier to healthy persons; (3) the protection of the individual by antityphoid vaccination.

(1) **Destruction of the Bacillus at Its Source.**—The bacillus leaves the infected patient by way of the excreta: the feces, urine, sputum and, rarely, in the pus of typhoid abscesses. Could these discharges from every typhoid patient and carrier be thoroughly disinfected immediately after discharge—or, to put it in other words, could the bacillus be killed at its source—typhoid fever would soon cease to exist. This is only theoretically possible. Unrecognized healthy carriers, mild, incipient and atypical cases, cases with delayed diagnosis or under the care of thoughtless physicians or nurses give abundant opportunity for the bacillus to escape and be at large. **Early and correct diagnosis** is an important factor in the prophylaxis of the disease. In a recognized case

of typhoid fever the responsibility for the prevention of further extension of the infection rests with the attending physician. To wait for the clinical and laboratory signs necessary for a positive diagnosis is a serious error. Prophylaxis should begin with the first suspicion of the presence of typhoid.

Destruction of the bacillus at its source is accomplished by the **disinfection of all excreta** as soon as they are discharged from the patient and the **sterilization of all persons or objects contaminated by them.**

STOOLS.—Disinfection of the stools requires care and time. **Heat** is the most efficient disinfectant. Its use is not practicable in home surroundings. In hospitals, camps and during epidemics, **disinfection of feces by boiling or by the action of steam** is practical and efficient. The fever wards in hospitals should be equipped with **closed hoppers for the sterilization by steam, of excretions, bed-pans and urinals. Chemical disinfection** is available in all cases and if carried out with due attention to detail, the results are satisfactory. The bath-room toilet should not be used until the patient is convalescent and the stools free from bacilli. The discharges should be received in a bed-pan or commode containing a small quantity of disinfectant solution. There should be added disinfectant solution in quantity equal to at least twice or three times the volume of the mass of excreta. The mixture should then be thoroughly stirred and all solid masses of feces broken up. Bacilli imbedded in hard fecal masses will resist the action of the disinfectant for hours or indefinitely. The receptacle should then be tightly covered and allowed to stand for several hours—two hours at least—before final disposal. After emptying, the receptacle should be cleaned and sterilized by boiling water, steam or disinfectant solution.

Carbolic acid in 5 per cent. solution is the most satisfactory and generally useful chemical disinfectant. The quantity used should be double the volume of the feces.

Fresh milk of lime is an efficient disinfectant and has the advantage of being readily available everywhere. To 100 parts of freshly burnt lime—calcium oxid—add 60 parts of water. The resulting product is slacked lime—calcium hydroxid. To prepare the milk of lime mix 1 part of this fresh slacked lime with 8 parts of water. The slacked lime must be kept tightly sealed and the milk of lime prepared fresh every day. The quantity used should be three times the volume of the feces. **Air-slacked lime is useless as a disinfectant.**

Other chemical disinfectants that may be used are **chlorinated lime,** 5 per cent. solution; **compound solution of creosal,** 2 per cent.; **solution of formaldehyd,** 10 per cent. Bichlorid of mercury is not effective for the disinfection of feces.

URINE.—Cole states that every specimen of urine from a typhoid patient should be regarded as a pure culture of typhoid bacilli. Each specimen should be disinfected as voided, by the addition of a 5 per cent. **solution of carbolic acid,** 1 part to 2 parts of urine, or 1-1000 **bichlorid of mercury solution,** 1 part to 20 parts of urine. The mixture should stand for two hours. It is often convenient to keep the urine in a covered

jar containing the proper amount of disinfectant for the day's excretion and to empty the jar every twenty-four hours. **The urinal should be kept immersed in a disinfectant solution when not in use.** Disinfection of the urine at its source, by the internal administration of hexamethylenamin is considered elsewhere.

SPUTUM—NASAL SECRETIONS.—Sputum and nasal secretions should be received in **gauze or paper and burned** at frequent intervals; or in **sputum cups** which are frequently **disinfected with carbolic acid or bichlorid solution.**

VOMITUS, PUS AND OTHER DISCHARGES.—Vomitus, pus and other discharges should be treated like the urine or feces.

BATH WATER.—This is too frequently discharged into the house drain, without treatment. It may be efficiently disinfected by the addition of one-half pound of **fresh chlorated lime** to each 50 gallons of water.

PERSONAL AND BED LINEN.—The patient's personal and bed linen should first be **soaked** for two or more hours **in a 5 per cent. carbolic acid solution, and then boiled.** Towels and handkerchiefs should be treated in the same way. Rubber sheets may be soaked in a disinfectant solution. **Mattresses, blankets and fabrics that cannot be boiled should be sterilized with dry heat or formaldehyd.**

DISHES, UTENSILS, ETC.—Dishes and tray service should be sterilized by a disinfectant solution or by boiling before being taken from the sick-room. **Bed-pans, urinals, syringes, rectal tubes and all instruments must be boiled or treated with one of the disinfectant solutions and when possible kept immersed in the solution. The sick-room should be kept scrupulously clean and, at the end of the illness, thoroughly disinfected.**

THE CHRONIC TYPHOID CARRIER.—The treatment of the chronic carrier is perhaps the most difficult of all the problems in the prophylaxis of typhoid fever that the sanitarian has to meet. The number of unsuspected healthy carriers that exists in every large community, the difficulty of their detection and the almost insurmountable obstacles to their control, make the prospects of eliminating this source of infection very gloomy indeed. The community can be fully protected against it only by **universal antityphoid vaccination.**

Detection of Carriers.—The carriers in a community may be identified by a **complete sanitary survey of the population**—a procedure which is ordinarily impracticable. In isolated groups of men, like bodies of troops, or in small communities where the disease is epidemic, such survey is possible and in certain instances has been carried out. Thus Müller found 165 carriers in 20,019 soldiers examined in 1916. Schorer, in 1919, examined 1,000 returning soldiers of the American Expeditionary Force selected from all divisions passing through the port of embarkation. No typhoid or paratyphoid carriers were found. Under regulations adopted by the War Department soon after the beginning of the European war, cooks, food and water handlers of the United States Army were systematically examined for the detection of the typhoid, paratyphoid and dysentery carrier state. In the first six

months 30,000 men were examined. The percentage of carriers found has not been reported. All convalescent typhoid patients were also examined. Search for carriers should be made wherever limited and local outbreaks of typhoid fever occur not traceable to contamination of the general water supply. **Careful and tactful inquiry into the medical history of suspected persons** should be made. A past history of continued fever or gall-stone colic should lead to the **bacteriological examination of urine and feces.** Several examinations at varying intervals are necessary to exclude the carrier state. A strongly positive Widal reaction is suggestive. In particular, **all persons,** especially women, **who have to do with the preparation and distribution of food**—even in the absence of a suspicious history—**should be rigidly examined.**

Supervision of Chronic Carriers.—**Health authorities should maintain supervision over the typhoid fever patient until bacteriological recovery is complete.** During the convalescent period urine and stools should be examined and the patient kept under observation until three or four negative cultures assure freedom from infection. Unfortunately examinations to determine bacteriological recovery from typhoid fever are not often made either in hospital or private practice. Graves, of Louisville, found that only 9 of 24 prominent hospitals of the country made such examinations.

Recognized carriers should be registered and kept under the supervision of the health authorities. How far it is possible to subject them to the restrictions necessary to the protection of the community is an unsettled question. Most carriers are not aware of their condition and their recognition is the first step in any effort to limit their pernicious influence. **The carrier,** made aware of his condition, **may possibly be educated to cooperate with the health authorities** and assist in guarding the community from contact with his excretions.

It is too much to expect that typhoid bacilli excreted by carriers can be destroyed at their source. We can hope only to guard against their transmission to the healthy. Experience shows that the majority of cases of typhoid fever that have been traced to carriers are infected through the medium of food and that the guilty carriers are cooks or persons engaged in other occupations that bring them in contact with food supplies. **Legislation** along the lines of the regulations in force in the army, **giving the health authorities a reasonable control over persons engaged in the preparation and distribution of food,** seems feasible, and would do much to limit the dissemination of typhoid fever by healthy carriers. In the absence of such legislation, **cooperation between physicians in charge of typhoid cases and local health boards** will materially aid in the diminution and arrest of outbreaks of carrier origin.

Treatment of Carriers.—The results of treatment of the typhoid carrier state have, up to the present time, been rather unsatisfactory. No method of treatment can be recommended that offers much prospect of a permanent cure, except **surgical resection of the focus of infection.**

(*a*) Medical Treatment.—**Vaccine therapy** immediately suggests it-

self as a promising method of dealing with a localized focus of typhoid infection. It has been repeatedly tried and, although many successful cases have been reported, its value is doubtful. Gay, as a result of his studies, concludes that "in most instances the results by vaccination are frank failures, as could be imagined when we consider that the individuals so treated are already highly immunized against typhoid fever, as indicated by the presence of antibodies in their circulating blood." We believe, however, that the possible benefit of vaccination warrants a trial in every case.

In intestinal carriers the focus of propagation of the bacilli is in the biliary passages, especially the gall-bladder. **Intestinal antiseptics,** as might be expected, **have proven useless.** Attempts to eradicate the focus in the gall-bladder by the **internal administration of drugs acting upon or through the biliary secretion have not been encouraging.** Various remedies have been administered with this object in view. **Hexamethylenamin,** administered by the mouth, finds its way into the bile both through the liver and through the walls of the gall-bladder. In large doses—at least 75 grains (4.87 grams) a day—it appears in the gall-bladder in a concentration sufficient to inhibit the growth of the typhoid bacillus. It is possible that the development of the chronic carrier state may be prevented by the persistent administration of this drug during the convalescent stage of typhoid fever. Theoretically it should be of use in the developed carrier condition. It should be given a trial, although reports of its effect are not very encouraging: 15 grains (0.972 gram) should be given four or five times a day, diluted in a glass or more of water. **Inspissated oxgall, bile salts, iodin and sodium bicarbonate have been given without permanently affecting the discharge of bacilli.** The anatomical relation of the gall-bladder and bile ducts, the obstruction to the free flow of bile offered by the tortuous canal of the cystic duct and the lodgment of colonies of bacilli in the walls of the bile passages make disinfection with our present resources practically impossible. As demonstrated by Blackstein, Welch, Gay and others the intestinal typhoid carrier state may be induced experimentally in rabbits. Opportunity is thus given for the laboratory study of the influence of various substances on the infected gall-bladder which may lead in the future to definite results.

The medical treatment of the urinary carrier is perhaps a little more satisfactory. **Hexamethylenamin,** given during the period of convalescence, will disinfect the renal pelvis and often prevent the development of the chronic carrier state. In the developed chronic carrier the bacilli may be made to disappear from the urine for longer or shorter periods by the administration of this drug. The drug should be given in full doses, 75 grains (4.84 grams) or more a day for a time, checking up its effect by repeated bacteriological examination of the urine. Hematuria or vesical irritation may be excited and require a reduction of the dose or suspension of treatment for a number of days. **Typhoid vaccine** may be administered **in conjunction with the course of hexamethylenamin.** Stakes and Clarke report two cases cured in this way. **Local irrigation**

of the renal pelvis through the ureteral catheter **with dilute solution of silver nitrate** has been suggested.

(*b*) Surgical Treatment.—*The chronic carrier state* may be cured by **resection of the focus of infection.** As we have seen, this focus *in the intestinal carrier* is the gall-bladder alone or both the gall-bladder and biliary ducts. When the gall-bladder alone is infected, a cure may result from **cholecystotomy with drainage, or cholecystectomy.** The latter is the more radical operation and the results are more certain. Neither operation will cure cases in which both the gall-bladder and ducts are infected.

In urinary carriers the primary focus of infection is the renal pelvis. Secondary foci may be in the bladder or ureters. *If only one kidney is involved,* its **removal** effects a cure. The secondary foci in the lower urinary tract clear up after the removal of the primary focus in the kidney. Nichols, Simmons and Stimmiel report from the Walter Reed Hospital the results of the surgical treatment of 6 chronic carriers—5 intestinal and 1 urinary—and cite one other successful result in an intestinal carrier. Cholecystectomy was done on the intestinal carriers: 3 were cured and 2 continued to discharge bacilli after operation. These writers believe that failure to cure the two cases was due to the fact that the infection involved both the gall-bladder and ducts. The urinary carrier was cured by **nephrectomy.**

In the light of these results **chronic carriers** who fail to clear up under fully tried medical treatment **should be treated surgically; the intestinal carriers, by cholecystectomy; the urinary carriers, by nephrectomy.** 'Removal of the kidney should of course be preceded by **ureteral catheterization.**

(2) **Prevention of the Transmission of the Bacillus.**—Isolation.—A patient suspected to be in the incubation or developed stage of typhoid fever should immediately be isolated, and every known barrier against the transmission of the disease should be thrown around him. As a general rule, this object can best be attained in a hospital where the routine for the prevention of the transmission of disease is always ready to function. In many of the hospitals of the United States typhoid fever patients are still treated in the general wards. They should, however, be **isolated in rooms or special fever wards and nurses assigned to their care who do not come in contact with the patients in the general wards.** With the usual precautions the danger of hospital infection is not great, although careless attendents are occasionally responsible for the transmission of the disease. In children's hospitals, where patients are in closer contact, the danger is greater. *If treated at home* **the patient should be in a room separated from the other members of the family and every precaution taken to prevent them from coming in contact with the patient's excretions.**

Physicians, nurses, orderlies and other attendants on the typhoid sick should observe special precautions to guard against the danger of carrying the disease to others. Hands soiled with the patients' excretions are the common guilty agents. A **disinfectant scrubbing of the hands**

should follow each contact with the patient. When using the bed-pan or urinal the nurse or orderly should wear **rubber gloves, and a rubber apron** should protect the clothing. **Typhoid nurses should not prepare the food for other patients or serve it. The sick-room should be screened, and excreta, soiled clothing and food remnants carefully guarded from flies.**

The proper disposal of sewage and the prevention of the transmission of typhoid fever through the medium of general water and food supplies are sanitary measures that come under the control of local and state boards of health.

Previous to the introduction of antityphoid vaccination the reduction of the typhoid rate had been slowly progressive throughout the country. This reduction was due in large measure to the **protection from sewage contamination of general water supplies or to their purification by filtration and chemical treatment.** The remarkably low typhoid rate of some European cities adequately sewered and provided with an abundance of pure water is convincing evidence of the importance of these factors in the prevention of typhoid fever. An outbreak of typhoid fever should lead immediately to the **thorough investigation of the water, milk and other foods consumed by this community. Bathing in polluted waters should be prohibited.** The rural swimming hole or the urban tank may be a prolific source of infection.

(3) **Antityphoid Vaccination.**—Benmer and Peiper, in 1887, and Chantemesse and Widal, in 1888, showed that mice could be protected from infection by the typhoid bacillus by inoculation with sterilized cultures of the organism. In 1896 A. E. Wright developed a vaccine for the immunization of human beings, and in the same year Pfeiffer and Kolle published the results of the vaccination of a few men with a vaccine prepared by a method similar to that of Wright. Wright's vaccine was prepared from cultures of the typhoid bacillus grown in bouillon for 2 or 3 weeks, then killed by heating to 63°C. for 1 hour, and preserved by .5 per cent. phenol. A single dose of 750 to 1,000 million was used for immunization. Pfeiffer's vaccine was grown on agar, suspended in salt solution and killed by heating to 56°C. In the few years following this original work a number of methods of preparation and administration of typhoid vaccine were developed and advocated by various experimenters.

Antityphoid Vaccination in Armies.—Vaccination on a large scale was first practiced in the British Army in India and in South Africa during the Boer War, under the direction of Wright. Wright's statistics showed a reduction in the incidence of typhoid fever among vaccinated men of at least 50 per cent., with a striking reduction in case mortality. In 1758 cases of typhoid fever in vaccinated men there were 142 deaths—a mortality of 8 per cent.—while in 10,980 cases in the unvaccinated there were 1,800 deaths—a mortality of 16.6 per cent. These results were obtained under the very unfavorable conditions of active service in the field. At the close of the war, notwithstanding these favorable results, the Medical Advisory Board reported against the continu-

ation of vaccination in the army. Later this decision was reversed and vaccination was again adopted in the British Army, in 1905. The statistics from the army in India from 1905 to June, 1908, were published by Leishman: 5,473 of 12,083 men were vaccinated. The case incidence per 1,000 in the vaccinated men was 3.8; in the unvaccinated, 28.3. Leishman's statistics showed a decided improvement over the original statistics of Wright, due to improvements in the method of preparation of the vaccine and in the technic of administration.

Antityphoid vaccination was quickly introduced into all the armies of the world, and always with the same remarkable reduction in the incidence and mortality of typhoid fever. In the French Army, before the outbreak of the recent war, there were striking examples of the prompt arrest of epidemics in a number of garrisons. At Avignon, in 1912, there were 2,053 soldiers. Of this number 1,366 were vaccinated, 525 before and 841 during the epidemic of that year. Among the remaining 687 men not vaccinated there were 155 cases of typhoid fever, with 22 deaths. No case occurred among the 1,366 vaccinated men. In 1913 all the troops of the garrison—2,420 in number—were vaccinated. There was no typhoid fever. In January and February, 1914, a severe outbreak occurred in the regiment stationed at Tours. Of the 2,134 men, 1,646 were vaccinated and 488 were not vaccinated. Among the non-vaccinated men there were 99 cases of typhoid fever, with 21 deaths. No case occurred among the vaccinated men.

The freedom from typhoid in the great armies mobilized in the recent European war, unprecedented in military history, was the final demonstration of the place that vaccination holds in the prophylaxis of typhoid fever. Improved sanitation had a certain influence in limiting the spread of the disease, but it is the conclusion of authoritative opinion that the brilliant results obtained in the prevention of typhoid fever were directly due to the general adoption of antityphoid vaccination.

In the United States Army antityphoid vaccination has been carried out with a uniformity and thoroughness unequaled in the other armies of the world, and the results obtained are justly famous. Vaccination was adopted on the advice of a mixed civil and military medical board in 1909, and was carried out under the direction of Colonel F. F. Russell, who had studied the conditions of antityphoid vaccination in England. Voluntary vaccination was begun in March, 1909; and vaccination was made compulsory for all persons in the military service under 45 years of age, in the last quarter of 1911. The brilliant results obtained by Colonel Russell and his co-workers gave evidence of the prophylactic value of vaccination that was incontrovertible. The decrease of typhoid fever in the United States Army following the introduction of vaccination is shown in Table 4 (p. 572).

The lowest recorded death rate from typhoid fever in the army prior to the introduction of vaccination was 27 per 100,000 in 1906, and the lowest morbidity rate was 320 per 100,000 in 1908. From these two low points, the best ever attained under sanitary measures alone, the

TABLE 4.

DECREASE OF TYPHOID FEVER IN U. S. ARMY FOLLOWING INTRODUCTION OF VACCINATION

Year	Vaccination	Cases per 100,000	Number Vaccinated	Army Strength
1906	None	572	.....	.....
1907	"	379	.....	.....
1908	"	320	.....	74,692
1909	Voluntary	335	830	.....
1910	"	243	16,093	81,434
1911	½ Compulsory	85	25,779	82,802
1912	Compulsory	31	all	88,478
1913	"	4.4	"	90,752
1914	"	7.5	"	92,877
1915	"	8	"	.....
1916	"	23	"	.....
1917	"	44	"	.....
1918	"	30	"	.....

rate fell precipitously following the introduction of vaccination to 4.4 and 31 per 100,000 respectively (Russell).

The appearance of paratyphoid fever among the troops mobilized on the Mexican border in 1916 and, with the entrance of the United States into the European war, the necessity of protecting the overseas troops against the paratyphoid fevers prevalent in France, led the Medical Department of the Army to adopt preventive inoculation against the paratyphoid fevers. It had already been demonstrated that vaccination against these fevers gave protection equal to that given by vaccination against typhoid. The practical difficulties involved in the separate administration of three vaccines to all the men of the great army that was being mobilized made it imperative to use a combined vaccine containing the three organisms, the *Bacillus typhosus*, the *Bacillus paratyphosus A* and the *Bacillus paratyphosus B*. Castellani and others had shown that injection of a triple vaccine developed antibodies of the contained organisms, active against each, and that the reaction was no more severe than when a single vaccine was used.

After an exhaustive study by Colonel C. F. Craig, of the effects of a triple typhoid vaccine prepared by the Army Medical School, this vaccine was adopted by the Army in 1917.

Practically all of approximately 4,000,000 men mobilized in the United States were immunized against typhoid and paratyphoid fevers with the triple vaccine. The effect of antityphoid vaccination upon the incidence and mortality of typhoid fever in this great body of men is shown by a comparison of the typhoid fever statistics of the United States Army in the recent European war, the Spanish-American war and the Civil War, submitted by Colonel D. C. Howard of the Office of the Surgeon General of the Army. It is to be noted that the figures for

the European war, although approximately correct, are based upon telegraphic reports and are subject to future revision.

From September 1, 1917, to May 2, 1919, there were reported 1901 cases of typhoid fever with 213 deaths, with an average strength of approximately 2,121,396. There were during the Spanish-American War, from May to September, 1898, with a mean strength of 90,042 men, 16,402 cases of typhoid with 1,654 deaths. In the Civil War, from July 1, 1861, to June 30, 1865, there were reported 77,544 cases of typhoid fever and 53,870 cases of typhomalarial fever (probably typhoid), with 28,345 and 4,790 deaths respectively. The following comparison gives emphasis to these statistics:

Number of deaths that occurred in European War, Sept. 1, 1917—May 2, 1919 (average strength approximately 2,121,396)	213
Number of deaths that would have occurred, if the Civil War death rate had obtained	51,133
Number of deaths that would have occurred if the Spanish-American War death rate had obtained..	68,164

ANTITYPHOID VACCINATION FOR THE CIVIL POPULATION.—No opportunity has yet been given to determine on a large scale the results of vaccination in civil communities. Vincent and Murantet cite observations of several epidemics in a number of towns in France in which the protection acquired by vaccination proved to be remarkably complete. In this country no instance of general vaccination of a threatened community has been published. There is no reason to believe, however, that the immunity conferred by vaccination in the army would not be duplicated by vaccination of the civil population, if carried out with the same thoroughness. In prisons, asylums and similar institutions where conditions can be controlled, results closely approaching those in military experiences have been obtained. Hatchel and Stover found that of 5,512 vaccinated individuals in the institutions of Maryland only three subsequently contracted typhoid fever—a morbidity rate of 58 per 100,000. The Department of Health of New York City, has published the results of the vaccination of individuals exposed to typhoid fever in various ways, chiefly in their homes. Of 8,101 exposed persons 534 were vaccinated. All of these escaped infection. Of the 7,567 persons not vaccinated, 161—over 2 per cent.—developed typhoid fever. Russell gives a report (Table 5, p. 574) of a small water-borne epidemic which occurred in Hawaii.

Compulsory antityphoid vaccination of the civil population cannot be expected. The wonderful results of military experience, however, should be widely published and vaccination should be urged upon individuals and communities by health authorities and physicians whenever danger of exposure to infection is recognized. The recent vaccination of over 4,000,000 young men of the Army and Navy should produce in the next few years a striking reduction of the typhoid rate in the

TABLE 5.

MORTALITY IN WATER-BORNE EPIDEMIC IN HAWAII

	Population on Castner Water System	No. of Cases of Typhoid	Cases per Thousand	Deaths		Mortality Rate per Thousand
				Number	Per cent.	
Vaccinated.....	4,087	55	13.45	4	7.4	0.97
Unvaccinated....	812	45	55.41	7	15.5	8.62

country at large. Should this prediction prove true it may hasten the more general adoption of antityphoid vaccination.

PROPHYLACTIC TYPHOID AND PARATYPHOID VACCINES.—The vaccines used by the United States Army and Navy have stood the test of an enormous experience and have become the standard preparations for prophylactic vaccination in this country. Vaccines for use by the civil population are prepared by various manufacturing chemists under license from the federal government, and by several state and municipal boards of health. With minor modifications in the detail of manufacture they are identical with the army vaccine.

Typhoid Vaccine.—The army typhoid vaccine is that of Russell. The bacilli are grown on nutrient agar for a minimum of twenty-four hours, washed off with 0.85 per cent. saline solution and killed by heating to 52.6°C. (126.7°F.) for one hour. The vaccine is then standardized and preserved in 0.25 per cent. tricresol. The vaccine as issued contains 1,000 million bacilli per cubic centimeter.

Typhoid-paratyphoid A and B Vaccine (Triple Typhoid Vaccine—T. A. B. Vaccine).—In the preparation of the triple vaccine the bacilli of the three organisms—one strain of the typhoid bacillus and two strains each of the paratyphoid bacillus A and the paratyphoid bacillus B—are grown separately and treated in the same manner as in the preparation of the straight typhoid vaccine. The five strains are then mixed in the proper proportions. As issued, the triple vaccine contains 1,000 million typhoid bacilli and 750 million each of paratyphoid A and paratyphoid B bacilli per cubic centimeter.

Triple Lipovaccine.—The triple lipovaccine adopted by the United States Army in 1918, and its use discontinued early in 1919, is prepared by drying and grinding the bacilli and suspending the ground organisms in cotton-seed oil. Oil of sweet almonds, olive oil and mineral oils have been experimentally used as a base. Some of the advantages claimed for the oil suspension were (1) the feasibility of giving the full immunizing dose at one injection; (2) the diminution of the systemic and local reactions; (3) the prolongation of the period of immunity due to slow absorption of the vaccine; and (4) the delayed autolysis of the vaccine. Notwithstanding these manifest advantages

experience with the lipovaccine revealed faults that caused its use to be discontinued by the Army.

Army Typhoid Vaccine.—The Army typhoid vaccine is grown from a single strain—the Rawling strain—imported by Russell from England. This strain was originally obtained from the spleen of a soldier who died of typhoid fever in England in 1900. Leishman found this strain gave a remarkably even emulsion when washed off agar with salt solution. This strain is pathogenic, relatively avirulent and distinctly toxic. Its efficacy is believed to depend upon its toxicity.

Paratyphoid Vaccines.—The paratyphoid vaccines are grown from four strains, Rogers and Meers para A and Cools and Rowlands para B. The Meers and Rowlands strains were imported from England and are the strains used in the English vaccine.

Gay and others are of the opinion that a polyvalent vaccine may give a better immunity than a vaccine prepared from a single strain and that recently isolated strains are more antigenic than those grown for a long time on culture media. Vaccines prepared from the Rawling strain, used almost exclusively in American practice, have given such satisfactory results that there seems at the present time no good reason for using other or multiple strains.

Dosage.—Typhoid vaccine is administered in three doses at intervals of from seven to ten days. For an adult, from 150 to 200 pounds in weight the first dose is 500 million bacilli, the second and third doses 1,000 million each. For small women and men the dose may be reduced in proportion to their weight. The dose for children should be reduced according to the age and development of the child: for children from 2 to 4 years, one-quarter; from 5 to 7 years, one-third; and from 8 to 12 years, one-half the adult dose.

The triple typhoid vaccine is given at the same intervals, 500 million typhoid bacilli and 375 million each of para A and para B bacilli in the first injection, and 1,000 million typhoid bacilli and 750 million each of para A and para B bacilli in the second and third injections.

McCoy, Gay and others have found that the interval between doses may be shortened and the injection given at three-day intervals or even on alternate days. Equal immunity is given as when the usual interval is observed and the reaction is no more severe. In emergencies, when rapid immunization is necessary, this procedure may be of great value.

Administration.—The vaccine is injected with aseptic precautions subcutaneously into the deltoid area of the arm, behind the spine of the scapula or in the subclavicular region. The skin of the area selected for injection should be cleaned with soap and water and rubbed with 5 per cent. solution of carbolic acid or painted with iodin.

Intramuscular injection may be followed by severe general and local reactions. Intravenous injection causes a violent general reaction with chill and high fever. Most of the severe reactions after vaccination are due to the accidental or careless injection into one of these structures.

The General Reaction.—In a few hours after the injection, there is

usually a *mild febrile reaction.* In Craig's studied cases fever was present in 32 per cent. after the first injection, in 86 per cent. after the second, and in 18 per cent. after the third injection. In the majority the rise is not above 100°F. (37.8°C.). In a few cases it rises to 101° or 102°F. (38.3° or 38.9°C.) and very unusually a degree or two higher. The high temperatures are often the result of the accidental injection into a vein. The fever is usually at its maximum in about twelve hours and has disappeared by the end of twenty-four hours. In a small number of cases the onset of the fever is delayed until twenty-four hours after the injection. General malaise, lassitude, slight chilliness and headache are present in about fifty per cent. of the cases. Pain in the back and legs is seen in a few cases and is occasionally severe. A mild diarrhea, nausea and vomiting, dizziness and cramps are rare symptoms. A slight nausea is quite common after the second injection. These symptoms of reaction disappear with the fall in temperature and are rarely of sufficient importance to keep the patient in bed. In army experience about one out of every 1,000 men was ill enough to send to the hospital.

Local Reactions.—The local reaction is more marked after the second injection than after the first, and is very slight or absent after the third. At the site of injection there is a congested area of skin with slight induration and sensitiveness to pressure. The areola is from 6 to 8 centimeters in diameter. In severe reactions the redness may extend from elbow to shoulder. Swelling and tenderness of the axillary glands on the side of the vaccination are usually present. The glands in the other axilla may also be involved. Some stiffness and pain on moving the arm may be present.

Immediately following vaccination there is a moderate leukocytosis, the count ranging from 7,000 to 11,000, which declines over a period of five days. A slight secondary rise then occurs lasting from seven to fourteen days. The differential count at the crest of the waves shows 60 to 63 per cent. polymorphonuclears.

Precautions and Contra-indications.—Unpleasant reactions after typhoid vaccination are favored by fatigue, over-eating, alcoholic indulgence, and the presence of any of the acute infections, including typhoid fever. *On the day of vaccination* the patient should **eat lightly and avoid physical exertion.** The injection is best given late in the afternoon after the day's activities, and followed when possible, by **rest in bed.** The reaction symptoms thus occur in the night and usually pass unnoticed. *Fever and other symptoms on the day after the vaccination* **require continued quiet and a careful dietary. Aspirin or one of the antipyretics** may be indicated.

In the presence of any of the acute infections vaccination should be postponed. Unquestionably in many instances of apparent severe reaction the violent symptoms are due to a coincident febrile disease. Persons vaccinated during the incubation period of typhoid or paratyphoid fever or suffering from a developed and unrecognized mild or ambulatory form often show sharp reactions. Vincent states that vaccination done in the incubation period of typhoid or paratyphoid may abort an

attack or ameliorate its course. In an outbreak under our observations in which a large number of exposed men were vaccinated—several of them in the first stage of the disease—it was the distinct impression that in some cases the disease was prevented or its course made milder.

Vaccination is contra-indicated in many of the chronic diseases, especially advanced arteriosclerosis, aortitis, myocarditis, cardiac decompensation, valvular heart disease, active tuberculosis, chronic pleurisy, diabetes and chronic nephritis with renal insufficiency. Vaccination of syphilitics with active lesions should be postponed. *Malarial subjects* should be **cinchonized** and be comparatively well before vaccination. Advanced age, infancy or pregnancy are not contra-indications. *In debilitated subjects and in those suffering from some chronic ailment* the risk of dangerous reactions may be avoided by the **administration of the vaccine in several small doses at proper intervals.** Severe reactions are apt to occur in persons sensitized to foreign proteins, and in the subjects of tuberculosis or nephritis.

It has been conclusively proven that antityphoid vaccination given properly and with reasonable attention to the temporary and permanent contra-indications to its administration is attended by no danger to life and with but insignificant temporary discomfort. An acute disease in the period of development at the time of vaccination may be an occasional complication but there is no evidence that the vaccination has an unfavorable influence upon the course of the complicating disease.

Duration of Immunity.—The duration of immunity conferred by vaccination against typhoid and paratyphoid fevers has not been definitely determined. For the individual this is not possible at the present time. Many are protected against infection for life, while others lose their immunity at periods varying from a few months to many years. Recent army experience shows that complete immunity was given to the vast majority of the soldiers for the period of the war by the single vaccination at the time of entering the service. It is safe to say that vaccination by the army method gives immunity, as a rule, for from two to three years. In the regular Army and Navy it is customary to revaccinate at each reënlistment. It has been observed that men begin to lose protection after three years.

Typhoid and Paratyphoid Fevers in the Vaccinated.—A small percentage of all vaccinated persons is given only partial immunity against the typhoid-paratyphoid group of fevers, and a still smaller percentage is given no protection. Failures in immunization in many instances may be attributed to the use of an improper vaccine, to faulty administration, or possibly to the fact that exposure may occur within too short a time after vaccination, before maximum protection has developed. Failure may occur, however, even when the conditions of a proper vaccination have been strictly observed. Such exceptions are to be expected and should not be used as an argument against vaccination. The immunity given by an attack of typhoid fever itself, like the immunity following other acute infections such as variola, scarlatina, etc., is only relative and does not give absolute protection against a subsequent attack.

Typhoid or paratyphoid fever occurring in vaccinated soldiers of the French and British armies in the recent war had a low mortality. The course of the disease was usually mild or abortive, and complications were few and rarely fatal. The incidence of relapse was not reduced. In the French army, Bech's statistics show a mortality of 2.7 per cent. in the vaccinated and 16 per cent. in the unvaccinated. Bernard and Paraf had a mortality of 5.3 per cent. in the vaccinated and 24.3 per cent. in the unvaccinated. Webb-Johnson collected 2,500 cases of typhoid and paratyphoid fevers occurring among vaccinated and unvaccinated soldiers in the British army. The influence of vaccination upon mortality and the occurrence of complications in this series of cases is shown in the following table:

TABLE 6.

INFLUENCE OF VACCINATION UPON MORTALITY AND UPON OCCURRENCE OF COMPLICATIONS (Webb-Johnson)

	Number of cases	Deaths	Mortality (Per cent.)	Complications (Per cent.)
TYPHOID FEVER				
Vaccinated	821	27	3.38	7.55
Not vaccinated	297	57	19.19	35.69
PARATYPHOID A				
Vaccinated	123	0	.00	.81
Not vaccinated	221	1	.45	10.85
PARATYPHOID B				
Vaccinated	239	1	.41	5.85
Not vaccinated	799	17	2.12	15.39

Vaughan, in his study of typhoid fever in the American Expeditionary Forces in France, found that the clinical history of the disease in vaccinated patients was practically the same as in the unvaccinated. The mortality in 270 cases, all of whom had received triple typhoid vaccine, was 11 per cent.

INDIVIDUAL PROPHYLAXIS

The devious and, often, hidden routes by which the typhoid bacillus is carried makes it difficult for the individual, by his own efforts, to escape infection.

Individuals should be warned against direct infection through contact with typhoid patients or, in case of unavoidable exposure, **should be instructed in measures of defense.** Physicians, nurses and others in attendance upon the sick are in especial danger of contact infection. The fingers directly, or indirectly by way of food, convey the infection. **Scrupulous cleansing of the hands should follow contact with the pa-**

tient or with any objects contaminated by him. A gown should protect the clothing of all who come in contact with the patient. Indirect infection by water, food, flies or fomites is difficult to guard against. **In times of danger only cooked foods should be eaten, and water**—unless obtained from a source above suspicion—**should be boiled.** Persons traveling or visiting infected communities should be especially on their guard against infection. Most important in individual prophylaxis, however, is the immunity given by **adequate antityphoid vaccination.** It is cheaply purchased and experience shows that it will protect against all ordinary exposure.

General Management

A patient presenting symptoms suggestive of the onset of typhoid fever should be sent **immediately to bed.** The frequent grave or fatal course of ambulatory typhoid shows the disastrous results of wasting the patient's energies in the early stage of the disease. Unless the home is of exceptional appointments, the hospital is the proper place for the care of the typhoid patient. In the country and in small villages a hospital may not be within reach, and the physician must make the best of inadequate facilities. In a city house of modern appointments, hospital conditions can be closely imitated. The sick-room should be large, well ventilated, quiet and sunny, with bathroom adjoining and isolated as much as possible from the rest of the house. An open fireplace for heating and ventilation, and for use as an incinerator, is a useful feature. Pictures, heavy curtains and all unnecessary furniture should be removed, hard wood floors well covered with removable carpets, windows well shaded and in summer properly screened. A hospital single bed, twenty-six or twenty-eight inches in height, should be so placed as to be accessible from all sides. A soft hair mattress protected by a rubber sheet and resting on woven wire springs will give the patient the greatest comfort. The bed clothing should be light, the pillow low, and all kept scrupulously clean. A day and a night nurse are essential for the best results. If the patient is a heavy man, a male nurse for night duty and to assist with the baths and other difficult attentions is a great aid. Efficiency and accuracy in the administration of the nursing routine are such important factors in the successful treatment of typhoid fever that **nurses of the best training and highest intelligence should be selected.**

In the country and in humble city homes the nursing of necessity may have to be done by members of the family or other unskilled attendants. This puts a heavy burden on the physician who must carefully instruct the attendants in the details of feeding, baths, disinfection of excreta, etc. Explicit, written instructions for each day's routine must be given. The physician even may be called upon personally to direct the baths and other difficult procedures.

The nurse should keep a **chart of the temperature, pulse, diet and other clinical notes. Attendants should be warned of the significance**

of the symptoms of hemorrhage and perforation and instructed to notify the physician immediately.

With the patient's immediate necessities provided for, attention must then be given to precautions against the spread of the disease. Every effort must be made to **destroy the bacillus at its source or to prevent its penetration beyond the confines of the sick-room.** The rules given in the section on Prophylaxis for the disinfection of the excreta and all infected clothing and utensils should be strictly enforced.

The patient must have **absolute physical and mental rest.** He must not rise from the bed and the bed-pan and urinal should be used from the beginning. Some patients have great difficulty at first in adjusting themselves to such conveniences and the nurse may have to exercise much tact and persistance in educating them.

Gossipy visitors must be excluded from the sick-room. Members of the family should have but limited admission. All business and annoying problems should be kept from the patient. Efforts to amuse and divert him are permissible only when he is mildly ill or well advanced in convalescence.

During the period of convalescence great care is required in guarding against the infection of other members of the household. The discharge of bacilli does not always cease with the end of the febrile period. The patient may remain a temporary carrier for several weeks, and **precautions against the spread of the infection must be continued until the stools and urine are free from typhoid bacilli.** Two or three negative cultures of the excretions are necessary to insure safety. The food consumed by the members of the household should receive careful supervision. **Water should be boiled and all foods should be cooked.** Finally all persons coming in contact with the patient or living in the house should be protected by **antityphoid vaccination.**

Diet.—The febrile period of typhoid fever lasts a month or more. It is attended by grave wasting of body tissue on one hand and by dangerous intestinal lesions on the other. **The selection of a system of diet adequate to repair the waste, and of such a character as not to offend the diseased bowel,** is one of the most important problems in the management of the disease. In the past the weight of authority has been in favor of a liquid diet of low nutritive value. The fear of hemorrhage, perforation and relapse has outweighed the fear of exhaustion. The tendency of modern clinicians, however, is toward giving food of greater variety and of higher caloric value. This tendency is the result of a more accurate knowledge of the metabolism in typhoid fever and the favorable experience of many able physicians with a liberal diet of high caloric content. Under the commonly prescribed fluid diet of low caloric value, the loss of weight during the course of the fever is progressive and often extreme. A loss of ten or fifteen per cent. of the body weight is usual, and it may be as great as thirty per cent. or more. A study of the food intake of a number of hospital cases under a milk and beef tea diet, made several years ago by the author, showed that the food value of the diet in these cases, until well into the period of conva-

lescence, rarely exceeded 1,000 calories and often was as low as 400 calories per day.

METABOLISM IN TYPHOID FEVER.—Von Hösslin, in 1882, studied a series of typhoid patients fed with a varied diet of rather low caloric value and concluded that foods were absorbed in typhoid fever almost as well as in health. A few years later several Russian experimenters, whose work is reviewed by Dubois, obtained similar results in studies made in Chadnowsky's clinic. Von Leyden and Klemperer, in 1904, also found that the absorption of foods in typhoid is nearly equal to that in health. These experimenters, by liberal feeding, could prevent wasting, although they were unable to keep their patients in nitrogen equilibrium, despite the high protein content of the diet. Recently the conclusions of these earlier observers have been corroborated and extended and the dietetic management of typhoid fever has been placed on a scientific foundation. In 1909, Shaffer and Coleman published the results of their work on protein metabolism in typhoid fever. This very important work, which fixed the attention of the profession on the possibilities of high caloric feeding in typhoid, was followed by researches along similar lines by Dubois, Lusk, Ewing and others in this country and by Kocher in Germany. The results, in part, of these investigations, upon which are based the efforts of modern clinicians *to maintain metabolic equilibrium during the long febrile period of typhoid fever,* are embodied in the following:

(1) The total body metabolism in typhoid fever increases with the rise in temperature and decreases as the temperature falls; there is an average increase over that of the normal individual of about forty per cent.

(2) Increased metabolism does not result from increased food intake as the metabolism of a typhoid patient on a liberal diet is but slightly raised above that of a fasting patient.

(3) Food in large amount, at least when the protein is kept relatively low, does not increase either the heat production or the fever in the febrile stage of typhoid. Food in itself has little or no dynamic action in typhoid fever.

(4) In typhoid fever there is a toxic destruction of protein, as shown by the negative nitrogen balance in the excretions.

(5) It is impossible to maintain nitrogen equilibrium on a diet containing an excess of protein and fat. With a diet carrying an excess of carbohydrates, and representing a daily intake of from 3,000 to 5,000 calories, nitrogen and weight equilibrium can be maintained, and even a gain in weight may be shown during the febrile period.

(6) Protein and carbohydrates can be absorbed throughout the disease as well as in normal individuals. Fat in large amount can be absorbed, but the percentage of absorption is somewhat lower than the normal, especially in the first and second weeks.

From the time of Graves, who wished his epitaph to be "He fed fevers," a few bold clinicians have advocated departure from the almost

universal practice of limiting food in fevers to liquids of low caloric value. Trousseau and Flint in their day, and F. C. Shattuck of Boston, Kinnicutt of New York, Barrs of Leeds and Buchuyev of Russia of the present period, have insisted that typhoid patients were underfed. In this country Shattuck's influence has been very great, and many practitioners have followed his teaching and have adopted a more liberal and varied diet in their treatment of typhoid. With the support recently given from the laboratory side by Coleman and his collaborators, the high caloric diet is meeting with the recognition it seems to deserve.

The value of a high caloric diet in typhoid fever must be determined by the results obtained at the bedside. Theoretically it is better for a febrile patient to be on a diet that will maintain metabolic equilibrium, provided he can digest and absorb it. Starvation is no more beneficial to a febrile patient than to a person in health. The question is, can the typhoid patient take sufficient food to hold his weight and not give rise to digestive disturbances more harmful in the end than a moderate loss of body weight? Liberal feeding is in favor with the profession at the present time, and accumulated clinical experience should soon put the question beyond controversy. The feeding of typhoid patients up to the limit of their digestive capacity requires good clinical judgment and careful individualization. *The dangers of overfeeding* are distinct and it is often very easy to overstep the limits of safety. Many patients cannot take or digest the theoretical food requirement during the early febrile period. The physician must then be content with a moderate loss of weight and hold himself on the alert immediately to take advantage of an improved digestion to raise the food intake to the quantity necessary to balance tissue waste. A loss of from five to ten pounds during the period of high fever is not of any great importance. *The bad effects of underfeeding* are due to the withholding of food in the periods of decline and convalescence when the appetite is returning and digestion has reached about its normal efficiency.

The papers of Barrs, Buchuyev and Shattuck appeared at about the same time. Buchuyev's views were extreme. He gave solid food to all typhoid patients who could take it, from the time they came under observation. Meat, bread, eggs, milk and cereals were included in the diet. He reported 398 cases with a mortality of 8.2 per cent. Only four were complicated with hemorrhage and one with perforation. The number of relapses is not given.

Barr's diet included minced meat, bacon, eggs, milk, bread and butter, cereal puddings, custards, stewed fruits and sponge cake. These articles were given in cases with moderate fever, an evening temperature of 102° F. (38.9° C.), and solid foods were not urged upon the patient, but given if asked for.

Shattuck's dietary included a wide range of foods, all of them of easy digestibility, high nutritive value and giving a small undigested residue. He gives the following list of articles and preparations which is suggestive rather than exhaustive:

All liquids, including broths and cocoa.
Soups—purée of oysters, clams, potato, etc., carefully strained.
Gruels—strained, if containing rough particles.
Ice cream, blanc-mange, junket, milk toast without crust, sherbet.
Eggs—raw, soft boiled, lightly scrambled.
Meat—finely minced, scraped raw beef.
The soft part of raw oysters, macaroni, rice.
Orange and grapefruit juice.
The soft part of baked or stewed apples.

In the Massachusetts General Hospital, from 1902 to 1910 inclusive, 491 cases of typhoid came under Shattuck's personal care and were given a liberal diet. There were 45 deaths—a mortality of 9.1 per cent. During the same period there were 2,160 cases fed on liquids under the care of other members of the staff. Of this group 238 died—a mortality of 11 per cent.

These statistics indicate that a liberal diet which includes a few simple and easily digested solid foods is not productive of harm, at least in the hands of expert clinicians. On the other hand it must be emphasized that thoughtless attempts to force feeding with solids in all typhoid cases, regardless of the condition of the patient, will often result seriously.

The studies of Coleman and his associates on the metabolism of typhoid fever, controlled by abundant clinical demonstration, have placed high caloric feeding upon a scientific and practical basis. A daily intake of from 60 to 80 calories per kilogram of body weight—a total of 4,000 to 5,500 calories—are necessary to obtain nitrogen and weight equilibrium. Coleman has shown that nitrogen balance can best be maintained by a diet with a moderate protein content. The optimum is from 62 to 94 grams of protein, representing 10 to 15 grams of nitrogen. Carbohydrates are the most important source of energy requirement and should constitute about one-half of the daily ration, reduced to calories. Fats, with their high yield of energy, are utilized in all stages of the disease. They are better borne and more completely absorbed in the third and fourth weeks and in convalescence.

Coleman advocates a diet consisting largely of milk, cream, butter, lactose and eggs, in combinations that will yield the necessary protein requirement and represent from 3,000 to 5,000 calories a day. Milk and eggs are the chief source of protein. From four to six eggs may be given in twenty-four hours. Carbohydrates are contained in the milk and cream. Lactose added to the milk and other foods supplies the bulk of the carbohydrate content. Fat is contained in the milk, cream, butter and the yolk of eggs.

The formulas suggested by Coleman, of milk, cream and lactose, giving food values from 1,000 calories up, will be found convenient as a basis in building up the dietary of the typhoid patient.

FORMULA GIVING 1,000 CALORIES A DAY

Milk, 1,000 c.c. (1 quart)	700	calories
Cream, 20 per cent., 50 c.c. (1¾ oz.)	100	"
Lactose, 50 grams (1¾ oz.)	200	"

For eight feedings, each containing 130 c.c. (4⅓ oz.). Approximate composition: Protein 36 grams, carbohydrate 97 grams, fat 50 grams.

FORMULA GIVING 1,500 CALORIES A DAY

Milk, 1500 c.c. (1½ quarts)	1000	calories
Cream, 50 c.c. (1¾ oz.)	100	"
Lactose, 100 grams (3¼ oz.)	400	"

For six feedings, each containing 260 c.c. (8¾ oz.). Approximate composition: Protein 50 grams, carbohydrates 175 grams, fat 70 grams.

FORMULA GIVING 2,000 CALORIES A DAY

Milk, 1500 c.c. (1½ quarts)	1000	calories
Cream, 250 c.c. (8⅓ oz.)	500	"
Lactose, 125 grams (4 oz.)	500	"

For seven feedings, each containing 250 c.c. (8⅓ oz.). Approximate composition: Protein 55 grams, carbohydrate 200 grams, fat 110 grams.

FORMULA GIVING 2,500 CALORIES A DAY

Milk, 1500 c.c. (1½ quarts)	1000	calories
Cream, 250 c.c. (8⅓ oz.)	500	"
Lactose, 250 grams (8⅓ oz.)	1000	

For seven feedings, each containing 250 c.c. (8⅓ oz.). Approximate composition: Protein 55 grams, carbohydrates 335 grams, fat 110 grams.

FORMULA GIVING 3,000 CALORIES A DAY

Milk, 1500 c.c. (1½ quarts)	1000	calories
Cream, 500 c.c. (1 pint)	1000	"
Lactose, 250 grams (8⅓ oz.)	1000	

For eight feedings, each containing 250 c.c. (8⅓ oz.). Approximate composition: Protein 60 grams, carbohydrate 345 grams, fat 160 grams.

The daily protein requirement may be obtained by the addition of from three to six eggs to any one of the formulas. For example, four eggs added to the first formula will increase the protein content to 62 grams, the fat to 74 grams, and the total calories to 1,320. Almost any

modification of the composition and energy value of the daily diet may be made by the addition of various allowable foods to some one of the milk formulas. In this way the diet can readily be adapted to the condition of the patient at any stage of the disease.

SAMPLE DIET, CONTAINING APPROXIMATELY 90 GRAMS OF PROTEIN AND 3,000 CALORIES.—Food administered in ten feedings, every two hours during the day and every three hours during the night:

220 c.c. (7 oz.) of the milk formula, giving 1,500 calories, is administered at one, four and nine o'clock A. M., and at one, three, seven and ten o'clock P. M.

Seven o'clock A. M.—1 egg, 1 oz. (30 grams) bread or toast, ½ oz. (15 grams) butter, 1 cup of coffee, 2 oz. (60 c.c.) cream, ⅓ oz. (10 grams) sugar.

Eleven o'clock A. M.—4 oz. (120 c.c.) bouillon, 1 egg, 1 oz. (30 grams) mashed potato, 1 oz. (30 grams) toast or crackers, ½ oz. (15 grams) butter, 4 oz. (120 grams) custard.

Five o'clock P. M.—1 egg, 4 oz. (120 grams) boiled rice, 1 cup of tea, 3 oz. (90 c.c.) cream, ½ oz. (15 grams) sugar, ⅓ oz. (10 grams) butter.

The following table gives a number of foods available for feeding the typhoid patient during the febrile and early convalescent periods, with their approximate composition and caloric value. For convenience, the composition is expressed in the number of grams and calories contained in one ounce, approximately 30 grams. Small fractions have been omitted. The figures are necessarily only approximate, but are sufficiently accurate for practical use in the ward or sick room.

TABLE 7.

GRAMS OF PROTEIN, FAT AND CARBOHYDRATE, AND NUMBER OF CALORIES CONTAINED IN 1 OUNCE (30 GRAMS)

	Protein grams per oz.	Fat grams per oz.	Carbohydrates grams per oz.	Calories per oz.
Milk Foods:				
Whole Milk	1.0	1.2	1.5	20
Cream, 20%	.75	5.5	1.3	60
Butter Milk	.9	.2	1.5	10
Fermilac	.9	.6	1.5	14
Skimmed Milk	1.0	.1	1.3	10
Whey	.3	.1	1.5	8
Condensed Milk, unsweetened	3.0	3.0	3.5	50
Malted Milk, dry	4.6	2.2	19	119
Butter	.9	25.5		240
Ice Cream	1.6	3.0	5.3	55
Cottage Cheese	6.0	.3	1.3	35
Full Cream Cheese	8.0	10.0	.7	130

TABLE 7.—*Continued.*

	Protein grams per oz.	Fat grams per oz.	Carbohydrates grams per oz.	Calories per oz.
Cereal Foods, uncooked:				
Wheat Flour, Farina	3.3	.5	23	110
Oatmeal	5.0	2.2	20	120
Cornmeal	2.8	.6	22	106
Rice	2.4		24	105
Pearl Barley	1.5	.3	25	107
Imperial Granum	3.3	.2	23	105
Mellin's Food	2.3		23	100
Cereal Foods, cooked:				
Wheat Bread	2.8	.4	16	80
Crackers	3.0	2.8	22	125
Shredded Wheat	3.1	.5	24	110
Oatmeal, boiled	1.0		3.5	18
Rice, boiled	1.0		7.3	34
Macaroni, boiled	1.0	.5	5	26
Cereal Gruels	.4		2	10
Sponge Cake	2.0	3.2	20	115
Potato, baked	1.0		6.0	30
Sugars:				
Cane Sugar, Lactose, Glucose			30	120
Eggs				
1 Whole Egg, weight, 50 grams	6.0	5.0		70
White, 1 Egg	3.6			15
Yolk, 1 Egg	2.4	5.0		55
Meat Foods:				
Scraped Meat	6.3	3.2		55
Meat Juice, home made	1.5	.15		7
Meat soup, broths, bouillon	1.4	.1	.4	8
Beef Juice, Valentine	3.0			12
Meat Juice, Wyeth	11.4			45
Beef Extract, Armour	4.8			19
Panopepton, 18% alcohol	2.0		3.5	60
Liquid Peptonoids, 17% alcohol	1.5		3.2	55
Oysters	1.7	.3	1.0	14
Wines and Spirits:				
Rhine Wine, Claret, Champagne — 9% alcohol				17
Sherry, Port — 18% alcohol				34
Whiskey, Brandy, Rum — 50% alcohol				105

MILK AND MILK PRODUCTS.—Clean milk produced under the conditions that obtain in the modern well-conducted dairy is the most satisfactory single article of food for the typhoid patient. Except when

there is a definite contra-indication to its use, it should form the basis of the diet in the febrile period of the disease. The fact that, when properly prepared and administered, it is digested by the youngest infant, seems to be conclusive evidence that it is a food adapted to the enfeebled digestion of the adult febrile patient.

Milk for the typhoid patient must be clean and of the best quality. Edsall has demonstrated, with his fever patients, the indigestibility of milk with a high bacterial count. Even clean milk, however, if given unmodified to the fever patient, may be the cause of indigestion, of tympanites and diarrhea. Undiluted milk will cause the same symptoms when given to healthy infants. This is met by the pediatrician by diluting and modifying the milk in such a manner as to adapt it to the digestive capacity and nutritive requirements of the infant. The lesson is plain. If raw, unmodified milk causes indigestion in the fever patient, it may be made acceptable by modifying it after the manner of infant dietetics. In our experience we have found that the formulas of Coleman make a very satisfactory foundation for a modified milk diet whether or not it is desired to push the daily intake to the full theoretical requirement.

In cases in which milk is distasteful or not well borne, or in localities where good, fresh milk is not obtainable, a diet with plain milk excluded must be given, although preparations containing milk as an important constituent may be taken and well digested. Such articles are condensed milk, fermented milk, whey, junket, ice cream, custards, cream soups, cream puddings, cream cheese, tea, coffee and cocoa.

Carbohydrates.—The carbohydrates have an important place in the typhoid dietary. Lusk and Shaffer and Coleman have shown that, in addition to their direct value as food, the carbohydrates have the property of sparing body protein both in afebrile and febrile conditions. In typhoid fever there is an increased need for carbohydrates and, unless this demand is met, the body protein wastes. Carbohydrates prevent loss of body protein to a greater extent than fat and even protein itself. The demonstration of this fact is one of the most important results of the recent studies in the metabolism of typhoid fever. There is also experimental evidence that a diet rich in carbohydrates is unfavorable to the growth in the intestinal tract of organisms of the colon-typhoid group.

Sugars are utilized to build up the caloric value of the typhoid dietary. Each ounce of any one of the sugars represents 120 calories. Milk-sugar is the most important of the group. This carbohydrate is easily digested and does not easily ferment. It is not very sweet and can be given in large amounts in the milk formulas, in beverages, and as the sweetening ingredient in various food preparations like ice cream, custards, gruels, etc. From eight to sixteen ounces or more may be given daily, and Coleman has found that these large amounts are well borne and do not cause digestive disturbance or predispose to tympanites. Cane-sugar is too sweet to be given in large quantity; one or two ounces a day may be given in lemonade and other beverages. Glucose and malt-

sugar are occasionally of use. In emergencies glucose is available for rectal and subcutaneous feeding.

CEREALS.—Cereals and other farinaceous foods carry a high carbohydrate content and a small percentage of vegetable protein. Bread, crackers, zwiebak, cereal gruels and puddings, porridge and mashed potatoes are light foods which can safely be given both in the febrile stage and in early convalescence. In cases in which milk must be excluded from the diet, the cereals in the form of gruel and porridge will have a prominent place. Milk and cream may be made more digestible and often are better borne if diluted with a gruel, whereas, if given pure, these foods would disagree. In the early stage of typhoid, when digestion is greatly impaired, the gruels are of especial value. All cereals must be thoroughly boiled and strained. The proprietary farinaceous and malted infant foods may be of distinct value in cases in which digestion is seriously impaired or diarrhea is troublesome. They have about the same composition as wheat flour.

EGGS.—Eggs form an important part of the typhoid dietary. They supply protein and fat in about equal proportions. Egg albumen is completely peptonized in the stomach, and the fat is well split up before it reaches the ileum; practically no undigested residue is left. From four to six eggs may be given in a day, soft boiled, coddled or beaten up with milk or one of the fruit juices. The white of egg is agreeably given as albumin water flavored with orange or other fruit juices and sweetened with lactose or cane-sugar.

MEAT FOODS.—Meat soups, broths, beef tea and bouillon are home-made infusions of beef, mutton, veal, chicken or shellfish. They are of low nutritive value—from four to eight calories per ounce. They contain a small percentage of protein but, as usually prepared, they are simply solutions of meat salts and extractives. They are popular in the home sick-room, but should be classed rather as agreeable and stimulating beverages than as foods. They have a distinct and valuable function in stimulating appetite and digestion, and in small quantities are useful in certain stages of typhoid fever, particularly in the late febrile period and in convalescence. They often have a decided laxative effect and may excite or aggravate a diarrhea. By the addition to them of eggs, milk, cream or cereals, they may be made to carry considerable nutriment.

Beef juice contains a relatively small quantity of extractives and from four to six per cent. of protein. This meat preparation is easily digested and is not apt to produce diarrhea. It is of value when milk cannot be given, and as the first step to the resumption of meat feeding. The raw meat flavor of beef juice is sometimes distasteful and can be disguised by serving the beef juice in broth, milk or sherry wine. The cream soups contain milk or cream, butter, flour and eggs and have a much higher nutritive value. They are agreeable and readily digested.

Gelatin in the form of calf's foot jelly, wine jelly or the home-made product is a useful food in febrile states. In the form of iced bouillon it is very grateful to the patient. It acts as a fuel food, like the fats

and carbohydrates, but differs from them in this particular—that its oxidation products are eliminated by the kidneys. It digests quickly, being completely peptonized in the stomach in one hour. The proprietary meat preparations are in general of low food value, except for the alcohol they may contain. Peptonized meat preparations are objectionable, as they are often toxic and very apt to produce diarrhea.

American practice is against the addition of meat to the typhoid dietary during the febrile period. It may be given in mild or uncomplicated severe cases when the fever is declining or in early convalescence. One-half to one ounce of scraped meat rolled into small balls and lightly broiled should be the first venture. Should this be well digested, the tender white meat of chicken or a broiled chop may follow. Until well into convalescence the quantity should be limited to from two to four ounces a day. It is quite common to see a rise of temperature follow the resumption of meat feeding.

Fruits and Fruit Juices.—Cooked fruit, like apple sauce, which can be eaten as a soft pulp, is occasionally permissible in mild cases and when convalescence is well established. In all cases of severity the fruit acids are better given in the form of the fruit juices, lemon, orange, grape and grapefruit. They are excellent vehicles for the administration of the white of egg and sugar. As lemonade, orangeade, etc., they agreeably assist the increase of the daily food intake. The fruit jellies dissolved in water and sweetened serve the same purpose. The fruit acids in excess may cause abdominal pain and diarrhea, and their effect should be carefully watched.

Beverages.—Water, far above the quantity taken in health, is necessary for the nutrition of the febrile patient and for the elimination of the toxins of the disease and the end-products of increased metabolism. The conscious patient may be urged to drink frequently from a water bottle placed at his bedside; the delirious or unconscious patient must be given water by the nurse every hour when awake, in as large amounts as he can be made to swallow. The quantity taken should be charted and the total twenty-four-hour intake summed up for the information of the physician at his morning visit. McCrae makes the rule that three quarts be the minimum daily intake. We are inclined to doubt the advisability of risking the possibility of cardiac overstrain by forcing water ingestion to the extent advocated by the late Doctor Cushing—two to four gallons a day.

Lemonades, orangeades and other preparations, cracked ice, iced tea and coffee may be used to tempt the patient to increase the amount of fluids taken. Gravely toxic patients who cannot be made to take sufficient water by the stomach should be given saline solution per rectum. If the rectum is irritable and the demand urgent, intravenous or subcutaneous administration is justifiable. The course of typhoid fever is often made milder in patients who take water in abundance. The tongue remains moist and clean, nutrition is better; the toxic delirium and stupor are less severe.

Tea, Coffee and Cocoa with Cream and Sugar.—These are grate-

ful and stimulating nutrients. They may be given hot or iced. They are apt to interfere with sleep and are best added to the morning meals. They gently stimulate the circulation and increase the urinary output. Strong coffee is a prompt and active cardiac stimulant in the shock of hemorrhage, perforation and other accidents.

ALCOHOL.—The routine administration of alcohol in typhoid fever either as a food or as a stimulant is unnecessary and unwise. The majority of patients go through the disease as well—perhaps better—without it. If other food of adequate caloric value is taken the addition of alcohol is superfluous. Children and young adults rarely require it, while it is often of distinct benefit to elderly patients and those accustomed to its use in health.

In moderate quantity and properly diluted it may be of great value as an emergency food in conditions of profound anorexia and at times when ordinary food cannot be taken or is not well borne. It does not prevent nitrogen waste, but spares fat and for a short period replaces carbohydrates in the diet. In febrile states especially it is rapidly oxidized, each gram of alcohol yielding seven calories, and one ounce of whiskey or brandy approximately one hundred calories. It is a direct stimulant to gastric secretion and motility, and hastens the absorption of the products of digestion. In the intestine it stimulates peristalsis and acts as a carminative and mild astringent.

In sudden circulatory failure alcohol acts as a stimulant, either reflexly from the stomach, or, after absorption, as an equalizer of the circulation. In the profound toxemia of severe cases attended with increasing cardiac asthenia and grave nervous phenomena, it improves nutrition, supports the circulation and relieves insomnia, delirium and other exhausting nervous symptoms. In the early days of the convalescence of severe and complicated cases it may be of decided benefit as a stimulant to appetite and digestion and as a general tonic. The possibility of the formation of a habit must always be borne in mind and the remedy should be discontinued at the earliest possible moment.

The effect of the administration of alcohol should be carefully noted and unless results are favorable it should be discontinued. The beginning doses should be small—2 to 4 drams of whiskey or brandy every four hours. It is rarely necessary to exceed one-half ounce every three hours, or four ounces in twenty-four hours.

During the febrile period a well aged whiskey or brandy is generally the most useful form for administration. The spirit should be diluted to an alcoholic strength of from five to ten per cent., one part of whiskey to from two to five parts of water. Claret or champagne—either clear or diluted with an effervescent water—may be better taken. Burgundy, sherry or port are more suitable for administration in the convalescent stage. Unless given to fill some special indication, alcohol is most effective when administered immediately before or with the regular feedings.

MANAGEMENT OF THE DIET.—The routine of the diet for each day should be prescribed by the physician at his morning visit. A feeding

chart should be kept by the nurse and the amount of food actually taken by the patient at each meal recorded. Each morning the total intake of food and fluids for the preceding twenty-four hours, with the approximate composition and caloric content, should be determined. Food should be administered at regular stated intervals and in measured quantity. Two-hourly feedings is the rule in severe cases. The frequency of the night feedings will be governed by the condition of the patient. Sleep is rarely prolonged, and in many cases the two-hourly interval can be continued throughout the night without interfering with sleep. Drowsy and stuporous patients can be aroused without detriment. The sleep that may come after a long period of wakefulness or delirium should be interrupted only in cases of necessity. Patients mildly or moderately ill who take abundant nourishment during the day may be allowed to sleep the night through or may be given one or two early morning meals.

For the first two days after the patient comes under observation only fluid food in moderate quantity should be given. Four ounces of milk diluted with two ounces of water or cereal gruel may be given every three hours. Following this the milk formula containing 1,000 calories may be given and the intake increased as rapidly as the patient's digestion will permit. Coleman has very properly emphasized the necessity of cautiously and gradually attaining the desired maximum food intake in an individual case. In the early period of the disease it is often impossible to push the intake above 1,500 calories without exciting a digestive upset.

As soon as it is shown that the milk formula is well borne the food may be increased by from 200 to 300 calories a day, until the daily intake is 3,000 to 4,000 calories, and the interval between meals shortened to two hours. One or more eggs, a cereal with cream, soft toast, custard, broth and other appropriate foods may be added and the effect of each article carefully observed. The stools should be frequently examined for curds and other undigested particles of food.

The appearance of abdominal discomfort or distention or of diarrhea is a signal for prompt revision of the diet. Relief may be obtained by a change in the proportion of the various articles in the diet, or it may be necessary for a day or two to return to diluted milk, albumin water, gruel or broth feedings at longer intervals. A complete rest of the stomach for several hours may be advisable. We have seen the fever decline and toxic delirium abate as a result of a short period of food restriction and increased elimination. By observing these precautions the optimum diet for a given case can be attained with a minimum of risk.

Hydrotherapy.—The cold bath is the most efficient measure we possess to combat pyrexia, toxemia and many of the grave symptoms and complications of typhoid fever. Since the earliest times the cold bath, administered in various ways, has had periods of popularity. James Currie, of Liverpool, proposed the cold effusion treatment in 1787, and it was extensively used in England and other countries. In the great British epidemic of 1817 to 1819 the method of Currie was followed

with perseverance, only to be abandoned later. The water cure had become a system of quackery and was shunned by the profession. In America, Robert Jackson employed the cold bath in the treatment of fevers as early as 1774. Nathan Smith, writing in 1824, was an earnest advocate of hydrotherapy, and he considered the cold bath the only remedy that favorably influenced the fever. E. Brand, of Stettin, in 1861 revived the cold bath treatment, and his numerous publications and favorable statistics fixed the attention of the medical profession on the value of hydrotherapy in the treatment of acute febrile and toxic states.

The cold bath given as a routine from the onset in all cases of typhoid fever, and with the exact technic advised by Brand, has not been popular outside of Germany. In America, tub baths, modified from the Brand method, have been extensively used in hospitals and to a more limited degree in private practice. Hydrotherapy in some form may be considered an essential part of the therapeutics of the disease.

THE TUB BATH.—*Brand Cold Friction Bath.*—This is administered from the onset of the disease every 3 hours, when the rectal temperature is above 102.5°F. (39.2°C.). The patient is first given a stimulant—one-half ounce of whiskey, or, what is preferred by many, four ounces of hot, strong coffee or tea. He is then undressed and covered with a sheet or a napkin around the loins. Pledgets of cotton are put in the ears and the dry skin of the hands and feet covered with vaseline. A rubber bathing-cap is desirable for women. The patient's face is bathed with ice water and a cold water compress applied to the head, and he is gently lifted by two attendants from the bed into the portable tub placed at the bedside. Adjustable strips of canvas clamped to the sides of the tub make a comfortable rest for the patient's body and legs. The tub is filled with fresh water, not above 70°F. (21.1°C.) or below 65°F. (18.3°C.). The entire body and extremities are submerged. The head is supported by an attendant, or on a suitable head rest. Continuous brisk friction of all the skin surface is an essential part of the bath, especial attention being given to the extremities. Repeated effusions to the head with cold water are very important in cases with predominant nervous symptoms. The duration of the bath is twenty minutes, unless untoward symptoms require it to be shortened. Complaints of chilliness and blueness of the fingers are usual and are not indications for ending the bath. Continued chattering of the teeth, cyanosis of the face and a weak pulse demand removal.

At the end of the bath the patient is lifted from the tub, gently dried, except over the abdomen, and lightly covered in bed with a sheet and blanket. Hot-water bottles are placed at the feet. Another hot drink and, a little later, food may be given. The temperature is taken one-half hour after the bath. A fall of from one to three degrees is usually noted. At the end of three hours the temperature is again taken, and if above 102.5°F. (39.2°C.), the bath is repeated.

Modified Tub Bath.—The cold bath of Brand, rigidly enforced, is heroic treatment, and most physicians prefer some modification of the

method that will make the bath more acceptable to the patient. By many the bath is not given until the patient's temperature is above 103° or 103.5°F. (39.4° or 39.7°C.). It is good practice to begin the bath treatment with the water at a temperature of 80° or 90°F. (26.7° or 32.2°C.) gradually reduced during the bath to 65° or 70°F. (18.3° or 21.1°C.) by the addition of cold water. As a rule we prefer to use such a graduated tub bath until the patient's confidence is obtained and his manner of reaction to the bath is determined. The warm bath gradually chilled is a modification particularly adapted to women, children and nervous men. The bath is begun with the water at a temperature of 3° to 4° below the temperature of the patient and cooled 3° or 4° every five minutes until it is below 90°F. (32.2°C.). The patient is then removed.

THE BED BATH.—Properly given, the bed bath is a fairly satisfactory substitute for the tub bath. It is the preferred form of hydrotherapy in many hospitals and by many physicians in the home treatment of typhoid fever. A shallow tub is made in the bed by a large rubber sheet. The sides of the sheet are stretched over a tightly rolled blanket placed on each side of the patient and held by clamps or long tapes tied to the bedstead. The ends of the sheet are stretched in the same manner over shorter rolls. The portable bath of the medical supply houses is very convenient, if available, or the sheet may be fastened to an improvised frame. Haven stretches two parallel ropes from the head to the foot of the bed and fastens the sides of the sheet to the ropes with clothes pins.

In the bed bath the patient's body is only partially immersed. The water is poured over the patient from a pail or pitcher, from large sponges or from the ordinary sprinkling pot. The trunk and extremities are continuously rubbed, as in the tub bath. The bath is continued for twenty minutes or made shorter if the condition of the patient demands. At the end of the bath the water is siphoned off with a rubber tube, the rubber sheet is removed and the patient lightly dried and covered with a linen sheet and blanket. As with the tub bath, a hot drink is given before the bath and after, if necessary, and cold compresses are applied to the head.

THE SPONGE BATH.—The patient is placed on a rubber sheet large enough to protect the bed. Cold compresses are applied to the head and chest and renewed every few minutes. They may also be placed over the large vessels under the arms and along the inner surfaces of the thighs. The sponges should be large and carry an abundance of water. The trunk and each extremity are successively bathed and rubbed, the whole bath lasting twenty minutes. The patient may be dried and covered as in the other baths, or allowed to remain five or ten minutes in a wet sheet and covered with blankets.

INFLUENCE OF HYDROTHERAPY ON THE COURSE OF TYPHOID FEVER.—As a rule the best results are obtained from tub baths; bed baths with effusions rank next in efficiency; sponge baths are the least disagreeable to the patient and have the least influence on the pyrexia and toxemia.

1. The febrile period of typhoid fever is not shortened by hydrotherapy, except that the baths may prevent complications that prolong the fever beyond the normal period. The immediate effect of the bath is to reduce the temperature from one to four degrees. The reduction is transitory and the temperature returns in a short time to its former height. During the remission the patient usually feels better. In the early stage when the temperature is in the ascendant, and during the height of the febrile period, the fall of the temperature after the bath may be insignificant; exceptionally a rise of a degree or more is seen. In the period of decline a sharp remission that continues for several hours is usually noted. It must be emphasized that the extent of the drop in the temperature is not necessarily a measure of the good effect of the bath. The degree of improvement in the general condition of the patient is of more significance.

2. Toxemia is reduced by hydrotherapy. Diuresis is increased, and the general improvement in the symptoms attributed to the presence of toxins in the circulation point to their increased elimination. The typhoid state is rarely seen when systematic bathing is carried out. The good effect of the bath is best seen in severe cases with delirium, stupor, subsultus tendinum and other symptoms of profound toxemia. In these cases the bath—preferably the tub bath—with the water tempered to fit the condition of the patient is a life-saving measure and should be given thoroughly and conscientiously.

3. The circulation is improved. The heart action is slowed, the pulse becomes smaller and firmer and the blood pressure rises 15 to 20 mm. Vasomotor paresis is lessened and the circulation is equalized. Thayer found a hyperleukocytosis immediately following the cold bath, and Gay suggests that this result may explain its beneficial effect.

4. The full respirations that are stimulated by the bath relieve pulmonary stasis. Passive congestion of the lungs, bronchitis and bronchopneumonia are less frequently seen and are favorably influenced if present.

5. The skin is kept clean and healthy and the liability to bed-sores is diminished. Thayer has found that the addition of alum, one-half pound to the tub, is of value in the presence of boils and other skin infections.

6. The mortality rate is lowered. Hospital statistics show a decided reduction in mortality with the introduction of routine bath treatment. Osler, from his experience at the Johns Hopkins Hospital, although deploring the disagreeable features of the bath, believed that it saved from six to eight patients out of every hundred. The general experience also in the larger hospitals of New York and Philadelphia was that the mortality under the cold tub treatment was reduced approximately fifty per cent. The figures of the Brisbane Hospital, Australia, published by F. E. Hare, give a mortality of 14.8 per cent. in 1,828 cases treated by the expectant method, and 7.05 per cent. in 1,902 cases treated after the introduction of hydrotherapy.

The bath in itself, however, may not be the only factor in the pro-

duction of the lowered mortality. The tubbed patient is, as a rule, better fed, better nursed and more closely watched than the patient treated on the expectant plan. Shattuck's results at the Massachusetts General Hospital were equally good with liberal feeding, good nursing and hydrotherapy in the form of sponge and bed baths. The recent advocates of an abundant diet in typhoid fever state that the beneficial effect upon the course of the disease and the lowered death rate that result from the cold bath treatment can be obtained as well without the baths if the patient is abundantly nourished. Coleman believes that high temperature is a danger only when the patient takes insufficient food, and that tubbing is unnecessary if the patient is well fed. He believes that hydrotherapy owes its value to reduction in the total metabolism. If this can be covered by food, the cold bath loses its purpose.

With all allowance for the enthusiastic statements of the advocates both of tubbing and of feeding, it may confidently be stated that **hydrotherapy and liberal feeding are the fundamental modern improvements in the treatment of typhoid fever.** Widely used they together will carry the patient through his long illness with the least possible discomfort and danger.

Brand and his followers urged that all typhoid patients should be treated by the cold tub bath. At the present time the rigid Brand treatment is carried out only exceptionally. In many hospitals where the method was systematically used for several years after its introduction, it has given way to milder forms of hydrotherapy. Patients are individualized and the various hydrotherapeutic methods are adapted to the condition of the patient and his environment.

In mild cases tubbing is unnecessary. A cold sponge bath morning and evening are requisite for cleanliness, and should be a routine measure in all cases. Two or three additional sponge baths may be given through the day, should the afternoon temperature reach 103°F. (39.4°C.). Cold compresses to the head, chest or abdomen for an hour or two at varying intervals may replace the antipyretic cold sponge. The ice-bag also is a grateful substitute.

In cases of average severity the tub or bed bath will be indicated toward the end of the first week when the temperature reaches 103° F. (39.4° C.). From one to three tubs during the afternoon and evening exacerbation of the fever usually suffice. The temperature of the first baths should be from 85° to 95° F. (29.4° to 35° C.) and reduced during the bath and at subsequent baths, according to the manner of reaction of the patient and the influence upon the temperature, pulse, respiration and nervous symptoms.

Severe cases should be tubbed from the outset, if possible. If the tub bath be not available, the bed bath thoroughly carried out should be substituted for it. The sponge bath alone is too feeble a substitute. The bath should be given every four to six hours if the temperature is above 103°F. (39.4°C.), or with a lower temperature, if stupor, delirium and other toxic symptoms are marked. It will rarely be necessary to give more than three or four baths in the twenty-four hours. If a bath is

given about nine or ten o'clock in the evening the effect will often carry through to the time of the natural morning remission and further night bathing will be unnecessary. In highly toxic and stuporous cases the regular intervals should be maintained night and day.

Tub baths should be begun with great caution or withheld entirely in gravely prostrated patients coming under observation late in the disease. Such patients are probably safer if treated with diligent nursing, good feeding and a few gently given sponge baths.

Infants and children respond well to the milder forms of hydrotherapy. Luke warm sponges, packs and bed baths are agreeable to them and are efficient.

Elderly patients are better sponged or bathed in bed. Reaction in such patients is sluggish and apt to be unsatisfactory. Usually they are better pleased and as well off if given the routine morning and evening sponge and only an occasional extra bath.

Tub baths should be given with extreme care, or discontinued toward the end of the third week when sharp remissions mark the course of the temperature. Cardiac asthenia and the danger of hemorrhage and perforation require that the patient be moved as little as possible. At this period the sponge bath is safer. Only the milder forms of hydrotherapy are permissible in the treatment of relapse.

CONTRA-INDICATIONS TO THE TUB BATH.—(*a*) In the Presence of Complications That Demand Absolute Rest.—Symptoms suggestive of hemorrhage or the appearance of blood in the stools require immediate interruption of all forms of hydrotherapy. Bathing should not be renewed until several days have elapsed after the arrest of the bleeding. Abdominal pain, pointing to the onset of perforation, peritonitis, appendicitis, cholecystitis or other acute abdominal inflammation, is a contra-indication. Phlebitis, pleurisy, severe bronchitis and other complicating infections, remote from the abdomen, demand temporary or permanent suspension of antipyretic baths.

(*b*) In the Presence of Conditions or Complications Marked by Extreme Weakness.—Constitutionally feeble, anemic and obese patients, and subjects of arteriosclerosis, chronic nephritis, chronic alcoholism or tuberculosis should not be treated with cold tub or bed baths.

SPECIFIC THERAPY

The specific therapy of typhoid fever by serums and vaccines is still in the experimental stage. The results obtained by a number of experimenters are encouraging, but not conclusive. In inexperienced hands the method is not without danger and it should be used only after careful study and full precautions against untoward effects. If possible patients receiving such treatment should be in hospitals where results can be carefully observed and recorded.

Serum Therapy: Passive Immunization.—A variety of methods of preparation of immune serums have been used. Von Yaksch and Walger used the blood serum of recovered cases of typhoid fever. Koenigsfelt

injected subcutaneously the patient's own blood serum in daily doses of 2 c.c. to 4 c.c. Horses, sheep and other animals have been used as sources of immune serums. Chantemesse employed a serum obtained from horses by immunization of the animals with a soluble typhoid toxin prepared from the filtrates of a five or six days' growth of the typhoid bacillus on a bouillon medium containing splenic pulp and defibrinated human blood. One thousand cases treated by this serum showed a mortality of 4.3 per cent. In the Paris hospitals during the period that these cases were treated the mortality was 17 per cent. Rodet produced a serum from horses by the intravenous injection of dead bacilli followed later by the injection of living bacilli and toxic bacterial extracts. Rodet treated 400 cases giving from 10 to 20 c.c. of the serum subcutaneously every other day. In cases treated early the course of the disease was markedly shortened. Étienne observed the same favorable results in 200 cases treated in this manner.

In order to guard against serious anaphylactic reaction, intravenous injections of any serum should be preceded by desensitization of the patient by the preliminary subcutaneous injection of 0.5 c.c. of the serum to be used. Evidence of hypersensitiveness is a contra-indication to further serum treatment.

Vaccine Therapy: Active Immunization.—The treatment of typhoid fever by antityphoid vaccine seems to be on firmer ground. The remarkable success of preventive antityphoid vaccination has given encouragement to the use of vaccines for the treatment of the established disease.

Fraenkel first treated typhoid fever by the subcutaneous injection of killed bacilli, in 1893. Many small groups of cases treated by antityphoid vaccines prepared by a variety of methods have been reported. Although many of these reports are very imperfect, the impression is gained from their study that vaccine treatment tends to shorten the course of the disease, lessen the number of complications and relapses, and reduce the mortality.

On the basis of experimental work on rabbits by Gay and Chickering, Gay was encouraged to treat typhoid fever by the intravenous injection of a sensitized vaccine sediment. This vaccine, owing to its sensitization and the removal of endotoxins, is not followed by untoward effects. The initial dose is 1/50 milligram, corresponding to 150 millions bacilli, administered intravenously. Gay reports 98 cases treated by this method. Treatment was begun on the average on the thirteenth day of the disease; 33 cases were aborted, 32 were benefited and 33 were not affected. The mild cases reacted better to the treatment, and analysis of the results shows a distinct shortening of the febrile period. Complications occurred in 13.2 per cent. of the cases; hemorrhage in 4 per cent. and perforation in 2 per cent. Relapse occurred in 10.2 per cent. The mortality was 6.6 per cent.

The subcutaneous injection of moderate doses of vaccine in typhoid fever is not followed by any reaction of importance. There may be localized swelling and tenderness at the site of the injection and the evening

temperature of the day of administration may rise a degree or two higher than on previous days.

Intravenous injection of a vaccine, however, is followed by a sharp and characteristic reaction. The phenomena of this reaction have been carefully observed and described by Gay. The injection is followed in from fifteen minutes to an hour by a chill which lasts from ten or fifteen minutes. A sense of involuntary muscular contraction rather than of coldness accompanies the chill. A rise of temperature of one to three degrees occurs, which reaches the maximum within three hours after the injection and then falls to normal or below in about twelve hours. The pulse rate is increased, the blood pressure rises, and there may be slight cyanosis and respiratory distress. The fall in temperature is often attended by a profuse sweat lasting several hours. Relief of unpleasant symptoms like headache is experienced, and the patient feels well. The rise in temperature after the injection is accompanied by a drop in the white-blood cell count to 3,000 or 2,000. As the temperature falls there is a rise in the leukocyte count to as high as 40,000, with a relative polymorphonuclear increase. This hyperleukocytosis is transitory and may be missed unless blood-counts are made at frequent intervals, every two hours.

This general reaction following the intravenous administration of typhoid vaccine is not specific in character. Other foreign proteins introduced into the blood stream produce reactions of the same type.

"No detailed method of procedure can be prescribed for treating any given case of typhoid fever by this method. The best results seem to be obtained by provoking a distinct but not too severe reaction of the type outlined. The dose necessary to produce such a result varies markedly with the individual and the particular balance already established between the typhoid bacillus and the reaction antibodies in the host. The temporary drop of temperature to normal may become permanent and remain there, in which case no further injections are required, except for the prevention of relapse. If the temperature again rises over a period of two or three days, the injection should be repeated in slightly increased amount, and so on, until the desired result is produced or further injections are judged futile. A considerable number of injections may be given with perfect safety. As many as fifteen or sixteen have been given in certain instances, but if no striking result is obtained following three or four injections at two or three day intervals, very little effect from further treatment may be expected" (Gay).

With experience of 1,200 injections Gay found that reactions like the above have not been harmful either immediately or remotely. Other observers, using different vaccines, have occasionally met with alarming or dangerous reactions.

Typhoid vaccine for curative treatment is marketed by several commercial houses, in ampules or syringes containing from 100 to 1,000 millions bacilli. It is identical with the prophylactic vaccine previously described. The practitioner is justified in using curative vaccine therapy if proper attention be given to dosage and the simple technic of ad-

ministration, and if his patient is in a hospital or at home under careful observation. The vaccine may be given subcutaneously or intravenously. The intravenous method requires more careful attention to the dose and the details of administration. It is more liable to be followed by unpleasant reaction phenomena. The initial dose should be small, and succeeding doses increased slowly according to the reaction produced.

Gay has summarized the recently published results of the vaccine treatment of typhoid fever: 2,582 cases were treated by 78 observers. An average of 65 per cent. of the cases were benefited. The average mortality was 11.6 per cent.

A vaccine is often of distinct value in prolonged cases in which convalescence is delayed, and in the treatment of local complications and sequelæ and the carrier state.

Treatment of Symptoms and Complications

Fever.—Fever is a defensive reaction to infection, and within certain limits it is—according to modern views—a conservative process. Its suppression is not always desirable and its violent reduction may be a clinical error. If the tissues are well fed and abundant excretion maintained, a temperature of the average height usual in typhoid fever is not in itself a source of danger. The chief danger in typhoid fever is the toxemia, the intensity of which is usually—but not necessarily—indicated by the height of the temperature. A grave toxic state may be present with but little rise in temperature, while on the other hand the good effects of hydrotherapy in reducing toxemia are often manifest with practically no reduction in the temperature. Coleman finds, in the use of the high calory diet, that the temperature may be lightly regarded if the patient can take an abundance of food.

Hydrotherapy.—For the control of fever and the metabolic disturbances that go with it, hydrotherapy has proven to be the most efficient remedial measure. The indications for the various forms of application of the bath treatment and the technic of administration have been considered in preceding pages.

Antipyretic Drugs.—The synthetic antipyretic drugs reduce temperature by their action on the heat-regulating nervous mechanism, lowering the point at which the temperature is maintained. They increase the dissipation of heat, and this is brought about by dilatation of the cutaneous vessels. Collapse often follows their too rapid action. They have no beneficial influence upon the toxemia of the disease. **The coal-tar antipyretics, therefore, have no place in the treatment of typhoid fever.** They are circulatory depressants and their routine use is harmful. The administration of these drugs in the early stage of typhoid fever tends to confuse the diagnosis and divert attention from proper methods of treatment. Given later in the disease, when the myocardium is weak and violent reactions are apt to follow the use of any antipyretic measure, they are a positive danger.

An occasional single dose of one of the more slowly acting members

of the group, **pyramidon or phenacetin, may not be harmful when given to relieve a painful symptom** like severe headache, but other and less objectionable remedies are usually available to meet such an indication.

Quinin in large doses is an antipyretic. It acts directly upon the tissues, diminishing nitrogen metabolism. Erb advised the administration of 20 to 30 grains (1.3 to 1.95 grams) in two doses during the evening of every second day, beginning in the latter part of the second week of the disease. The effect of the drug is prolonged, lasting from twenty-four to forty-eight hours. Like other antipyretic remedies its action is most pronounced in the declining period of the disease.

Toxemia.—Free elimination should be maintained by the **liberal administration of water.** The tactful and persistent nurse may be able to give an abundance of fluids by the mouth. If not they must be introduced in other ways. *Stuporous or comatose patients* may be given **water or nutrient fluids by the stomach tube,** 500 c.c. to 800 c.c. (17 to 27 fluid ounces) every eight or twelve hours. **Small enemas,** 300 c.c. to 500 c.c. (10 to 17 fluid ounces) **of normal saline** may be given two or three times in the twenty-four hours. The solution should be of body temperature or slightly warmer and injected slowly. The continuous drop method is very satisfactory. Beginning every six to eight hours, 500 c.c. (17 fluid ounces) of **normal saline** may be given. The solution may be given a nutrient value by the **addition of 2 per cent. of glucose.** A diarrhea or an irritable bowel may interfere with this treatment.

Hypodermoclysis may be resorted to if other methods fail. From 1,000 c.c. to 2,000 c.c. (34 to 68 fluid ounces) of sterile saline solution may be injected into the loose connective tissue under the breasts, in the axillary region or into the thighs—areas not subjected to pressure. Necrosis is a positive danger and the fluid must be given slowly and with great care. In desperate cases intravenous injection is justifiable. The solution must be prepared from distilled water and the aseptic technic must be perfect. A chill and increased fever sometimes follow the injection.

Gastro-intestinal Symptoms and Complications.—Severe *vomiting* is an unusual symptom in typhoid. When present, the stomach should be given rest for a few hours and no food or only the blandest fluids should be given. **An ice-bag or a hot compress over the upper abdomen** is useful. **Bits of ice or a carbonated water** may be given, or frequently repeated teaspoonful doses of **peppermint or chloroform water or chalk mixture. A hypodermic injection of morphin** will relieve when other measures fail. Other obstinate cases will respond to **gastric lavage.**

Abdominal Pain.—Severe abdominal pain is an important diagnostic sign of perforation and other grave abdominal complications. It should not be masked by an anodyne. **It is imperative that opium be withheld at least until the cause of the pain is determined.** Mild persistent pain is a symptom of indigestion and may be relieved by attention to the diet. An excess of fruit juices or cold drinks not infrequently excites

colicky pain. **External applications with correction of the diet** usually bring relief. **The hot-water bag, electric heater or hot stupe** are useful. A carminative, like **peppermint, chloroform water or brandy** may be given in addition.

CONSTIPATION.—Constipation is the rule in typhoid patients who are carefully and properly fed. The condition is favorable and **should not be interfered with by laxatives or purgatives.** A single cathartic dose of calomel, castor oil or a saline may be given without harm if the case is seen at the beginning of the invasion period, although it will have no beneficial influence on the course of the disease. Repeated purgation, even in the first week, may excite a diarrhea difficult to control; after this time a cathartic is distinctly contra-indicated. **The daily administration of a small soap and water enema** will empty the lower bowel with the least disturbance to the inflamed and ulcerated small intestine. This routine should be kept up until convalescence is established and the bowel resumes its normal function. One ounce of a good brand of **liquid petrolatum** given each evening during the declining and convalescent periods is often a very satisfactory substitute for the enema.

DIARRHEA.—Diarrhea is not a necessary symptom of typhoid fever, and, when present, its cause should be carefully sought. An unsuitable diet is the common cause. It may be a symptom of extensive ulceration involving the colon, or of a severe infection.

The appearance of diarrhea calls for an **immediate revision of the diet.** The total daily intake of food may be too high, or there may be an excess of some one article of the diet. The symptom can usually be controlled by a re-arrangement of the dietary. Meat soups and extracts are a frequent cause. Milk or, more frequently, cream is the offending article. The stools should be examined, and if curds are found the milk should be given more dilute or otherwise modified, or stopped entirely. In exceptional cases it may be necessary to cut off all food for a day and give nothing except water by the mouth. As soon as the diarrhea is checked, feeding with albumin water, cereal gruels or whey may be begun and the diet again built up to the proper calory content, with milk, eggs, cereals and lactose.

The semisolid foods in the high calory diets are not apt to cause the trouble. Coleman has found that patients entering the hospital with profuse diarrhea develop normal stools after a few days of high calory feeding.

It has been shown that the putrefactive bacteria predominate in the stools of patients with persistent diarrhea, and that a favorable change to the fermentation type of intestinal flora may be brought about by increasing the carbohydrate content of the food—particularly the lactose. The administration of **pure cultures of the Bacillus acidophilus** has been suggested to hasten the transformation.

Drugs may be necessary if the diarrhea resists the changes in the diet. **Bismuth subnitrate or subcarbonate,** 10 to 20 grains (0.65 to 1.3 grams) **suspended in chalk mixture,** 2 to 4 drams (7.8 to 15.5 grams) may be given every two to four hours. In severe cases **opium**

should be added to the bismuth, one to two teaspoonfuls of **paregoric** or 2 to 4 grains (0.13 to 0.26 gram) of **Dover's powder** in capsule or syrup after each bowel movement. Given in this way the frequency of the dose of opium will be automatically regulated by the severity of the diarrhea. **Tannigen,** 5 grains (0.324 gram) every four hours, is a valuable astringent. Very frequent movements with symptoms of irritation of the lower bowel may be relieved by **enemas of starch water,** 6 ounces (178 c.c.), and **laudanum,** 15 minims (0.92 c.c.). Prolonged colon irrigation with **warm saline solution** is valuable in profoundly toxic cases with diarrhea and tympanites.

Intestinal antiseptics seem to have the confidence of many practitioners for the control of diarrhea and tympanites. The author (Jennings) fails to observe any decided beneficial effect from their use. **Salol** is the drug most frequently prescribed. It may be given in 4 grain (0.26 gram) doses alone or combined with the chalk mixture and bismuth.

Tympanites.—Although a common symptom and, when moderate, not a dangerous one, tympanites should always receive serious consideration. Once the bowel becomes overdistended tympanites is a grave complication and very difficult to relieve. It usually—but not necessarily—is associated with diarrhea, and the same causes may be responsible for the symptom. Faulty diet is the common immediate cause. In severe form tympanites is a manifestation of profound toxemia with paralysis of the musculature of the intestinal wall.

The first appearance of meteorism demands **immediate attention to the dietary and revision in detail along the same lines as indicated for the treatment of diarrhea.** An excess of lactose or other carbohydrate may be the error in one case or an excess of protein food in another. For the milder degrees of distention, after attention has been given to the diet, the **ice-bag** may be applied intermittently to the abdomen. **A hot-water or turpentine stupe**—made by wringing a flannel compress out of hot water containing one teaspoonful of turpentine to the quart—is the most useful external application. **A hot turpentine enema**—one-half teaspoonful to two quarts of water—will often give relief. If these simple measures fail **a rectal tube** may be passed carefully into the bowel and allowed to remain until expelled.

By the mouth, the simple carminatives will aid in giving relief. **Turpentine**—5 to 10 minims (0.3 to 0.6 c.c.), given in emulsion or soft capsule—is the most valuable internal remedy.

Hypodermic injection of **solution of pituitary extract**—1 c.c. (16 minims)—or **physostigmin sulphate**—1/50 grain (0.0013 gram)—should be given in severe cases. The remedies act as stimulants to the muscular wall of the bowel.

Intestinal Hemorrhage.—The nurse should be warned of the possibility of hemorrhage, and instructed to notify the physician at once at the first sign of blood in the stools, to stop the administration of all food and water, and to keep the patient absolutely at rest and wait further instructions.

Hemorrhage is arrested by the formation of a clot in the ruptured

bleeding vessel. The available measures favoring coagulation are (1) the arrest of intestinal peristalsis; (2) the administration of remedies which act locally upon the bleeding surface; (3) the administration of substances which increase the coagulability of the blood.

The patient should be kept on his back with **complete mental and physical rest.** Every active and passive movement must be avoided as far as possible. All forms of hydrotherapy must be stopped. The patient should not use the bed-pan or urinal, but should void his excretions in pads covering a draw-sheet. No food or drink should be given by the mouth. He may be allowed small pieces of ice to allay thirst. A large **ice-bag** should be applied to the abdomen. **Opiates must be given with caution.** Perforation and hemorrhage are frequently associated complications. Opium masks the pain and other symptoms upon which the diagnosis of perforation depends, and this grave accident may be obscured until the favorable time for surgical treatment has passed. *When the patient is very restless* the necessary quiet may be obtained by the **hypodermic administration of morphin.**

Astringents by the mouth are probably without value and they now are little used in the treatment of internal hemorrhage. **Turpentine,** advocated by Murchison, 10 minims (0.6 c.c.) given in an emulsion every four hours, may be of use in adynamic cases. **Adrenalin** has a selective action upon the splanchnic area, powerfully constricting the vessels. Its use has been strongly advocated by Forchheimer and others. It should be given by hypodermic injection, 1 c.c. (16 minims) of the 1-1000 solution, or the same quantity diluted with 500 c.c. (17 fluid ounces) of normal saline, by hypodermoclysis. The possibility of increasing the bleeding by the rise in general blood pressure which it causes, before time is given for its local constrictive action, should be borne in mind.

The salts of calcium increase the coagulability of the blood. **Calcium lactate** is the preferable salt, given in doses of 20 to 40 grains (1.3 to 2.6 grams) every four hours. **Injections of blood serum** are sometimes of value. A number of preparations containing **thromboplastin** are put out by manufacturing chemists. They all markedly reduce the coagulation time of the blood. Prompt action may be obtained from them by subcutaneous or intravenous administration.

In profuse hemorrhage, when the patient is in collapse and life is threatened, stimulants must be given even at the risk of further bleeding. **Brandy, champagne, camphor and strychnin** are valuable. The alcoholic stimulants are of particular value because of their food content and their feeble action on blood pressure. **Normal saline administered by the drop method or by hypodermoclysis,** in quantity just sufficient to lift the patient out of the collapse, is sound treatment. **Transfusion of blood** will save life when other measures fail. The perfection of the technic of the operation has made transfusion an easy and a safe therapeutic measure.

Food and water in small quantity should be begun on the second day after the cessation of the bleeding and gradually increased in quantity.

The feeding and bath routine in operation before the hemorrhage should not be reached until four or five days after the bleeding has stopped.

PERFORATION.—There is no medical treatment for perforation except measures to relieve pain. The complication is certainly fatal without surgical interference. **Surgical council should be called immediately** with the onset of symptoms suggestive of perforation, and the physician and the surgeon together should decide upon the advisability of operation. If the diagnosis is reasonably certain and an expert surgeon is at hand there is no alternative to immediate operation. If the symptoms are vague and the diagnosis doubtful, decision is very difficult. Many operations have been done for suspected typhoid perforation when no perforation was found. The death rate in these cases has been high, not from the operation itself, but from the grave condition of the patients at the time of operation. Of 19 such cases reported by Mitchell from the Pennsylvania Hospital, 8 recovered and 11 died. The exact diagnosis of perforation is so difficult, the danger of delay so great and the added risk from operation so small, that **exploration is justifiable if there is a reasonable suspicion that perforation has taken place.** Most authorities will agree with the opinion of Mikulicz, the first surgeon to operate for typhoid perforation, who said, "If there is suspicion, don't wait for an exact diagnosis; explore immediately for it is free from danger."

CHOLECYSTITIS.—**Rest, an ice-bag over the right upper quadrant, and anodynes to relieve pain** make up the medical treatment of cholecystitis. **Urotropin** in full doses, 75 grains (4.86 grams) or more a day, will inhibit the growth of organisms in the gall-bladder and may be given a trial. *Mild cases* with moderate fullness of the gall-bladder usually recover under **medical treatment.** *Severe cases* with great distention and marked local and general symptoms may require **cholecystotomy and drainage.** The operation is a dangerous one and should be advised only after full consideration. Perforation of the gall-bladder is a common accident in the severe cases and is uniformly fatal. Keen is "decidedly of the opinion that in distention of the gall-bladder prompt surgical interference is the best. It is far better to prevent perforation than to remedy it after it has occurred."

Nervous Symptoms and Complications.—Severe nervous symptoms are manifestations of toxemia and are much less frequently seen in patients who are well fed and systematically bathed.

HEADACHE.—Headache may be severe in the first week of the disease. It usually is softened and made endurable by a **cold compress or ice-bag to the head. Bromid of sodium,** 30 grains (1.95 grams), repeated after an interval of three hours, may give relief. In exceptional cases an analgesic may be required. The temptation is great to administer one of the synthetic antipyretics, but for reasons already given this should be withheld if possible. Probably no harm can come from the administration of 5 grains (0.324 gram) of **pyramidon or phenacetin,** repeated in one hour if necessary. If this fails to give relief it is better to discard the antipyretic drugs and allay the pain with a **hypodermic**

injection of codein, ½ grain (0.032 gram), **or morphin,** ⅛ grain (0.008 gram).

INSOMNIA.—Insomnia is best overcome by the **bath treatment.** A cool or tepid tub bath at eight or nine o'clock in the evening will usually give a few hours of sleep. This should not be disturbed and the nurse should be instructed to time the administration of food and other attentions so as to give the patient **as many hours of sleep at night as possible.** When the wakefulness is persistent one of the hypnotics may be given: **trional**—10 to 15 grains (0.65 to 0.97 gram), **veronal** or **medinal**—5 to 10 grains (0.324 to 0.65 gram), or **morphin**—¼ grain (0.016 gram), hypodermically. In the insomnia of adynamic states, one-half to one ounce of whiskey or brandy often acts well.

DELIRIUM.—Delirium is controlled in the same manner as insomnia. **A tepid or cold bath and ice to the head** have a decided sedative influence. **Veronal**—2 grains (0.13 gram), every four hours, **or pyramidon**—5 grains (0.324 gram) repeated in one hour, are useful. **Morphin hypodermically** will give these patients the rest that is absolutely necessary. *Violent delirium* may be quieted by **lumbar puncture** and the withdrawal of from 10 to 20 c.c. of spinal fluid. The delirious typhoid patient should never be left alone.

MENINGITIS.—Meningitis is a very grave complication of typhoid fever. **Lumbar puncture for diagnosis and treatment** is a most valuable measure. In meningismus and the serous form it may ward off a fatal result. The puncture may be repeated every second day.

Cole believes that in typhoid meningitis the **intraspinous administration of an antityphoid serum** is indicated, if the typhoid bacillus can be isolated from the spinal fluid, using the same technic that is employed in the serum treatment of meningococcus meningitis.

PSYCHOSES.—The delirium of the febrile stage may persist into convalescence and merge into a posttyphoid psychosis. The treatment of this condition belongs to the alienist. The mental disturbance is largely an exhaustion phenomenon and is to be treated by **supportive measures. High calory feeding during the febrile period** prevents the profound exhaustion so often seen in convalescence and the well-fed patient rarely shows persistent mental disturbance. Many cases can be treated at home, but *if the psychosis is prolonged and severe* **institutional treatment will be better.**

Circulatory Symptoms.—MYOCARDIAL WEAKNESS.—Myocardial weakness may be evident in the latter part of the febrile stage. When the blood pressure falls and the heart becomes rapid, weak and irregular cardiac stimulation is necessary. **An ice-bag over the heart** slows and strengthens ventricular contractions without the possibility of a drug reaction. **Strychnin** may be given: 1/40 to 1/20 grain (0.0016 to 0.0032 gram) every four to six hours. *In elderly patients,* alcoholic subjects and those who have been unable to take adequate food, **whiskey, brandy or wine** is a valuable stimulant. It is rarely necessary to give more than 6 ounces (178 c.c.) of whiskey or its equivalent in the twenty-four hours. A tablespoonful in hot sweetened water every three or four hours is

usually sufficient. *If the heart becomes progressively more rapid and feeble,* **digitalis** should be given. A standardized preparation in doses equivalent to 1½ grains (0.0974 gram) of powdered digitalis may be given every six or eight hours for two days and then the interval between doses lengthened to twelve hours. *In urgent cases* **the drug should be given hypodermically. Saline infusions,** 500 to 750 c.c. (17 to 25 1/3 fluid ounces) every six hours are valuable. In sudden and serious heart failure, **camphor, caffein or ether** may be given hypodermically and **aromatic ammonia or compound spirits of ether** by the mouth—½ dram (1.88 c.c.)—frequently repeated.

PHLEBITIS.—**Absolute rest of the affected limb** is necessary. It should be placed on a pillow slightly elevated, and all rubbing avoided. The leg may be **covered with cotton and lightly bandaged or kept wet with a lead and opium lotion.** An anodyne—**morphin hypodermically**—is often necessary to relieve pain. The leg must be kept quiet for at least a week after the acute symptoms have subsided, and for five or six weeks it should be little used. **An elastic fabric bandage or stocking** should be worn after the patient gets up and until the swelling subsides.

Respiratory Symptoms and Complications.—BRONCHITIS—PNEUMONIA—PLEURISY.—The mild bronchitis which is so common in typhoid fever requires no special treatment. Severe bronchitis, pneumonia and pleurisy are treated in the same manner as when these diseases are primary. **The bath treatment** is an important prophylactic of the hypostatic congestion which so frequently leads to pulmonary infection.

LARYNGITIS.—Ulcerative laryngitis may often be prevented, or serious results from it avoided, by **careful and persistent oral antisepsis.** If aphonia or dyspnea develop, **inhalation of benzoin** should be used. **A spray of adrenalin**—1-1000—may be used in an emergency to tide the patient over a period of danger. Whenever laryngeal obstruction is present an **early tracheotomy under local anesthesia is imperative.** Postponement of operation leads to chondrial necrosis with deformity, stenosis and loss of voice. "All lesions disappear as if by magic after an early tracheotomy" (Jackson).

Urinary Symptoms.—RETENTION OF URINE.—Retention of the urine is a symptom of importance and should be carefully watched for. It may occur early in the disease, before the patient has become accustomed to the use of the bed-pan or urinal. At this time it is usually nervous in origin and may be overcome by **hot compresses to the hypogastrium or hot rectal irrigations.** Later it is a manifestation of profound muscular debility. Overdistention favors infection, and if not readily overcome by the above applications the patient must be **catheterized.** This must be done by the physician, or at least by an expert attendant. The **strictest asepsis** is required and **urotropin** should be given **after the operation.**

BACILLURIA.—Typhoid bacilli may be recovered from the urine in from 25 to 30 per cent. of all cases of typhoid fever at some period of the disease. They appear in the third or fourth week or during convalescence. The organisms may pass through the urinary tract without causing any signs of inflammatory reaction, or a few pus cells in the urine

may indicate the presence of a mild pyelitis. Bacilluria or pyelitis yields readily to treatment by **urinary antiseptics.** If possible, **frequent cultures** should be made of the urine toward the end of the febrile period and the **administration of urotropin should be begun at once if bacilli are found.** In the absence of means to demonstrate bacilli, the urine should be frequently **examined microscopically and the antiseptics should be given if pus cells are present.** It is good practice to anticipate the invasion of the urinary tract and give urotropin in the third and fourth weeks in all cases. **Urotropin with acid phosphate of sodium,** 10 grains (0.65 gram) of each, may be given three times a day.

A persistent bacilluria or a pyelitis may yield to treatment by **a typhoid or colon vaccine.**

Glandular System.—Either typhoid bacilli or the pyogenic cocci may invade the various glandular organs and cause an inflammation that may go on to abscess formation. Parotitis, mastitis and orchitis are the most common. The application of **ice** is the most generally useful measure. Occasionally a **hot compress** will give more relief. *When suppuration occurs* **the treatment is surgical.**

Skin.—Bed-sores.—The treatment of bed-sores should be **preventive.** Both physician and nurse must assume a large part of the responsibility for the development of this complication. In certain profoundly toxic cases sloughing of dependent areas of skin may take place in spite of all precautions, but when bed-sores develop in cases of moderate severity it is evidence of careless nursing. Well-fed patients and those who are systematically bathed rarely have this trouble. **Frequent change of position** must be insisted upon. **Clean linen and a careful make-up of the bed** are essential. At least twice a day the **skin of the lower back and buttocks should be inspected and rubbed with alcohol.** Any areas of redness must receive special attention, and all pressure relieved from them by **ring cushions.** The suspicious areas should be cleansed with **soap and water,** bathed first with a **weak bichlorid solution,** and this followed with **alcohol,** and, finally, dusted with a **borated talcum powder.** For over-red and suspicious spots **ichthyol collodion** may be applied.

If an actual break in the skin takes place, the treatment should be that of indolent ulcers under other circumstances. **Perfect cleanliness, alcohol and zinc oxid ointment** will usually suffice to stimulate healing. When the edges of the ulcer are undermined it may be packed with **iodoform gauze, or with gauze moistened with balsam of Peru.**

Management of Convalescence

The convalescent typhoid patient must be carefully watched and his activities controlled until well after the end of the fever period. Experience with high caloric feeding shows that when it is possible to keep up an abundant diet during the febrile period, convalescence is shortened and the complications of this period made less frequent.

As a rule the patient should be **kept in bed for a week after the evening temperature becomes normal,** and he may then be allowed to

sit up and gradually get on his feet. A little overexertion or excitement is very apt to bring on a recrudescence of the fever and there is always the menace of true relapse resulting from it. Patients who have been kept on a low liquid diet throughout the course of the disease are very sensitive to diet changes, and **meat and other solid foods must be added with great caution.** Abundantly fed patients have little trouble in passing to a full diet soon after the fever has abated.

The possibility of hemorrhage and perforation is present during the convalescent period, and a **diet leaving little residue** after passing through the upper digestive tract **must still be adhered to. Cathartics must be withheld,** and a daily emptying of the lower bowel obtained by a **simple enema. A well refined liquid petrolatum,** one or two ounces a day, will often keep the bowels in good condition and replace the enema.

Other complications and sequelæ must be anticipated and promptly met. Secondary infections by the pyogenic organisms are not uncommon.

The patient is still a carrier. **Rigid care of the excretions** is demanded until repeated cultures from the urine and feces demonstrate that bacteriological recovery is complete.

Some degree of anemia is usually present and a tonic of **iron, quinin and strychnin** is of value.

The resumption of business requires caution. The patient's strength returns slowly and it may be two or three months before he is able to take up his former activities. **A period of rest away from home surroundings** will hasten his return to normal.

Recrudescence and Relapse

Any return of fever after convalescence has set in must be met by an **immediate return to the rigid rest and diet régime of the febrile period.** The bowels should be thoroughly emptied by an **enema** and the food reduced to the **blandest fluids** for a day or two.

True relapse is a re-infection and demands the **same treatment in all its details as the original attack.** Tubbing is, however, rarely required, although it may be necessary in severe cases. Usually milder hydrotherapeutic methods are adequate.

Treatment of Typhoid Fever in Infancy

In the infant the adjustment of the diet in typhoid fever is comparatively simple. Briefly, it is the adjustment of a milk formula to suit the impaired digestion of the sick infant.

During the first and second weeks the formula which the child was taking at the time of the onset of the infection reduced 25 per cent. or 50 per cent. will be suitable. Whole milk diluted with one or two parts of a 5 per cent. milk sugar solution will usually be well taken. The cereal gruels may be added later and the caloric content of the formula increased by a higher percentage of milk-sugar. The protein content and caloric

value of each day's feeding should be recorded and an effort made to keep the food value as near the normal requirement as possible. **Malted or dextrinized cereal foods** can often be advantageously used **as additions to the milk formulas. Fermented milk or whey** may be useful if the stomach is irritable. **Beef juice, fruit juices and broths** are not so well borne but are occasionally helpful. During the period of intestinal irritability the **milk may be sterilized** by a short exposure to the boiling temperature. **An abundance of water** should be given.

Stimulants are rarely required in typhoid fever in the young child. In the third week of the disease, when nutrition is failing and the heart action is weak, the addition to the food of from 1 to 4 drams (3.75 to 15 c.c.) of **brandy** in the twenty-four hours may be of distinct advantage. Each dram of brandy will give an additional value of fourteen calories to the food and it may be taken and assimilated when an adequate amount of other food cannot be given. **Strychnin, digitalis and other drug stimulants are of doubtful value.**

Diarrhea is present in about one-half of the cases and, when the movements exceed three a day, will require correction. **Bismuth subcarbonate**—4 grains (0.26 gram)—**in chalk mixture**—1 dram (3.9 grams)—will best control it. It is best administered after each bowel movement. Given in this way the frequency of dosage is automatically regulated by the varying requirements of the patient's condition. **The occasional addition** of 5 to 10 minims (0.3 to 0.6 c.c.) of **paregoric** to this prescription may be necessary. It is particularly beneficial if the movements are frequent and accompanied by abdominal pain.

Constipation will require attention. **A routine cathartic** is usually given **before the diagnosis is made,** and further administration is unwise. The lower colon should be thoroughly emptied each day by **irrigation with a simple enema.**

For the control of *high temperature,* **hydrotherapy** is the most effective. **Antipyretic drugs must be avoided. A bath may be given every four to six hours** if the rectal temperature is 103° F. (39.4° C.) or over. **A tepid sponge may be efficient but the best results are obtained from the full bath.** The full bath is easily given to the infant. The water should be at a temperature of 100° F. (37.8° C.), and the bath continued with **gentle friction** for eight to ten minutes. The cooling of the water that will take place during the bath is all the reduction that is necessary. When nervous symptoms are marked, even a higher temperature of the water—up to 105° F. (40.6° C.)—may give better results and be followed by quiet and a moderate reduction of temperature. Infants do not endure the cool bath well, and a bath at a temperature of 90° F. (32.2° C.) often leaves the child prostrated with a cold, blue skin and a weak pulse—a result that cannot but be harmful. *For marked nervous symptoms,* in addition to the bath as above directed, **bromid of sodium,** 2 to 4 grains (0.13 to 0.26 gram) **in syrup,** may be given.

The treatment of the *period of convalescence* is chiefly a problem in infant feeding and requires the careful adjustment of the food to the

nutritional requirements of the infant and its ability to digest and assimulate it.

PROGNOSIS

Cause of Death.—Death in typhoid fever results from (1) the intensity of the toxemia; (2) severe localization of the infection; and (3) complications and sequelæ.

All of the organs and tissues suffer from the lethal effects of the typhoid toxin. The heart, the vasomotor and heat regulating mechanisms, and the nervous system are most conspicuously influenced. The effect upon mortality of the individual localizations and complications is considered in detail in another section.

In 580 fatal cases reported by Curschmann from Hamburg and Leipsic 46.9 per cent. died of toxemia, and 53.1 per cent. died of localizations and complications. Perforation, hemorrhage, pneumonia and nephritis were the causes of death in 241 of the latter group of 305 cases. In this country at the present time the disease is certainly less virulent. Elsner, from a careful study of available autopsy findings, places the mortality rate from toxemia at 24 per cent. Writers generally estimate that toxemia is responsible for about one-third and complications for about two-thirds of the fatalities.

Mortality.—The case mortality rate of typhoid fever generally accepted at the present time is about 10 per cent. Statistics from many sources give rather wide variations from this figure.

The death rate of typhoid fever in New York City for 1917 in 1,442 reported cases was 15.8 per cent. The average annual mortality from 1908 to 1917 in a total of 28,083 cases was 15.18 per cent. This probably fairly represents the mortality in a large number of cases of all ages and conditions, under varying epidemic influences, and treated by a variety of methods, and of sufficient severity to be recognized and reported. It is quite certain that many mild and atypical cases which recovered are not included in these figures.

The mortality of hospital-treated cases varies from 7 to 22 per cent. Of 21,371 cases admitted to the hospitals of the Metropolitan Asylum Board of London over a period of thirty-six years, 16.3 per cent. died. The mortality in Osler's wards at the Johns Hopkins Hospital was 9.1 per cent. In private practice the mortality is probably lower, from 5 to 12 per cent.

Factors which influence the mortality of the disease and are valuable guides to prognosis are (1) the age of the patient; (2) the type of the prevailing outbreak or endemic; (3) the severity of special symptoms; (4) the presence of complications; (5) the treatment; (6) antityphoid vaccination.

Age.—After the period of infancy and childhood there is a steady increase in the mortality percentage of the disease. In infancy it is about 20 per cent. The lowest rate, from 6 to 7 per cent., is between the ages of five and ten years. From ten to twenty-five years of age the

tality is increased slowly from 8 or 9 to 10 or 12 per cent. At forty years the rate is from 18 to 24 per cent. After the age of forty years the disease has a very grave prognosis, with a death rate of from 25 to 35 per cent.

TYPE OF PREVAILING OUTBREAK.—The mortality varies greatly in different communities and in different epidemics and endemics in the same community. The type of the disease will be virulent in one section and mild in another. Sudden outbreaks in districts previously free from typhoid often show a high mortality. The disease is also apt to be more fatal at the beginning of an outbreak. In certain years serious complications are common.

SEVERITY OF SPECIAL SYMPTOMS.—Except in infants and young children a pulse-rate persistently above 120 is cause for apprehension. In exceptional cases, women and nervous men have a rapid pulse from the onset of the disease, without other symptoms of gravity. Persistent temperature above 104°F. (40°C.) indicates a severe infection, and repeated elevation above 105°F. (40.6°C.) without marked remissions adds to the gravity of a case. The outlook is serious when high fever continues through the third and fourth weeks. Severe diarrhea and meteorism are common in some outbreaks, and increase the mortality rate. Cases with marked nervous manifestations are serious. Liebermeister observed a mortality of over 50 per cent. in cases with early and severe delirium and of about 70 per cent. in cases with continued stupor and coma.

COMPLICATIONS AND SEQUELÆ.—Any complication, however mild, affects the prognosis unfavorably. It tends to prolong the illness and favors the development of other complications.

INFLUENCE OF METHODS OF TREATMENT.—It is difficult properly to evaluate a method of treatment in typhoid fever, which varies so widely in severity from year to year and in different epidemics, without the observation of a large number of cases extending over a long period. Available evidence of this kind is strongly indicative that the **bath treatment** has very favorably influenced the mortality. The statistics of the Brisbane General Hospital, Queensland, reported by F. E. Hare, are convincing. In 1,828 consecutive cases treated by the expectant method during the years 1882 to 1886 the mortality was 14.8 per cent.; 1,902 consecutive cases treated with cold and tepid baths during the years from 1887 to 1896 showed a mortality of 7.5 per cent. Equally satisfactory results have been obtained in a number of the hospitals of this country and Europe. It can be confidently stated that the treatment of typhoid fever as carried out in well-equipped modern hospitals is an important factor in the reduction of the mortality.

ANTITYPHOID VACCINATION.—Typhoid fever, when it occurs in individuals who have been vaccinated, pursues a much milder average course than it does in unvaccinated patients, and complications are very much less frequent and fatal. The recently published report of Webb-Johnson of the British Army shows the influence of vaccination on mortality and on the incidence of complications. In 297 cases of typhoid fever, unvaccinated, the mortality was 57, or 19.19 per cent. In 821 cases, vaccinated, the mortality was 27, or 3.28 per cent. In the unvacci-

nated group complications occurred in 35.69 per cent.; in the vaccinated group in 7.55 per cent. The experience of Vaughan in the American Army in France (*see* p. 578) does not bear out these favorable results.

Mode of Death.—Sudden death takes place in from 3 to 4 per cent. of the fatal cases. In Osler's series of 137 fatal cases there were 4 sudden deaths. It occurs more frequently in men than in women. It is an accident usually of the third week, more rarely of convalescence. Autopsy findings are inadequate to explain the fatal result in about one-third of the cases. Cerebral anemia and reflex syncope have been given as causes. In the remaining cases with positive autopsy findings, acute myocarditis, pulmonary embolism and thrombosis and cerebral embolism are the conditions that have been found.

Incomplete Recovery.—Typhoid fever is a serious disease, aside from its high immediate mortality. The weeks of bacteriemia with high fever and profound toxemia gravely impair cell-function and may leave the patient in a state of prolonged or permanent ill health with disabling pathological conditions and a decided curtailment of longevity. Many of the complications result in permanent damage to structure and function, or initiate chronic infective or degenerative diseases which are remote causes of death. The effect of typhoid fever on the mortality of recovered cases was studied by Dublin from the data of a life insurance company. Fourteen hundred and twenty-eight cases of recovered typhoid were investigated. Of this number 54 died during the first three years following recovery. The expected mortality of this group was 26.

Among the important disabling sequelæ are the following: a state of permanently deranged metabolism, the patient never regaining his former trophic level; gall-stone disease and chronic intestinal catarrh; chronic laryngeal obstruction from ulceration and necrosis; pulmonary tuberculosis and pulmonary abscess; chronic myocarditis, arteriosclerosis and thrombophlebitis; chronic renal or bladder infection; hemiplegia; incurable psychoses and degenerative brain and cord lesions.

PATHOGENESIS AND TISSUE CHANGES IN TYPHOID FEVER

We have the following questions to consider:

(1) The manner in which the typhoid bacillus enters the body.
(2) The cause of the general reaction to the infection (fever).
(3) The tissue injury and tissue reactions which result.
(4) The manner of elimination and healing.

As to the first of these, the portal of entry is only approximately known. The typhoid bacillus as shown in the section dealing with Etiology is taken into the mouth from some one of the many sources, and gains entrance to the tissues somewhere in the gastro-intestinal tract. There are no adequate data fixing any particular part of the gastroenteric tract as the point through which the *Bacillus typhosus* gains entrance to the tissues. Indeed, there is no reason whatever for believing

that some one place is to be sought for rather than several loci. Suggestive facts exist favoring the tonsils and pharynx, the intestinal epithelium, and the lymphoid tissue of the intestine as occasional portals of entry.

It is certain that the typhoid bacillus does not multiply to any extent in the intestinal tract. The few bacteria taken into the mouth at the time of infection do not increase in the gastro-enteric tract, but first gain entrance to the body proper and are later eliminated into the intestine. The general assumption that gastric juice will kill typhoid bacilli is not strictly correct, since it has been shown that moderate acidity does not sterilize the *Bacillus typhosus* (Kitasato). The typhoid bacilli which we cultivate from the intestinal tract in cases of typhoid fever do not represent bacteria which have been taken into the mouth at the time of infection and which have multiplied in the gastro-enteric tract, but they are bacilli that are being eliminated from the blood and tissues by way of the intestines.

It is frequently assumed that the portal of entry is the lymphoid apparatus, particularly the Peyer's patches in the ileum, because here we usually find the most characteristic anatomical changes of the disease. The fact that the Peyer's patches are injured points rather to the intestinal lesions as the result of the susceptibility of lymphatic tissues to injury by the typhoid bacillus. The changes in the lymphatic apparatus are probably a result of the invasion of the body as a whole by the typhoid bacilli rather than a door through which they enter the body.

The typhoid bacillus gains entrance to the gastro-intestinal tract through the mouth. Somewhere in the course of its passage toward the anus it is absorbed into the lymphatics and thence passes on to the regional lymph-nodes. This may be anywhere from the tonsils or pharynx to the sigmoid, but certain considerations make it probable, if not certain, that the usual portal of entry is found in the last few feet of the ileum. The relative stasis in this part of the bowel compared to the upper portions is well known, and the richness of the lymphatic apparatus and other considerations point to this portion as that especially differentiated for absorption. The fact is that the mesenteric nodes draining this region show the earliest anatomical injury in typhoid infection. The question of broken or unbroken epithelium is purely academic. Injury to the intestinal mucosa has never been shown to be necessary, and moreover the ease with which leukocytes can pass in and out of an uninjured mucosa shows that the entrance of an active organism like the typhoid bacillus might be determined by the chemotactic conditions present, and not by the presence or absence of an actual hiatus in the tissue. There is abundant evidence in the respiratory as well as in the gastro-enteric and genito-urinary tracts that unbroken epithelium of mucous membranes is not a barrier to the entrance of bacteria, but that the ability of an organism to gain entrance into these localities depends upon the specific properties of the organism itself.

Having entered the lymphatics, the bacillus is filtered out by the

regional lymph-nodes. Thus the mesenteric nodes are the first tissues to be subjected to the effects of the typhoid bacillus after it has gained entrance into the body.

The most significant fact in the pathogenesis of typhoid fever is the predilection the typhoid bacillus shows for the lymphatic apparatus. The organism multiplies in the lymph-nodes, spleen and bone-marrow as well as in the bile. From the first three of these localities it gains entrance to the blood. There is no evidence that it multiplies in the blood stream; on the contrary, it is rapidly destroyed. Even the blood of a normal individual has considerable ability to kill typhoid bacilli, and in an infected individual during the course of the disease this bactericidal power of the blood increases markedly.

It is probable that the entrance of the bacillus through the gastro-intestinal tract, the invasion and multiplication in the lymph-nodes, and the "overflow" into the thoracic duct and blood stream all take place during the incubation period of the disease, before the patient is sick. In other words, the bacteria could be recovered from the mesenteric apparatus and blood stream before the appearance of the first symptoms of typhoid fever.

Typhoid fever is best designated as a bacteriemia, in that the bacteria are present during the course of the disease in the characteristic foci mentioned above, and also in the blood stream.

The general reaction to the infection, that course of clinical events which we call typhoid fever, does not commence until the organism is well entrenched in its various foci. The bacteria, by their presence, set up various phenomena in the host which, taken together, constitute the clinical manifestations characteristic of the disease.

The fever is undoubtedly caused, as Vaughan has shown, by the poisons liberated from the bacilli as a result of their disintegration. According to Vaughan the invading organisms are to be considered as foreign proteins. They stimulate by their presence the production on the part of the body-cells of substances which digest them and prepare them for assimilation into the tissues. It takes a certain time for the body-cells to become proficient in the manufacture of these substances (ferments?), and this time is represented by the incubation period of the disease. One of the end-products of the disintegration of the bacterial protein is a poison, and this, by its constant production in small quantities, causes the fever. In addition to this specific bacillary poison, toxic substances are undoubtedly liberated from the injured and necrotic foci in the lymphoid apparatus and bone-marrow, and in addition to these we have the whole train of metabolic and mechanical results produced by high fever. These effects will be referred to in connection with the specific changes produced in the various organs. The practical questions which arise from the consideration of Vaughan's views regarding the fever as the result of the reaction between immune bodies and the infecting organism are very important and are dealt with in the discussion of the therapeutic use of vaccines and of the products of the typhoid bacillus.

Tissue Changes—Morbid Anatomy.—GENERAL.—A superficial inspection of the body presents no appearances characteristic of typhoid fever. The rose spots disappear after death. There is more or less emaciation, depending upon the length of the illness. Cases autopsied after long illness may show special appearances due to complications: parotitis, arthritis or decubitus. Rigor mortis is well developed.

MUSCLES.—Zenker first described the characteristic "fish flesh" transformation of the muscles known as Zenker's necrosis. The change is found only in the more severe cases in which there has been high and prolonged fever. The rectus abdominis and muscles of the thigh are most often affected. In the gross this waxy degeneration gives a whitish, waxy appearance to the sectional muscle, which has been compared to fish flesh. Microscopically the muscle-fibers are found under these conditions to have lost their striations, and their ability to take acid stains uniformly. The muscle-protoplasm is collected inside of the wrinkled sarcolemma in pale, irregular lumps. There is frequently rupture of the capillaries between the fibers, giving rise to small hemorrhages. Occasionally these hemorrhages are larger, and at autopsy we have found diffuse suggillations of blood involving the muscles, and loose areolar tissues of the whole lower half of the abdominal wall. These muscle changes, Zenker's necrosis and hemorrhages, are not confined to typhoid but are found more frequently in this disease than in others.

GASTRO-ENTERIC TRACT.—The upper portions of the tract are relatively little affected. In cases of long standing, ulcerations of the pharynx and esophagus are sometimes found. These are usually small, indolent ulcers, seldom over 1 cm. in diameter, and with very little reaction around their margins. Their etiology is not clear. They are not specific lesions of typhoid, but are usually classed along with ulcers of epiglottis and laryngeal structures as "cachectic ulcers."

No changes are found in the stomach or duodenum which can in any way be referred to typhoid fever.

The small bowel, in cases uncomplicated by perforation or hemorrhage, is usually collapsed and fairly empty. On opening the lumen of the bowel we find the upper portion fairly normal or moderately congested. As the lower jejunum and ileum are approached the agminated follicles or Peyer's patches are found to be swollen and raised above the surface of the mucosa. At first they have a pinkish color by reflected light, but a little lower down we find them more swollen and presenting a blanched appearance. These represent the early intestinal lesions of typhoid. Since the earliest systematic descriptions by Chomel and Louis the progress of the intestinal lesion of typhoid fever has been divided into four stages corresponding roughly to the four weeks of the ordinary disease course:

(1) *Stage of Swelling of the Peyer's Patches.*—Our knowledge of the mechanism of production of the characteristic typhoid lesion is due to Mallory. During the first week the lymphoid tissue, solitary, agminated follicles and Peyer's patches become swollen and project above

the surface of the mucosa. The Peyer's patches appear as oval plaques extending lengthwise of the bowel. The solitary follicles, imbedded more deeply in the mucosa, may not be apparent, or may project beyond the mucosa as pedunculated points. Examined microscopically at this stage we find the swelling to be due not so much to lymphoid hyperplasia in the strict sense—although the lymphocytes are increased in number—as to the accumulation in the lymph-follicles and in the reticulum and sinuses of large mononuclear macrophages. These cells have an abundance of light-staining protoplasm and pale recticular nuclei. In many of them are found red-cells, lymphocytes and tissue débris. They are variously designated as endothelial leukocytes (Mallory) and as mononuclear wandering cells. Whether they have a specific origin from endothelium by proliferation of the lining cells of the lymph- and blood-spaces, or whether they represent a form of undifferentiated mesodermal wandering cell or polyblast (Maxinow), has not been satisfactorily settled.

The macrophages pack themselves so tightly in the sinuses and tissue-spaces that the lymphoid tissue is to a degree destroyed by them, so that in a well-developed lesion the lymphocytes only appear in patches. The normal structure of the lymph-node is destroyed, and the patch consists of a dense mass of these large mononuclear cells with relatively few lymphocytes. This is the stage of greatest swelling, and the swelling is due not only to the increase in the cell-content of the patch, but also to the edema which develops in the tissue, due to the local circulatory disturbance. This local circulatory disturbance arises from occlusion of the blood-vessels which nourish the lymphoid tissue, and is due in part to the external pressure on the capillaries exerted by the closely packed macrophages, in part to plugging of the vessels themselves by the large mononuclears loaded with tissue débris, and in part to minute thrombi (Mallory), due to the endothelium of the capillary being lifted up by the accumulation of cells and fibrin beneath.

(2) *Stage of Necrosis.*—This vascular occlusion leads to anemic necrosis of the patch, with the formation of a slough. While in the gross the lesion seems well confined to the lymphoid tissue, microscopically it is evident that the wandering cells are numerous outside the Peyer's patch. The necrosis in the severer grades often extends beyond the lymphoid tissue limits laterally into the mucosa, and deeply to the muscularis or even to the peritoneum.

At the height of the stage of swelling in a mild case resolution may occur before the slough forms, and the tissue be restored to normal by the disappearance of the wandering cells. More frequently the patch undergoes necrosis as a whole or in part, and the slough forms. At this stage we may find the pale, white, swollen and felt-like patch becoming a dirty brown color, due to the imbibition of bile, or one of various shades of mottled, dark red or slate color, due to small hemorrhages. When the patch does not undergo necrosis as a whole but only in small, pit-like areas, probably corresponding to the lymph-follicles around a central vessel, we get the appearance described by Chomel as "plaques

à surface réticulée." Up to this stage the microscopical appearance of the lesion is unique, in that practically no polymorphonuclear cells are involved in the process. The typhoid bacillus, and whatever poisons are liberated from it throughout the body, tend to depress the usual polymorphonuclear inflammatory reaction. This is true of the lesions elsewhere in the body as well as of those in the intestine. Even secondary infections, usually accompanied by active leukocytosis, are able in the typhoid patient to stimulate only a feeble response. As the tissue of the area dies, a moderate collection of polymorphonuclears occurs at the margin between the necrotic and the healthy tissue. These begin to liberate leukoproteases that digest the coagulated lymph and dead cells and cause the slough to begin to separate. This usually occurs around the edge when massive necrosis of the patch has occurred, so that we find the edges loosening from the healthy tissue and curling up or rolling under. The separation gradually works toward the center, and finally the dead slough separates entirely, leaving the ulcer.

(3) *Stage of Ulceration.*—The fact that tissue beyond the margin of the patch has been involved in the process is most evident at this stage, when the slough separates and leaves a more or less irregular ragged area extending well beyond the limits of the original Peyer's patch. Sometimes the ulceration is very superficial, including only the upper layers of the mucosa, and leaving some lymphoid tissue and epithelial crypts. But the usual typhoid ulcer extends down to the muscularis, leaving a fairly clean floor covered with a thin gray exudate and a few shreds of fibrin. Often the whole patch does not undergo necrosis but the slough separates in several larger or smaller areas, leaving irregular ulcers connected with narrow passages and separated by bridges of still intact mucosa. The ulceration is more extensive toward the last few inches of the lumen. It is not uncommon to find the last six or twelve inches a mass of confluent ulcers with bridges of mucosa left in their midst.

(4) *Stage of Healing.*—The typhoid ulcer is unique in its ability to heal without scar-tissue contraction and consequent disturbance of bowel function. There is apparently a complete restitutio ad integrum. The lymphoid tissue regenerates, and is covered in by epithelium without increase in fibroblasts and their usual hyaline transformation to scar-tissue, so that after the healing of a typhoid ulcer we find perhaps at the most an atrophy of the submucosa, causing a slight depression and some increased pigmentation. The colon is moderately involved, according to Murchison, in one-third of the cases. The solitary lymph-follicles show numerous ulcerations. These are more apt to occur or to be more numerous in the cecum. Sometimes a special form of typhoid, *colotyphus,* is recognized in which the ulceration of the colon overshadows that of the ileum, or is confined to the colon. The ulcerations are said to be large, with their long diameters lying transversely of the gut. Cases with extreme gaseous distention and meteorism with multiple perforations in the bowel have been recorded by Kaufmann. Excessive

growth of the lactic acid bacillus has been found in these cases, accounting for the excessive gas.

The important complications of the intestinal lesions are perforations and hemorrhages. The hemorrhages occur from erosion of the exposed vessels of the area at the time of the separation of the slough. Perforations the size of pin points are found at the base of a small, deep ulcer, or in a larger area they may be even a centimeter across, at the base of a large ulcerated area. Excessive peristalsis probably plays a rôle in the formation of the larger perforations. Observed from the peritoneal side, the ulcer always has a blue black or dark red, mottled, discolored margin. This is important, in view of the fact that perforations are sometimes reported which are the result of postmortem rough handling of the intestinal coils on the part of the prosector. There is very little reaction by the peritoneum and omentum after perforation does occur. The slight exudate is thin, grayish and watery. There is no well-marked plastic exudate firmly gluing the coils of the intestine together, but only the appearance of a few fibrin flakes in the exudate. It is important to remember that although perforation usually occurs in the last twelve inches of the ileum it may appear higher, and that it may be in the appendix or large bowel and is not infrequently multiple in any location.

Hemorrhage.—After death from hemorrhage a large amount of unclotted blood may be found in the bowel. The bleeding vessel cannot be found. Sometimes clots may be detached from the base of one or several ulcers. A hemorrhagic form of typhoid is sometimes recognized in which multiple hemorrhages in the skin and mucous membranes occur.

Lymphatic System.—The swelling of the mesenteric lymph-nodes is probably the earliest lesion of typhoid fever. Usually the nodes draining the last few inches of the ileum are most involved; they may become very large, representing in the aggregate a mass as large as an orange. In the gross they are gray, pale pink or slate colored. On section they are moist and softened, showing small areas of liquefaction necrosis. They may break down entirely and rupture into the abdominal cavity, giving rise to the indolent low grade peritonitis characteristic of typhoid perforation. The lymph-nodes in other portions of the body usually present no appreciable gross swelling. Microscopically the lesion in the mesenteric nodes is identical with that in the lymphoid tissue of the intestine. The lymphoid structure and surrounding tissue becomes packed with mononuclear macrophages and small areas of liquefaction necrosis occur from vascular occlusion. The other lymph-nodes of the body show a moderate sinus catarrh. The number of macrophages escaping from the intestinal lymphatic apparatus into the thoracic duct and thus into the venous circulation may be so great as to cause small pulmonary emboli, as in the case reported by MacCallum. Hemorrhages into the substance of the lymph-nodes are common.

Spleen.—Acute splenic tumor in typhoid is quite constant. The organ weighs from 600 to 900 grams (19.3 to 28.9 ounces) and is so extremely soft that it seems to flow and flatten out on the table when

removed at autopsy. On section the pulp oozes and flows out of the capsule in the form of a thick, reddish brown paste, and the Malpighian corpuscles are scarcely recognizable. Microscopically we find the characteristic macrophages and a pathology similar to that in the lymph-nodes and intestine, with the addition that the organ is extremely engorged with red blood-cells. A very large proportion of the macrophages are engorged with red-cells and with crystals and amorphous masses of blood-pigment. The spleen may rupture, resulting in a fatal hemorrhage. Focal necroses occur within the spleen as in the lymph-nodes, and large necroses beneath the capsule (infarcts) are not uncommon. Cases autopsied late in the disease, after a long illness, may show no enlargement of the spleen. The organisms tend to disappear from the spleen as the agglutinins rise in the blood, and the spleen tends to decrease in size as the disease progresses to a favorable conclusion. It is said that there is a relation between the persistence of the splenic tumor and relapse.

Blood and Bone-Marrow.—The most distinctive finding in the blood is the leukopenia. The white count after the first few days, during which there may be a mild leukocytosis, seldom above 12,000, shows a decrease to 4,000 or even less. This decrease is due to a falling off of the polymorphonuclears and to the practical disappearance of the eosinophils. There is a relative increase in the lymphocytes, and especially in the large mononuclear cells. Late in the course there is usually a severe anemia. A hemorrhagic diathesis may develop, and a decrease in the number of platelets is said to occur. Typhoid bacilli are more or less constantly present throughout the course of typhoid fever. They are present in greater numbers during the first week, and their cultivation from the blood serves as the best method now known for early diagnosis. The bone-marrow has been shown by Longcope to undergo characteristic changes in typhoid. In general these are analogous to those in the lymph-nodes and in the spleen, with the addition that the specific marrow elements are affected. There is marked invasion of the sinuses, with the characteristic macrophages. These are found to be actively phagocytosing red-cells and tissue detritus. Many focal necroses occur, containing dead cells and fibrin. According to Mallory, these focal necroses represent the end-result of the characteristic typhoid reaction, a so-called "typhoid nodule" consisting of aggregations of endothelial leukocytes (macrophages). The lymphocytes are apparently increased in number and the myelocytes are distinctly reduced. The reduction in these elements explains, of course, the decrease in number of the neutrophil and eosinophil polymorphonuclears in the circulating blood. This depression of bone-marrow function is such that the intercurrent peritonitis which develops after perforation usually fails to bring out a leukocytosis, and other intercurrent infections like pneumonia may fail to raise the white count above seven or eight thousand. The aneosenophilia may be of diagnostic value, as was pointed out by Thayer. As recovery is established, the leukocyte count and number of eosinophils return to normal.

Gall-bladder.—The bacteria reach the gall-bladder very early in

typhoid fever, and remain for an indefinitely long period. Gay and Claypole, confirming work done by Chirolanza, showed that typhoid bacilli might be isolated from the gall-bladder within half an hour after intravenous injection of typhoid bacilli, even when the cystic duct was tied. The gross pathology caused by the presence of typhoid bacilli in the gall-bladder is usually not great during the course of the disease. The importance of the gall-bladder in this fever is rather in relation to the carrier condition and to later attacks of cholecystitis with gall-stones. There is usually a mild degree of catarrhal inflammation throughout the cholangenic system during the course of the disease. This may be so severe as to cause the disease picture to be ushered in by gall-bladder pain and jaundice, with a chill. But usually the gall-bladder inflammation leads to nothing more distinctive than occasional pains in the upper right abdomen, which tend to abate as the disease progresses. Purulent cholecystitis with leukocytosis may occur. Typhoid fever must be admitted to the first rank of those diseases which have a definite etiological relationship to gall-stones.

The liver presents characteristic changes. It is usually enlarged, swollen and cloudy on section. Microscopically, the characteristic "typhoid nodules" are found, which have been differently designated as "lymphomata" and as "focal necroses." It is easy to convince oneself that both of these latter appellations apply to different stages of the same lesion.

One observes many small miliary collections of cells somewhat resembling miliary tubercles, which are found to consist of large numbers of the characteristic macrophages or endothelial leukocytes crowding the sinuses between the cell-cords. These macrophages are filled with phagocytosed red-cells and cell-detritus, or are free of other material and actively dividing. They enclose and push aside cords of liver-cells and finally become so dense that they break down themselves and are replaced by tissue-detritus and fibrin. The question as to whether these areas represent mechanical plugs of macrophages swept in by the portal circulation, or whether clumps of bacteria or their poisons attract them, is not clearly settled. The authors believe that they represent local reactions to the actual presence of bacilli, as in the case of the miliary tubercle. The difficulty in demonstrating bacilli in such lesions in tissue sections is well known. Besides these nodules we find the individual liver-cells to be swollen and edematous, with granular, vacuolated and fat-containing protoplasm and pale-staining nuclei. Around the portal vein in the lymphatics and diffusely throughout the connective tissue of Glisson's island we find wandering macrophages.

Heart and Blood-vessels.—There are no specific changes in the heart. The heart-failure occasionally assigned as a cause of death is to be referred to degeneration of the myocardium. Endocarditis is rare, though vegetative lesions containing typhoid bacilli have been found. Pericarditis is also rare, and when found is usually part of a complicating intercurrent infection like pneumonia or pleuritis. The myocardium presents no characteristic changes, although a great variety of

lesions have been described in individual cases. The heart-muscle is usually soft, flabby, and dark brown in color, and somewhat mottled, due to fatty changes. Microscopically we find marked brown atrophy evidenced by collections of brown pigment at the extremities of the muscle-nuclei, more or less accumulation of fine, fat droplets within the muscle-cell, albuminous granules and increase of fluid. Frequently none of these changes can be demonstrated. Interstitial myocarditis, with marked infiltration with round cells and multiple miliary abscesses, has been found.

The blood-vessels are not infrequently attacked, probably because of the general tendency of the typhoid infection to affect endothelial cells and tissues. Thayer has described early arteriosclerosis as an important concomitant of typhoid fever, but this is probably as common in other severe infections as in typhoid. The growing conviction that arteriosclerosis is in large part a result of repeated infections of various types might be pointed out in this connection. Active arteritis with autochthonous thrombus formation, especially of the smaller vessels, is an occasional accident. Most frequently these occur in the extremities, ear and parotid gland. Thrombosis is more frequent in the veins, especially in the left femoral, leading to phlegmasia alba dolens. Naturally the prognosis is much better in the cases of venous thrombosis than in those of arterial occlusion.

Respiratory System.—Ulcers of the larynx occur not uncommonly in the later stages of the disease. They are found at the base of the epiglottis, in the posterior portion of the vocal cords, and in the aryepiglottidean folds. The cartilage may be involved. It is not clear that they represent specific lesions as in the case of the ulcers of the intestine. Diphtheritic laryngitis and tracheitis are rare findings.

The lungs present several types of lesion. There is a form of lobar pneumonia which occurs in cases with pneumonic onset and the physical signs of pneumonia, which probably represents an early localization of the typhoid bacillus in the lung, the so-called "pneumotyphoid." Later in the disease, lobar pneumonia may also develop, either from the typhoid bacillus, which is rare, or due to secondary invasion by the pneumococcus. The cases due to the pneumococcus are said to show a characteristic hemorrhagic type of lesion. This is an interesting observation, in view of the fact that a hemolysin has been isolated from the typhoid bacillus; but hemolysis does not play an important rôle in ordinary typhoid fever.

Lobular pneumonia due to terminal mixed infection is a common event.

Nervous System.—All writers especially remark the fact that although this disease gets its name from a nervous system manifestation, the changes in the nervous system are not anatomically recognizable. Degenerations of the peripheral nerves have been described, but are clinically and anatomically unimportant. Occasional perivascular round-cell infiltration of the cerebral vessels is noted, but this finding always raises the question of another etiology. Typhoid meningitis is occasion-

ally met with. It may be either serous and associated with round-cell infiltration of the meninges, or typically purulent, with a spinal fluid resembling that of the epidemic form. The typhoid bacillus should be isolated from the exudate before a diagnosis of typhoid meningitis is made. The last 11 cases of "clinically diagnosed" typhoid meningitis which the author has autopsied have proved to be tuberculous. The exudate in purulent typhoid meningitis is not distinctive but contains a large proportion of mononuclear wandering cells.

GENITO-URINARY SYSTEM.—The kidneys show the usual parenchymatous degeneration of acute infection. Typhoid nodules like those in the liver are said to occur occasionally. Acute hemorrhagic glomerular nephritis is a rare complication. Miliary abscesses have been described. The pelvis and ureter are usually normal, although they may show petechial hemorrhage. Colon bacillus pyelitis sometimes occurs. The bladder is rarely affected, although typhoid bacilli occasionally multiply in it and are eliminated in enormous numbers. The cases showing bacilli in the urine usually have a trace of albumin. The prostate is not known to be primarily affected by the typhoid bacillus, although abscess or fibrous atrophy of the testis or typhoid epididymitis occasionally occurs.

The typhoid bacillus has been cultivated from the uterus when typhoid occurred during pregnancy. The child dies in utero or soon after birth, from typhoid bacteriemia. The placenta offers no barrier to the passage of the bacilli. It has not been proved that recognizable lesions of the placenta are present in cases of placental transmission. Mastitis is a rare complication.

OSSEOUS SYSTEM.—Bone complications are not very uncommon. They sometimes occur during the febrile attack, but most frequently they are found months or years after the typhoid attack. A thickened, elevated periosteum is found, raised from the bone cortex by a thin, stringy pus which extends down into the bone substance. Sequestra may be present. Typhoid bacilli can be cultivated from the pus. The lesions are very refractory to treatment and recur easily. It is said that an acute mixed infection, especially with *Bacillus pyocyaneus*, occurring accidentally, has been known to effect a cure.

Typhoid spine, with the *x*-ray evidence of spondylitis and perispondylitis, is not uncommon. The joints are rarely involved, but the arthritis, when present, may be mono- or peri-articular.

HISTORICAL SUMMARY

The history of typhoid fever may be divided into three periods.

The *first period* extends from the early history of medicine to the time of the final identification, upon clinical and pathological grounds, of typhoid fever as a disease entity, distinct from typhus and the other continued fevers.

The *second period* includes the few years between the recognition

of the disease as a distinct clinical entity and the discovery of the *Bacillus typhosus.*

The *third period* extends from the discovery of the specific organism of the disease to the present time.

Each period is marked by distinctive developments in our knowledge of the disease.

Hippocrates, during two successive autumns, met many cases of continued fever having the clinical features of typhoid fever. Galen certainly saw the disease which he described under the name *hemitritæus.*

From the early part of the seventeenth century, when Spigelius spoke of the disease as common in Italy, typhoid fever has been described by a great number of writers under a variety of names, suggested by distinctive clinical features or the author's conception of the nature of the disease.

Bretonneau, in 1826, first showed the constancy of the intestinal lesions of the disease, which he considered a type of inflammation of the bowels, and named it *dothientéritis.* He also was one of the first to suggest that the disease was due to a poison and was communicable. Louis, in 1829, published his elaborate work and first named the disease *typhoid fever.* This name was adopted by Chomel in his "Clinical Lectures," 1834, and since then it has been in general use, except in England, where *enteric fever* is the accepted name.

By this time—the beginning of the nineteenth century—the clinical history and gross morbid anatomy of typhoid fever had been well studied and a clear picture of the disease developed. The French observers, however, still held to the view that typhus and typhoid fevers were identical, and this confusion was general throughout other countries.

Thomas Willis of England, in 1659, first attempted to differentiate typhoid from typhus fever. Gilchrist, in 1734, Laugrish, in 1735, and Huxham, in 1739, added to the distinctive features of the two diseases. In England and elsewhere typhoid fever continued, however, to be considered a modified form of typhus until William Gerhard of Philadelphia, in 1837, finally established the differential clinical and postmortem criteria of the two diseases. Gerhard states that, up to the time of his writing, no one had clearly stated that the two diseases were always distinct, until the publication of a note in the *Dublin Journal,* in September, 1836, by Lombard of Geneva after his study of the fevers of Great Britain. Gerhard's views were, however, opposed by both French and English physicians. Shattuck of Boston, 1839, who studied typhoid and typhus fevers in England and France, upheld Gerhard's doctrine and was supported by Valleix and Rochoux in France and Barlow in England. Murchison and other English physicians remained unconvinced until Sir W. Jenner, in 1849, confirmed and amplified the distinctions laid down by Gerhard. Since that time, the view that typhoid fever is a disease distinct from typhus fever has not been seriously questioned.

The outstanding addition to our knowledge of typhoid fever in the *second period* of its history was the remarkable demonstration by Wil-

liam Budd of England, in 1856, of the communicability of typhoid fever through the excreta of the patient and the routes of conveyance of the infection. From the early part of the last century the doctrine of the contagiousness of typhoid fever had been held by a few able observers. Nathan Smith of New England, 1824, from his unique experience with typhoid fever among isolated communities considered the contagiousness of typhoid so evident that it scarcely needed demonstration. Bretonneau a little later, 1829, demonstrated that the disease was transmitted from one person to another. Chomel was inclined to the contagion theory but remarked that in France not one physician in a hundred regarded typhoid fever as contagious. Louis adopted the contagion theory in the second edition of his work, 1841. Murchison adhered to the theory of the spontaneous origin of the infection.

Budd demonstrated by careful epidemiological studies (1) that the infection is contained in the intestinal discharges of the patients; (2) that the disease is transmitted from the sick to the well through the medium of the stools; (3) that the infection is conveyed to healthy persons by water, milk, etc., contaminated by the dejecta of typhoid patients; and (4) that the infection may be thrown off by convalescents for an indefinite time after clinical recovery from the disease. Budd also laid down rules for the prevention and arrest of epidemics. It is interesting to note that the observations of Budd, like those of Nathan Smith, were made in rural districts where contagion can be more readily traced than in cities.

The *third period* of the history of typhoid fever begins with the discovery of the specific organism of the disease in 1880, by Eberth. Gay gives equal credit to Klebs and Koch who independently demonstrated the organism in typhoid-infected tissues at about the same time. Klebs named the organism the *Bacillus typhosus*.

The specific bacillus was found in the stools of typhoid patients by Pfeiffer in 1885, and in the urine by Hueppe in 1886. In 1887 Vilchur isolated the bacillus from the circulating blood, laying the foundation for the conclusion that typhoid fever is primarily a bacteriemia and that the intestinal lesions are usual but incidental local manifestations of the infection.

In 1894 Chiari showed that the gall-bladder quite regularly harbored the bacilli during and following the disease—a fact of great importance in the understanding of relapse and the carrier state. The agglutination method of differential diagnosis was introduced by Widal in 1896. The laboratory methods for the positive diagnosis of typhoid fever were then complete.

The knowledge of the bacteriology of typhoid fever enabled the methods of infection and routes of conveyance of the organism to be studied with accuracy. The dissemination of the disease by contaminated water and food, by flies and other fomites and by human carriers, could now be positively demonstrated.

In 1893 Frankel suggested the specific treatment of typhoid fever by the subcutaneous injection of killed cultures of the typhoid bacillus.

Antityphoid vaccination—the crowning event in the history of typhoid fever—was introduced by Wright and by Pfeiffer and Kolle in 1896. The possibilities of prophylactic vaccination against typhoid fever have been shown by the experience of the vast armies engaged in the recent world war. Could preventive vaccination be made universal throughout the world the history of typhoid fever would be ended.

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CHAPTER XXXVIII

THE PARATYPHOID INFECTIONS

By C. G. Jennings, M.D.

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Definition.—The paratyphoid infections are acute febrile diseases caused by the invasion of the blood stream by members of the paratyphoid group of microörganisms, and manifested clinically by either (1) a continued fever closely resembling typhoid fever, or (2) a gastro-enteritis, frequently of choleraic type.

In this article consideration is given only to the infections produced by two members of the group: the *Bacillus paratyphosus A* and the *Bacillus paratyphosus B*. These two organisms produce the great majority of human paratyphoid bacteriemias.

Etiology.—Predisposing Causes.—In general, the influence of predisposing causes upon the developments of typhoid fever and the paratyphoid infections is the same.

There is one distinction of importance. The *Bacillus paratyphosus B* causes disease in some domestic animals as well as in man, and is present also in the intestines of certain normal animals. It may live and multiply in infected meat. From infected meat it may be transmitted to various other foods. The dietetic habits of a people may thus predispose to paratyphoid B infections. Persons who eat largely of beef, veal and pork, prepared without adequate cooking, may be infected. The consumption of sausage, minced and preserved meats predisposes to infection. In Germany, where foods of this character are largely consumed, infections by the *Bacillus paratyphosus B* have been markedly prevalent.

Methods of sewage disposal which render possible the contamination

of the water supplies of communities or households predispose to the prevalence of paratyphoid fever as they do to typhoid. Both of the paratyphoid infections may be water-borne. Paratyphoid fever A, more closely related to typhoid fever than paratyphoid fever B, is water-borne with the same relative frequency as typhoid fever. An impure water supply is of the same importance as a predisposing factor of paratyphoid fever A as it is of typhoid fever. Water courses or wells, free from the possibility of pollution by human excreta, many be contaminated by animal carriers of the *Bacillus paratyphosus B*. Ingestion of such waters predisposes to infection by this organism.

Exciting Cause: Bacteriology of the Organisms.—The paratyphoid group of microörganisms, in their bacterial reactions and pathogenic properties, lies intermediate between the *Bacillus coli* and the *Bacillus typhosus*.

(*a*) *Morphology: General Characteristics.*—The morphology, general characteristics and group relations of the paratyphoid organisms are considered in the section on the Bacteriology of Typhoid Fever (p. 457).

(*b*) *Distribution inside the Body.*—In their distribution in the body the paratyphoid organisms show the same tendency to localization as the *Bacillus typhosus*. Both para-organisms are uniformly present in the blood stream, but apparently their stay in shorter and blood culture is more uncertain than in typhoid fever.

The organisms exist in great abundance in the intestinal tract and they are readily recovered from the stools very early in the course of the disease. The gall-bladder is always invaded, and their persistence in this viscus is the usual cause of the prolongation of the carrier state. From the relative frequency of jaundice in paratyphoid fever it would appear that the bile ducts are more frequently invaded than in typhoid fever. The bacilli are excreted by the kidneys and in many cases—although not so frequently as in typhoid fever—they may be recovered from the urine. In the outbreaks in the armies in France the cerebral membranes were not infrequently the seat of localization. Localized pus formations occur in about the same relative frequency as in typhoid fever.

(*c*) *Distribution outside the Body.*—With the notable exception that the flesh and intestinal tract of some of the domestic animals frequently harbor the *Bacillus paratyphosus B*, the distribution outside the body of the paratyphoid organisms is the same as that of the bacillus of typhoid fever.

(*d*) *Modes of Conveyance.*—Water and contact, as in typhoid fever, are the most important methods of conveying the infection of paratyphoid A; food is of secondary importance. In sharp contrast, food is the most important medium of conveyance of the infection of paratyphoid B; water and contact are of secondary importance.

Infections by the *Bacillus paratyphosus B* are commonly transmitted by meat foods. The bacilli may be present in the meat of diseased animals, in healthy meat contaminated by contact with diseased meat, or in the intestinal contents of healthy animals or human carriers. Vege-

table food of various kinds may be contaminated and become the medium for the transmission of the disease.

Carriers.—From our present knowledge, paratyphoid carriers appear to exist in about the same relative proportion as typhoid carriers. Because of the transmission of the disease by food infection the carrier state is a highly important factor in the etiology of the disease.

Hilgerman estimates that 3.6 per cent. of paratyphoid cases become carriers. Among 157 convalescents from paratyphoid fever in India, 10 were found to be carriers; 9 were acute carriers and recovered before the end of three months; the remaining case recovered in five months.

Krumwiede in 1916 found 4 per cent. of healthy carriers among 786 men of the 14th Infantry, New York State Guard, recently returned from the Mexican border. All these men were exposed to the infection that precipitated an outbreak in which 211 of the 1,000 men of the command had paratyphoid fever. This probably represents an abnormally high percentage of carriers among healthy persons. Berry states that in these groups of men the carrier state did not tend to persist. Under the influence of a more healthy environment many cases spontaneously recovered in a few weeks.

A large majority of paratyphoid carriers are fecal carriers. Urinary carriers are exceptional, and pus carriers rare. As with typhoid carriers, the bacilli live and multiply in the gall-bladder and are excreted with the feces; or they live and multiply in the pelvis of the kidney and are excreted in the urine.

Flies, etc.—Conveyance by flies and other unusual modes occurs with about the same frequency as in typhoid fever.

(*e*) *Types of Infection.*—(*i*) Typical Infection.—The typical infection by the *Bacillus paratyphosus A*, like the typical infection by the *Bacillus typhosus*, is a bacteriemia causing a fever of the continued type, with localization of the bacilli in the gall-bladder, the lymphatic structures of the intestine, the mesenteric glands and the spleen.

The typical infection by the *Bacillus paratyphosus B* is also a bacteriemia with localizations, and the additional characteristic of a tendency to produce gastro-enteritis.

(*ii*) Mild Infections.—The existence of healthy carriers with no history of acute febrile illness recognizable as an attack of paratyphoid fever is evidence that slight infections may occur. It is also reasonable to assume that the organism may enter the gastro-intestinal tract without the development of infection. This is evidenced by the absence of infection in vaccinated individuals as compared with the unvaccinated —both subjected to the same opportunities for the introduction of the organisms into the alimentary canal.

Mixed infections of the paratyphoid bacillus with other water-borne organisms are not uncommon. In many outbreaks of paratyphoid infection due to the ingestion of a highly polluted water, the onset of paratyphoid fever is preceded by an attack of gastro-enteritis, due to the presence in the water of some other infection. Mixed infections of paratyphoid A and dysentery were not infrequent in the British

forces at Gallipoli. The two paratyphoid infections may exist in the same subject at the same time; or infection by either of the paratyphoid organisms with typhoid fever may take place. Cases have been reported in which an apparent intercurrent relapse of paratyphoid fever has proven to be the onset of a complicating typhoid infection.

(*iii*) Local Infections.—Local infections by the paratyphoid organisms occur, as in typhoid fever, and with about the same frequency.

Prevalence.—The existence of the paratyphoid infections as distinct clinical entities has been known only since 1896. In all probability the disease has coëxisted with typhoid fever from remote times. It has now been identified in practically all parts of the world.

According to Bainbridge, no case of paratyphoid fever had been reported in England previous to 1912; since that time many cases have been recognized. This author states that but two small outbreaks had been reported in France up to the same year. In Germany, previous to the war, the disease was quite prevalent, particularly in the southwestern part. During the war the disease became very prevalent in the Allied armies. French observers believe that the men were infected in the territory re-occupied after the Battle of the Marne, which had been fouled by paratyphoid carriers among the German invaders. The Enteric Fever Commission, in 1906 to 1908, first recognized the disease in India; and since then it has been found to be widely prevalent in the northern half of the country. In the United States, Proescher and Roddy, in 1910, found paratyphoid fever A in eight per cent. of 262 cases presenting the symptoms of typhoid fever. The disease prevailed quite extensively among the troops mobilized along the Mexican border in 1916. It is now occasionally identified whenever bacteriological methods are applied in the differential diagnosis of acute febrile diseases presenting the symptoms of typhoid fever.

Paratyphoid fever is a much less common disease than typhoid fever. It is impossible to state how prevalent it is in this country. It is not often reported and few cases are recognized outside of the large cities. A fair estimate of the actual prevalence of the disease may be made by comparing the number of cases of paratyphoid fever with typhoid fever in epidemics in which the two diseases have prevailed coincidently and have been differentiated.

Kayser, in Strasburg, from 1901 to 1907, examined bacteriologically 505 cases presenting the clinical characteristics of typhoid fever. The typhoid bacillus was recovered from 437 cases and the paratyphoid bacillus A from 5 cases—about 1 per cent. Proescher and Roddy of Pittsburgh found paratyphoid A in 8 per cent. of 262 cases examined. During 1910, in the British Army in India, there were 306 cases of typhoid fever and 44 cases of paratyphoid A—about 15 per cent. German statistics from 1906 to 1909 collected by Uhlenhuth and Hübener show 57,955 cases of typhoid fever and 1,662 cases of paratyphoid—about 3 per cent. Boycott estimates that in England about 3 per cent. of the enteric cases are paratyphoid infections. In 1917 and 1918 there

were in the whole United States Army 1,065 cases of typhoid fever and 127 cases of paratyphoid—12 per cent.

In some of the war districts of Europe paratyphoid infections became relatively more frequent than typhoid fever. Unquestionably this condition was due to the fact that in the early period of the war the troops were immunized against typhoid fever but not against paratyphoid. To the end of 1916, 2,534 cases of paratyphoid fever and 1,684 cases of typhoid fever had occurred among the British expeditionary forces in France and Belgium. Among the British troops in Gallipoli and Lemnos 5,700 cases of enteric fever occurred. Of this number, 93 per cent. had paratyphoid fever and 7 per cent. typhoid fever.

Relative Incidence of Paratyphoid Infections A and B.—The relative incidence of paratyphoid infections A and B varies in different localities and at different times in the same locality. In Germany, before the war, about 90 per cent. of the paratyphoid cases were para B infections. In eastern France in the early part of the war para A infections markedly predominated; later the proportion was reversed. Of 735 cases treated by French observers and identified by blood culture, 572—or 84.6 per cent.—were para A infections, and 113—or 15.4 per cent.—were para B infections. Among the British troops in India paratyphoid A infections largely predominated.

Webb-Johnson's analysis of the enteric cases admitted to the largest British isolation hospital in France during the first two years of its operation shows 344 cases of paratyphoid A and 1,038 cases of paratyphoid B. In the Dardanelles campaign in 1915 paratyphoid B was the more prevalent infection during the warm months. About the end of October paratyphoid A infection became more common, and by December it had almost entirely replaced paratyphoid B. Of the 127 cases occurring in the American Army 86 cases were para A and 41 cases para B; approximately two cases of para A to one of para B.

In this country, so far as recorded, the paratyphoid A infections are in large majority. Chamberlain, with the troops on the Mexican border, in 1916 observed 250 cases: 245 cases of para A and only 5 cases of para B. Statistics from the civil population are not available.

Symptomatology.—Infection by organisms of the paratyphoid group may be classified into the following clinical types:

(1) *Paratyphoid bacteriemia,* or *paratyphoid fever,* clinically similar to typhoid fever.
(2) *Gastro-intestinal Inflammations.*
(3) *Local Inflammations.*

The *Bacillus paratyphosus A* causes infections of clinical Types 1 and 3. It rarely if ever causes infections of Type 2. The *Bacillus paratyphosus B* causes infections of all three clinical types. It frequently produces infections of Type 2.

(1) PARATYPHOID FEVER.—Previous to the isolation of the paratyphoid organisms the paratyphoid bacteriemias were grouped clinically

either with typhoid fever, in the prolonged cases, or with the febrile intestinal derangements of undetermined etiology in the short course cases. Older clinicians will recall their difficulties in attempting to classify the mild enteric infections which were frequently met and which could not conscientiously be called typhoid fever. In our own experience we have vivid recollections of many cases of fever in which the mode of onset and early symptoms seemed to justify a presumptive diagnosis of typhoid fever, only to have them end suddenly and discredit our diagnostic acumen. Present knowledge makes it quite probable that many of these cases were paratyphoid fever.

(*a*) *Clinical History.*—The clinical history of paratyphoid fever bears a close similarity to that of typhoid fever. Although a few cases run the long and severe course of typical typhoid fever, paratyphoid is, in general, a less severe infection and corresponds more closely in its course to the mild and short duration forms of typhoid. Certain clinical differences are to be noted between the two diseases but, as Gay well says, "these differences are not any greater than might occur between individual cases of typhoid fever, and could certainly never be used for the purpose of differential diagnosis of the one disease from the other in any given case." This close similarity makes a detailed description of the symptomatology of paratyphoid fever unnecessary. The group clinical characteristics of the two diseases will be considered and special features and symptoms compared.

There are practically no clinical differences between the two forms paratyphoid fever A and B. A study of many case records, however, shows that in the fever caused by the *Bacillus paratyphosus B* abdominal symptoms tend to be more in evidence.

Period of Incubation.—The average period of incubation is from ten to fifteen days. It may be as short as five days. Headache and general malaise are occasionally noted during this period. In waterborne outbreaks an afebrile diarrhea is a common symptom.

Period of Invasion.—Symptoms during Progress of Disease.—The onset may be insidious, with gradually increasing intensity of the symptoms, as in typical typhoid fever. A sudden onset, with a rapid evolution of the symptoms, is more frequently seen. There are the same lassitude, headache, shivering, loss of appetite, thirst, nausea and general muscular pain as in typhoid fever. Severe occipital headache and backache are frequent, and abdominal pain, colic and vomiting are apt to be more pronounced than in typhoid. Cramps in the calves of the legs is a common and suggestive symptom. Diarrhea and constipation occur with about equal frequency. In the para A infections which occurred on the Mexican border diarrhea and other abdominal symptoms were very unusual. In Robinson's cases vomiting occurred in twenty-four per cent. Herpes of the lips and face is not uncommon, while in typhoid fever it is quite rare. Sore throat also is frequent.

The temperature rises more abruptly than in typhoid fever, often reaching the maximum for the attack on the second to fourth day, and the fastigium is reached by the end of the third or the beginning of

the fourth day. The fastigium is short, lasting four to seven days. During this time the fever continues with remissions or intermissions and the general symptoms are similar to those of the same period of mild typhoid fever.

Defervescence begins about the ninth or tenth day of the illness with wide oscillations in the temperature and a general amelioration of all symptoms. Headache often persists through the period of decline, a condition which is rarely met in typhoid. The disease terminates quite uniformly by lysis. The period of decline is short and is usually complete in four or five days.

Paratyphoid fever curves show great variation in type and may resemble the curves of the continued or remittent malarial fevers.

The total duration of the febrile period is in general much shorter than in typhoid fever, usually being under two weeks. Two-thirds of Robinson's cases were free from fever inside of a week after admission to the hospital. Severe cases may run the long tedious course of typical typhoid fever.

Convalescence.—Convalescence is apt to be slow and attended by persistent muscular debility and an irritable nervous system. While in bed the temperature remains, as a rule, below normal and the pulse slow. Exercise, excitement or a digestive upset easily causes transient rise of temperature or tachycardia.

Relapse.—Relapse occurs about as frequently as in typhoid fever—in about ten per cent. of the cases. Relapse is short in duration, averaging eight or nine days, and, in general, pursues a mild course. A slight evening temperature persisting after defervescence is a frequent prelude to relapse (Fig. 1).

(*b*) *Special Symptoms.—Temperature.*—The temperature chart shows a curve that is quite distinct from that of the average case of typhoid fever. The temperature rises quickly, with irregular remissions and intermissions, and usually reaches the maximum, 103° to 104° F. (39.4 to 40° C.), by the third or fourth day—often as early as the second day. After a short fastigium, also marked by decided and irregular remissions, the temperature falls with wide daily oscillations and reaches the normal in four to six days. After defervescence a persistent slight evening rise is often seen interrupted by recrudescence and short intercurrent relapses, and extending the febrile period to three or four weeks (Fig. 2).

A course with regular remissions is occasionally met (Fig. 3). Excessive temperatures—above 104° F. (40° C.)—are unusual and a continuous high fever, so often present in typhoid, is very rare.

Pulse.—The pulse rate is slow in relation to the height of the temperature. Robinson found this symptom even more marked than in typhoid fever, a rate of 48 to 60 with temperatures up to 102° F. (38.9° C.). Dicrotism is unusual, although the pulse is soft.

The Rose Rash.—The characteristic rash has been found in about sixty per cent. of the cases. The spots appear, as a rule, late in the febrile period—from the seventh to the nineteenth day; occasionally

as early as the fifth day. Wiltshire found spots during the febrile period, usually appearing within a day or two of lysis, in about two-thirds of his cases. In the other third they came during the period of decline or with the recrudescences of the early convalescent period. They are apt to appear in crops at intervals of three to seven days and during intercurrent relapse. Often they do not appear until after

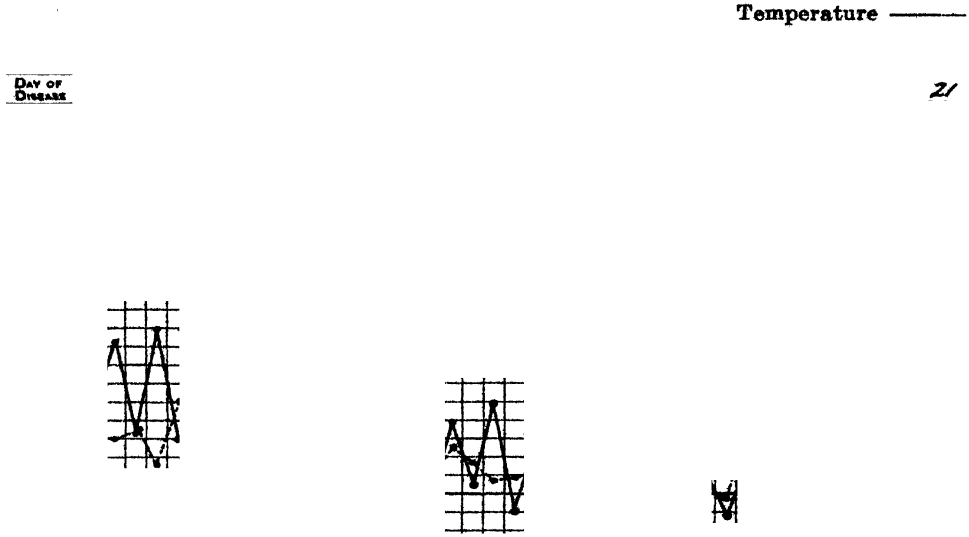


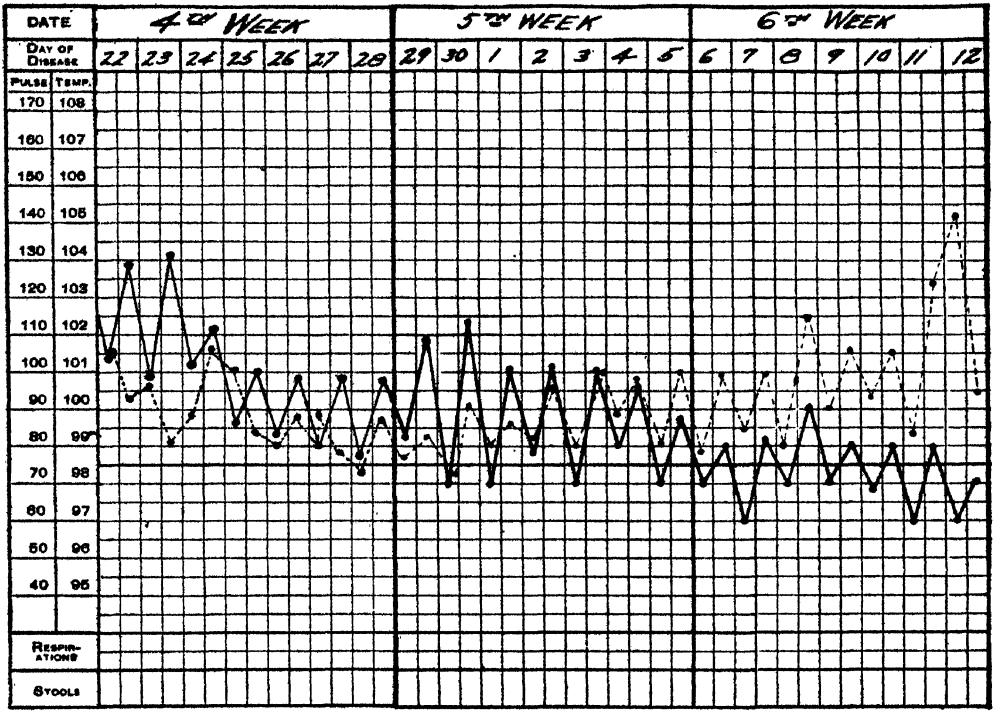
FIG. 1.—CHART IN

Course prolonged by intercurrent relapse. (Observation

the temperature has reached the normal level and for this reason may be overlooked. The distribution of the rash is usually upon the abdomen and lower chest. In number the spots vary from a half dozen to about a hundred. A very abundant and widely distributed rash is occasionally seen. Writers describe two distinct types of rash which may occur independently or mingled together in the same patient. One type is identical in every respect with the rose rash of typhoid fever. The other, the paratyphoid type, has certain distinctive characteristics. The individual "paratyphoid spot" is larger than the typhoid rose spot, more often elevated, and is lenticular in outline. It is much darker in color, does not completely disappear on pressure and, when it fades, leaves a slight temporarily pigmented and desquamating

area. The spot bears a close resemblance to the individual macule of the eruption of measles. These distinctive spots may be few in number or quite numerous. According to Wiltshire, they constitute a distinct diagnostic feature in favor of paratyphoid fever, particularly when they appear as the temperature is falling.

Symptoms of the Respiratory Tract.—The frequence of *epistaxis* and



PARATYPHOID A.

at Fort Sam Houston, Col. [now Maj. Gen.] M. W. Ireland.)

of the symptoms of *catarrhal inflammation* of the respiratory tract is about the same as in mild typhoid fever.

Abdominal Symptoms.—*Nausea* and *vomiting* are common early symptoms much more frequently in paratyphoid than in mild typhoid fever. *Diarrhea* is a frequent symptom, occurring in from one-third to two-thirds of the total cases reported. It is a symptom of the first three or four days of the invasion period and frequently marks the day of onset. In water-borne infections it may precede the febrile period by a week or more. It is not often severe and declines with the appearance of lysis. It is a much more constant symptom in paratyphoid B fever than in mild typhoid. Of the cases studied by Vaughan in the American Expeditionary Forces, diarrhea was a symptom in 65.2 per

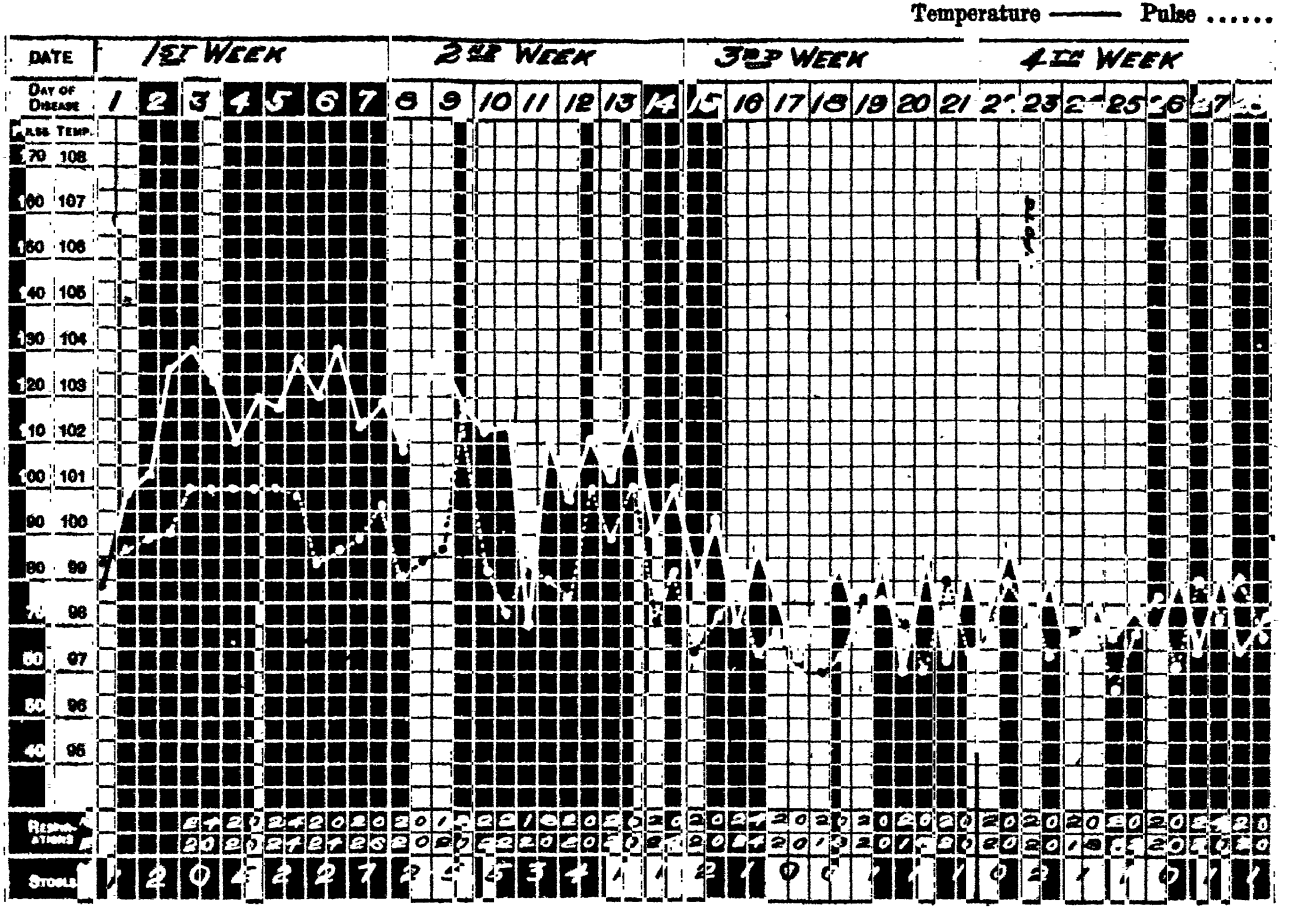


FIG. 2.—CHART IN PARATYPHOID B.

Sudden onset; persistent slight evening fever after lysis. (After Wiltshire.)

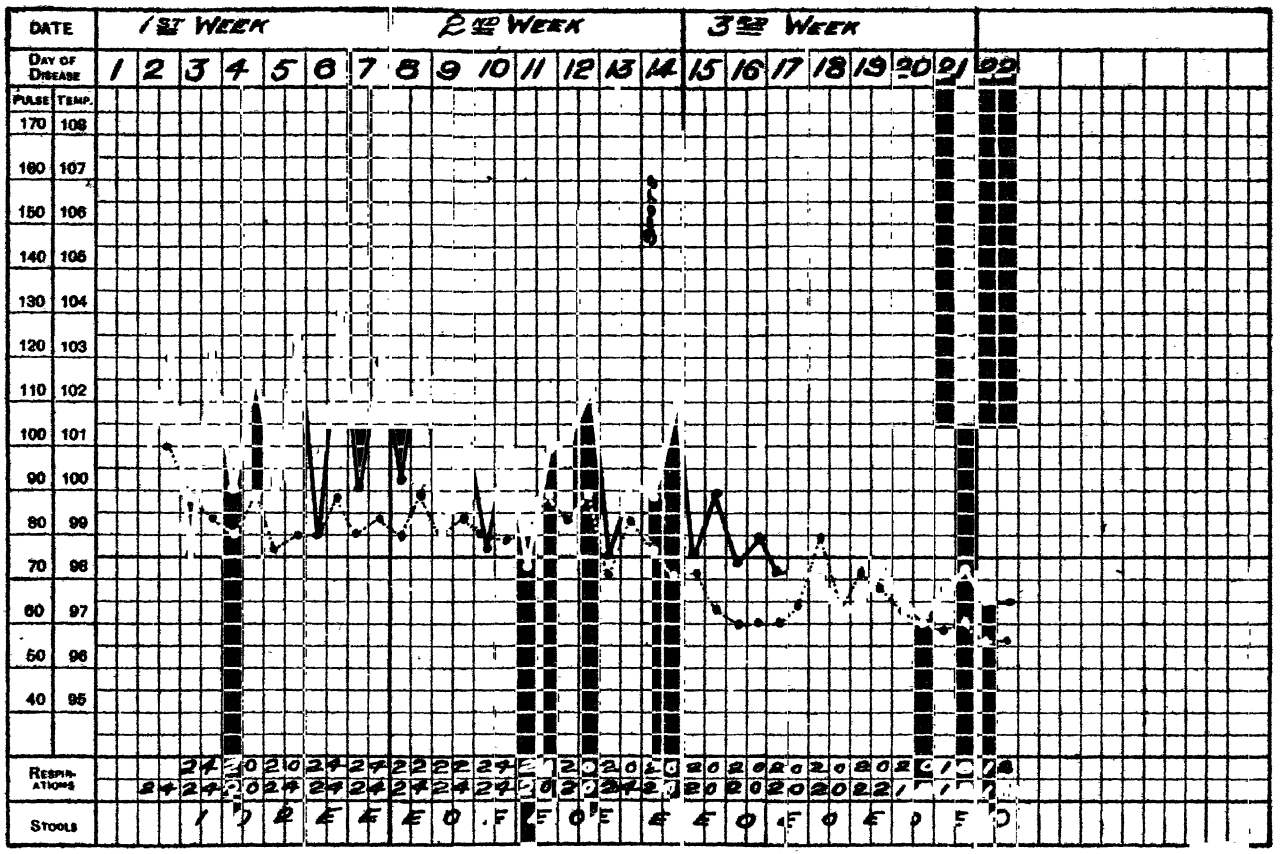


FIG. 3.—CHART IN PARATYPHOID B.

Sudden onset; remittent type of temperature. (After Wiltshire.)

cent. of the cases of paratyphoid B, and in 33.3 per cent. of the cases of paratyphoid A. The stools are composed of loose, unformed fecal material and are brown in color. The light colored "pea soup" stool of typhoid fever is not often seen. As above stated the *Bacillus paratyphosus A* does not cause gastro-enteritis. In the reported American outbreak in which cases of paratyphoid A infection predominated, diarrhea was exceptional. It is reasonable, therefore, to

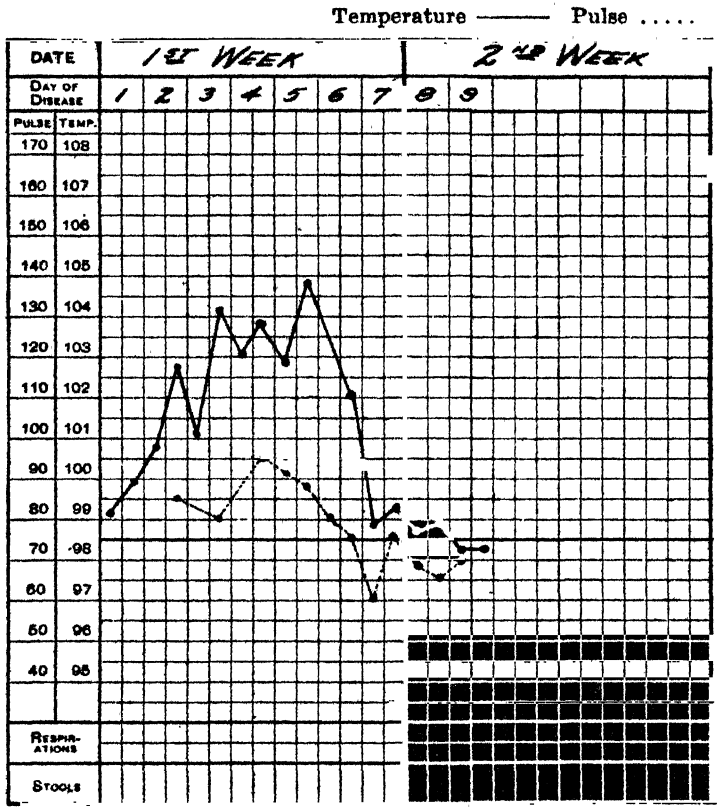


FIG. 4.—CHART IN PARATYPHOID A.
Short course. (After Hurst.)

assume that in outbreaks in which diarrhea affects a large percentage of those attacked the incidence of paratyphoid B infections is relatively high. *Pain* is a frequent symptom of the early days of the disease, perhaps more frequently observed than in typhoid fever. It may be severe and be accompanied by *rigidity* and *tenderness*, especially in the right lower quadrant. Such cases may readily be mistaken for appendicitis. The *spleen* is palpable only in about 25 per cent. of the cases. It rarely shows the marked enlargement so common in typhoid. On the other hand the *liver* is more frequently enlarged in paratyphoid fever. *Jaundice* is a frequent symptom in some outbreaks.

Nervous Symptoms.—There is a marked *absence of nervous symptoms of severity.* Headache is often of longer duration than in typhoid, but not more severe. Mild mental confusion is not uncommon but delirium is very exceptional. The patient is mildly apathetic but rarely shows the stupor so common in typhoid, and rarely develops the typhoid state.

(2) Gastro-intestinal Inflammations.—Gastro-intestinal inflammations of paratyphoidal origin are caused by the *Bacillus paratyphosus B.* The *Bacillus paratyphosus A* rarely, if ever, has been found to be the cause of this clinical type. A clinically identical gastro-enteritis—one of the forms of food poisoning—may also be caused by the *Bacillus enteritidis* of Gärtner, a member of a subgroup of the paratyphoid organisms.

The symptoms are those of a gastro-enteritis of the food poisoning type. *The period of incubation* is short, the symptoms coming suddenly from twelve to thirty-six hours after the ingestion of the infected food. The extreme limits are one hour and four days. The short interval between the ingestion of the poisoned food and the onset of symptoms is probably due to the fact that the gastro-enteritis is a local process excited by the toxins elaborated in the food by the bacillus and is not a manifestation of a bacteriemia.

It is difficult to explain why a bacteriemia with clinical symptoms of the typhoidal type does not more frequently result from such an infection. In Whitman's 52 cases of paratyphoid B infection all recovered as soon as the local inflammation subsided.

Invasion begins with nausea and vomiting, abdominal pain and diarrhea. *Headache* is an initial symptom in about one-half the cases. *A chill or repeated shivering* is usually present. There are often *faintness and dizziness* or, in severe cases, *collapse with small pulse and cold wet skin. Stupor or coma* are occasionally observed. *Abdominal tenderness* may be a marked feature and, as in the paratyphoid fever type, the attack may closely simulate appendicitis. The *temperature* rises quickly to a moderate height and reaches its maximum during the first day or two of the illness. It varies in height from 101° to 104° F. (38.3° to 40° C.). It pursues an irregularly remittent course and falls rather abruptly.

In this type of infection the *rose spots* are present in about the same percentage as in the typhoidal type, although they often do not appear until after defervescence.

Severe attacks may assume the clinical characteristics of cholera nostras.

The disease runs a *short course* and terminates in from three to eight days. In an outbreak reported by Whitman, of 53 cases, the duration of the shortest was three days and the longest seven days.

Convalescence is usually slow and often followed by a long period of muscular weakness and mental depression.

(3) Local Inflammations.—Local inflammations may be caused by either of the two paratyphoid organisms. These inflammations occur with about the same frequency as in typhoid fever and tend to invade the

same structures. Meningitis is more often produced by the paratyphoid organisms than by the typhoid bacillus. The gall-bladder is constantly invaded and cholecystitis is not very rare. The rather frequent occurrence of jaundice indicates a greater tendency for the infection to invade the bile ducts than is shown in typhoid fever.

The symptoms of the various local inflammations caused by mem-

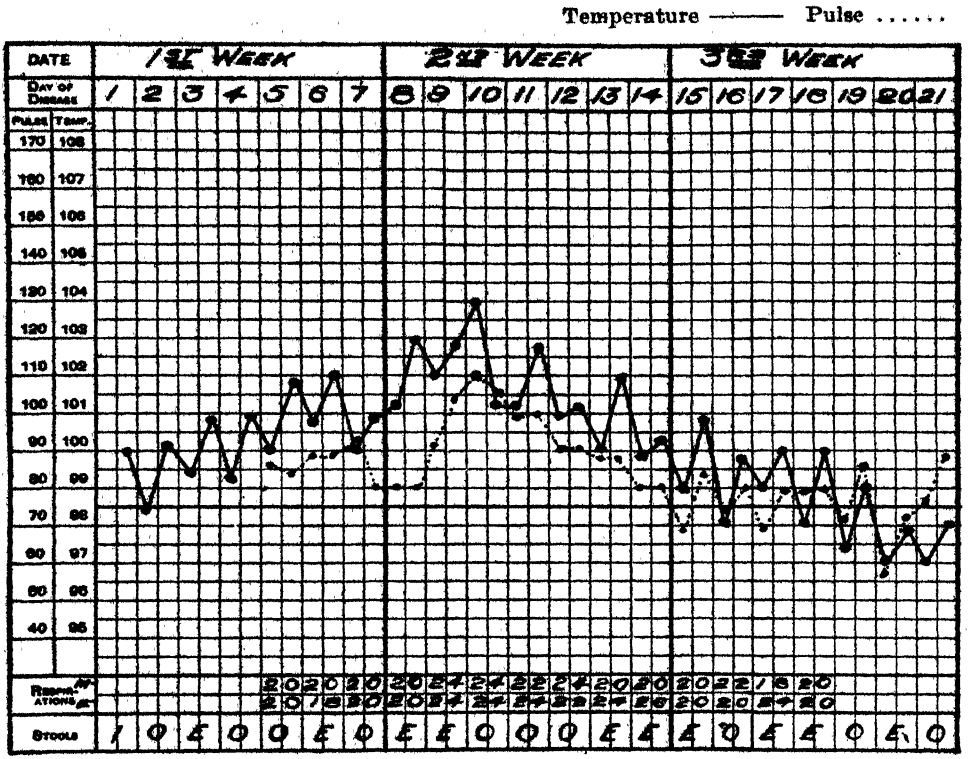


Fig. 5.—Chart in Paratyphoid B.

Steplike rise of temperature of invasion period. (After Wiltshire.)

bers of the paratyphoid groups of microörganisms are the same as when they are the result of other infections.

Diagnosis.—Clinical Diagnosis.—The problem of the clinical diagnosis of paratyphoid fever requires the analysis of the same symptom-complex that is presented by typhoid fever. Differentiation from other acute febrile diseases is made from the same clinical data that are available in the differentiation of typhoid fever.

In paratyphoid, as in typhoid fever, a presumptive diagnosis only can be made from clinical findings. Laboratory confirmation, by the agglutination reaction or by the recovery from the blood, stools or urine of the specific organism of the disease, is essential to a positive diagnosis.

The frequency of short duration cases of paratyphoid fever in the recent war areas of France and the simultaneous prevalence of *influenza* made the differential diagnosis of these two diseases a question that often came up for consideration. Wiltshire gives the following points in favor of a diagnosis of paratyphoid fever: "The more gradual onset of symptoms and ascent of fever; the absence of coryza; the rarity

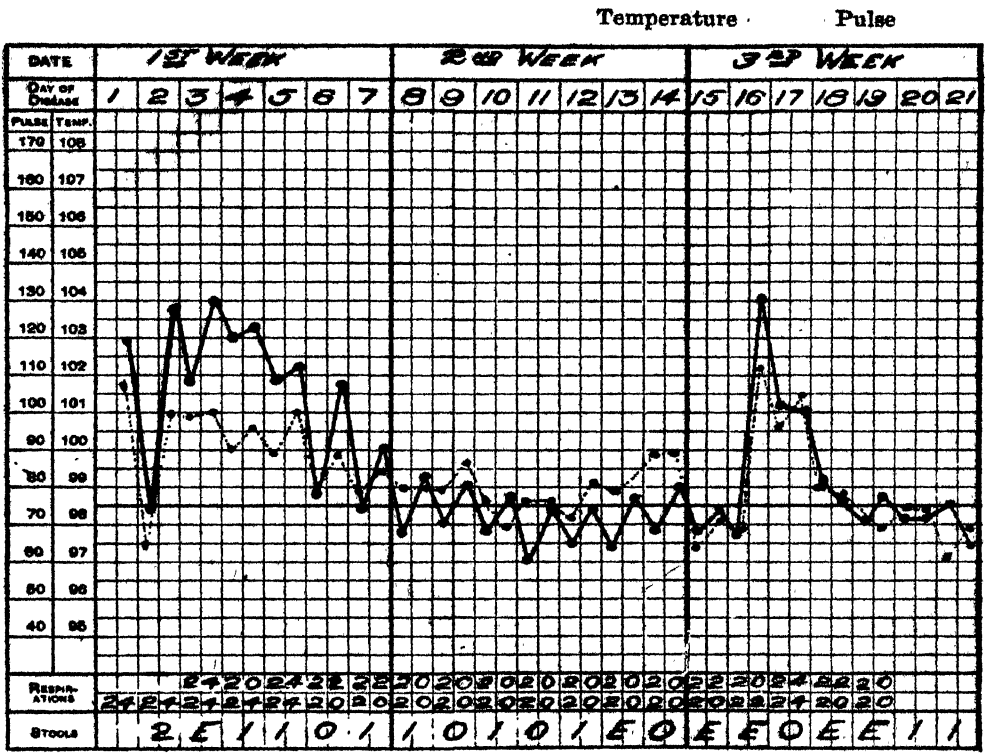


FIG. 6.—CHART IN PARATYPHOID B.

Sudden onset; short course; recrudescence on 16th day. (After Wiltshire.)

of rigors; the absence of early cough; the gradual onset of prostration, and its mild character compared with the degree of fever; the occurrence of diarrhea; abdominal tumidity; the absence of signs of cardiac embarrassment during the febrile stage; the absence of postfebrile psychoses and affections of special sense."

Is it possible clinically to differentiate between paratyphoid fever and typhoid fever? Before the clinical experience gained in the recent war, checked up by abundant laboratory investigation, writers answered this question with an emphatic negative. With individual and isolated cases this answer still holds good. Wide variations from group characteristics are so frequent in both diseases that individual cases cannot with certainty be distinguished one from the other.

The main clinical differences between paratyphoid and typhoid fever, as presented in large groups of cases, have been brought out with distinctness by observers in the war zones and may serve for making a presumptive diagnosis in outbreaks either of paratyphoid or of typhoid infection, or in epidemics in which both diseases prevail together.

The following points are *in favor of a diagnosis of paratyphoid fever:* the abrupt onset often accompanied by vomiting and chills; the shorter duration of all stages of the febrile period; the early appearance of marked remissions of fever; the very slow pulse and infrequent appearance of dicrotism; the moist and cleaner tongue; the greater frequency of gastro-intestinal symptoms; the darker color of the stools; the frequency of jaundice and enlargement of the liver; the infrequency of a palpable spleen; the different character of the rose spots and their appearance when other symptoms are improving; the greater frequency of herpes; the absence or mild character of the nervous symptoms except headache; the persistence of headache after defervescence; the frequency of occipital pain and of joint and muscle pains.

These clinical characteristics of paratyphoid fever are significant when applied to cases in the aggregate; a positive differential diagnosis from typhoid fever in any given case is not possible, however, without the aid of *laboratory examinations.*

Paratyphoid infections of Type 2—the gastro-intestinal inflammations—can be differentiated from *gastro-enteritis due to other causes* only by the recovery of the paratyphoid organism from the blood or stools. In the local inflammations—Type 3—diagnosis will be made by the recovery of the bacillus from the affected organ or tissue.

Laboratory Diagnosis.—The technical details for the laboratory diagnosis of paratyphoid fever are identical with those of typhoid fever and may be found in that section. (See page 518.)

Blood Culture.—Recovery from the blood of one of the paratyphoid organisms is conclusive evidence of a paratyphoid bacteriemia, or paratyphoid fever. Figures are not available that give the percentage of positive findings. It is certain that this percentage is lower than for typhoid fever. The paratyphoid bacillus remains in the blood stream for a shorter time than the typhoid bacillus and, for this reason, is more difficult of isolation. Diagnosis by blood culture was the method of choice with the armies in France.

Fecal Culture.—Paratyphoid bacilli are excreted by the feces in abundance and quite continuously during the course of paratyphoid fever. Positive findings are more frequent than in typhoid fever and in much higher percentage in the early stages of the disease. Krumwiede examined the stools of 57 cases of paratyphoid fever occurring among the men of the 14th Infantry, New York National Guard, with the following results: Positive findings: period of incubation, 15 per cent.; 1st week, 83 per cent.; 2nd week, 50 per cent.; 3rd week, 33 per cent.; 4th week, 20 per cent.; 5th week, 15 per cent. and 6th week 20 per cent. The technic of fecal culture is much simpler than that of blood culture and, judged by the excellent results obtained by

Krumwiede, the bacteriological examination of the feces is the most satisfactory method of laboratory diagnosis of paratyphoid fever.

The Agglutination Test.—The value of the Widal reaction in the differential diagnosis of paratyphoid fever is still the subject of controversy. That it is not as reliable a method in paratyphoid as in typhoid fever has been demonstrated, and in recent years the reliability of the test has become further vitiated by the introduction of antiparatyphoid vaccination. Satisfactory conclusions can be drawn from the test only when it is made by an expert and when due consideration is given to all the possibilities of error.

Complications.—The complications of paratyphoid fever are of the same general character and relative incidence as of typhoid fever, but far less frequent. In the outbreaks along the Mexican border complications were rare and unimportant. In civil practice in this country they are also infrequent. Under war conditions in Europe the percentage was higher and in some sections in France paratyphoid fever closely followed typhoid in the incidence and severity of complications.

In Webb-Johnson's series of cases of paratyphoid fever, of the two most important complications, hemorrhage occurred in 17 cases—1.22 per cent., and perforation in 5 cases—.37 per cent. In 1,118 cases of typhoid fever during the same period and under the same conditions, hemorrhage occurred in 50 cases—4.74 per cent., and perforation in 9 cases—.80 per cent.

The influence of prophylactic vaccination in ameliorating the severity of paratyphoid fever is shown by his statistics to be very great. The incidence of all complications is reduced to an insignificant number. In 364 vaccinated cases there was but one instance of perforation. The percentage of complications in the cases of paratyphoid B fever was nearly double the percentage in the cases of paratyphoid A.

Clinical Varieties.—*Mild Forms.*—The recent reports of the disease as it has occurred among troops in this country and Europe show that mild forms of the paratyphoid infections are very common. They bear only a faint resemblance to typhoid fever and, except for the laboratory studies of the medical officers of the army, they would probably have been classified as cases of digestive derangement, influenza or fever of undetermined etiology. It is quite certain that such cases also occur among the civil population but escape identification. They are rarely admitted to the hospitals, but come under the care of physicians in private practice and recover and pass from observation before an opportunity is given for laboratory study.

Treatment.—Paratyphoid and typhoid bacilli escape from infected individuals by the same routes. Transmission also of both infections is by the same channels, with the single conspicuous difference that the *Bacillus paratyphosus B* more frequently gains entry into the human organism through the medium of infected food.

Prophylaxis.—The specific measures for the prevention of typhoid fever by the *destruction of the bacillus at its source* and by the *prevention of its transmission from the sick to the well* apply with equal force

to the prevention of the paratyphoid infections. The transmission of the paratyphoid organisms by food infection can be prevented by cleanliness in food distribution through sterilization of all food supplies. Unlike the *Bacillus typhosus* the paratyphoid organism multiplies in infected meat which has been imperfectly cooked, or in well cooked meat which has been contaminated after cooking by unclean hands, cooking utensils or flies. Preserved and canned meats, minced meats and sausage are especially liable to act as such culture media and should be given special consideration.

The carrier problem has the same significance here as in the prophylaxis of typhoid fever. Carriers should be sought among those who have to do with the preparation and distribution of food and, when found, treated in the same manner as typhoid carriers. All persons who of necessity must be in contact with carriers should be protected by vaccination.

Antiparatyphoid Vaccination.—This subject has been fully considered in the section on antityphoid vaccination. The evidence available at this date confirms the opinion that vaccination against paratyphoid infections gives an immunity equal to that given by vaccination against typhoid fever. Among over 2,000,000 men of the American Army in the camps and cantonments in this country during the war, paratyphoid as well as typhoid fever was practically unknown. Even under the necessarily defective sanitary conditions at the front in France, and in men subjected to the terrible physical and mental strain of battle conditions, the immunity given by vaccination was broken down in but very few instances. In the whole American Army at home and abroad during the years 1917 and 1918 only 127 cases of paratyphoid fever occurred.

Medical Treatment.—The medical treatment of paratyphoid fever is identical in all its details with the medical treatment of typhoid fever. The paratyphoid B infection with the clinical characteristics of gastro-enteritis do not differ in any way from gastro-enteric infections from other organisms and should receive the same treatment. Convalescence should be guarded with the same care as in typhoid fever. Hemorrhage has been observed after convalescence appeared to be well established. **Rest in bed** should be enjoined **for at least a week after defervescence.**

Prognosis.—The mortality of paratyphoid fever under peace conditions is very low. No death occurred in the cases in the American Army on the Mexican border. Sacquepec found only 4 deaths in 2,725 cases—.15 per cent. Under war conditions the mortality is higher. In Webb-Johnson's series of 1,020 cases not protected by vaccination 18 died—1.75 per cent. All of 362 vaccinated cases recovered. In some small groups of cases observed in the French Army the mortality reached 3 per cent.

As a rule the para B infections have a higher mortality than the para A infections. Webb-Johnson recorded a mortality of 2.12 per cent. in para B infections and .45 per cent. in para A infections. Vaughan reported a mortality of 4.3 per cent. in the paratyphoid B infections, and

0 per cent. in the paratyphoid A infections. In an occasional outbreak in France the proportion was reversed.

As in typhoid fever, death usually results from one of the complications—most commonly hemorrhage or perforation. Toxemia alone is rarely fatal.

Pathology.—There is nothing in the morbid anatomy of the paratyphoid infections that distinguishes them from typhoid fever or that distinguishes the two infections A and B from each other. In the few autopsy studies recorded there was found a more extensive ulceration of the colon than is usually found in typhoid fever. The ascending colon is most frequently the seat of ulceration, and in rare cases the process may involve the whole length of the colon. In many cases of para A infection there is no intestinal ulceration and no postmortem evidence of intestinal inflammation.

Historical Summary.—Knowledge of the paratyphoid infections is of recent date. The first of the paratyphoid group of organisms to be discovered was the *Bacillus enteritidis,* isolated by Gärtner in 1888, from the spleen of a patient who died from meat poisoning. In 1896 Achard and Bensaude isolated an organism, distinct from the Eberth bacillus, from two cases of clinical enteric fever, which they named the "paratyphoid bacillus." In one case the bacillus was recovered from the urine and in the other from a complicating purulent arthritis. Gwyn, in 1898, working in Osler's clinic, cultivated a paratyphoid bacillus which he described as the "paracolon bacillus," from the blood of a patient presenting the clinical features of typhoid fever. In 1901 Schottmüller obtained by blood culture, from patients presenting the symptoms of typhoid fever, two bacilli which Brion and Kayser named *Bacillus paratyphosus A* and *Bacillus paratyphosus B.*

The demonstrations of these early workers have been verified by subsequent research. During the recent war the paratyphoid infections have prevailed extensively among the troops at the front, and much has been added to our knowledge of the clinical history of the disease. It has been shown that both the paratyphoid organisms cause a bacteriemia with symptoms similar to those of typhoid fever. The para A bacillus practically always produces this type of the disease; it rarely if ever excites a gastro-enteritis. The relation of the para B bacillus to the typhoid-like cases on the one hand and to the food-poisoning type on the other have been the subject of much difference of opinion. Food poisoning epidemics have been very common in Germany, due either to the *Bacillus enteriditis* or to the *Bacillus paratyphosus B.* Bainbridge, writing in 1912, held that food poisoning is not caused by the *Bacillus paratyphosus B* but by other closely related organisms of the paratyphoid group and that infection by this organism produced only typhoid-like symptoms the same as paratyphoid A. Studies made possible by the recent wide prevalence of the disease in Europe appear to have demonstrated that either type of clinical phenomena—the typhoid type or food-poisoning type—may be the result of infection by the *Bacillus paratyphosus B.*

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CHAPTER XXXIX

COLON BACILLUS INFECTIONS

By C. G. Jennings, M.D., and A. F. Jennings, M.D.

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Definition.—Colon bacillus infections are acute or chronic febrile diseases caused by the invasion of the blood stream or tissues by the *Bacillus coli communis,* and are manifested clinically by either a continued fever somewhat resembling typhoid fever or by local inflammations with pus formation, of which inflammations of the urinary tract, the biliary tract and the peritoneum are the most common.

Etiology.—Predisposing Causes.—*Age, Sex, Social Conditions, etc.*—The disease is common to all *ages* though infants and children are more frequently affected. *Females* are more often affected than males, because of the greater liability to constipation and the ease with which the infection travels through the genitalia. *Social condition, hygiene, occupation and environment* have little or no bearing on the disease. *Individual susceptibility* depends more on associated disease than on a natural lack of immunity.

Other Diseases.—Hirschprung's disease is frequently complicated by *pyelonephritis of the colon bacillus type,* according to Langstein. *Congenital malformations of the kidney* predispose to the infection.

Pyelitis and *pyelonephritis* occur in about 20 per cent. of *pregnant women.* The reason for its occurrence is not well understood. Cabot believes that the usual etiological factors are accentuated at this time.

There is no evidence that the conditions necessary for ascending infection are present.

Trauma.—Colon bacillus infection occasionally occurs in newly-married women, and is the result of the trauma to the genitalia and the entrance of the organism by this route.

EXCITING CAUSE: BACTERIOLOGY OF THE ORGANISM.—The bacteriological description of the colon bacillus will be found in the section on the Colon-Typhoid Group of Organisms in the chapter on Typhoid Fever (p. 457).

Mode of Infection.—Colon bacillus infection is the result of auto-inoculation by the organisms of the patient's intestinal canal. While cases due to infected water supply or to direct contact with the organism occur, they are too rare to be of clinical interest. The bacilli enter the body through the intestinal wall, through the skin in the region of the external genitalia and through the lower urinary tract. Minute breaks in the continuity of the intestinal mucous membrane are sufficient to cause entrance of the bacilli. Chronic constipation and acute enterocolitis are the most common diseases causing these breaks. Operations upon the abdominal or pelvic organs, ulceration of the colon, intestinal cancer and parasitism may be followed by colon infection. It is sometimes a complication of typhoid fever. C. A. McWilliams states that colon bacilli may be found in the sac of a strangulated hernia ten hours after the onset.

If the bacilli are carried away in the veins they enter the portal system and eventually the liver, while if they go by way of the lymphatics they enter the thoracic duct, are discharged into the general circulation, and finally reach the kidney. C. Franke has demonstrated lymphatic communication between the right kidney and the ascending colon. It is improbable that the bacteria reach the kidney by this route.

The external genitalia are constantly soiled by colon bacilli, and if abrasions exist the organisms may enter the lymphatics and then the blood stream. Similarly, in infections of the bladder and prostate, the bacilli may reach the blood stream by way of the lymphatics. In either case the bacilli are eventually excreted through the kidney. The extreme frequency with which infections of the bladder or external genitalia are followed by pyelonephritis has led to the theory that the bacilli ascend the urinary tract. The fact that the usual route of infection is by way of the lymphatics and blood stream has been proven by Cabot and Crabtree. It is generally believed that ascending infection occurs only when there is obstruction to the urinary flow, with a patent ureterovesical valve.

Virulence of the Organism: Resistance of the Tissues.—In addition to the presence of the colon bacillus, two other factors are to be considered in the production of disease: the virulence of the organism and the resistance of the tissues. The colon bacillus normally has low virulence, but in acute enteritis or other intestinal disease its virulence is increased. Park and Williams state that 0.25 c.c. of a bouillon culture of the colon bacillus recovered from a case of acute diarrhea may be fatal to a guinea

pig, while 2.5 c.c. of a culture from the normal intestinal contents are necessary to cause the death of the animal. Cholelithiasis or obstruction of the common duct lowers the resistance of the liver to the colon bacillus. Urinary calculus and trauma render the kidney more susceptible to infections by the colon bacillus. Scarlatina, diphtheria and measles are more commonly followed by colon infections of the urinary tract than are the other febrile diseases. It is possible that the kidney has been damaged by the toxins of the disease before infection takes place.

Symptomatology.—CLINICAL FINDINGS.—Infections by organisms of the colon group may be classified into the following clinical types:

(1) Bacteriemia clinically similar to mild typhoid fever.
(2) Local inflammations.
(3) Bacteriemia with local abscess formation.
(4) Secondary implantation of the bacillus upon a tissue already damaged.
(5) Terminal invasion of the blood and organs.

(1) *Bacteriemia Clinically Similar to Mild Typhoid Fever.*—The onset is gradual, with fever, headache, pains in the epigastrium, abdomen and extremities, loss of appetite, sometimes nausea and vomiting, diarrhea or constipation. Rarely the onset is sudden, with chill. The temperature gradually rises, reaching a height of from 101° to 104° F. (38.3° to 40° C.) in several days, and from then on it falls by lysis to normal from the tenth to fourteenth day.

The disease does not pursue the prolonged course of typhoid fever. Exhaustion and emaciation are less severe. Diarrhea of a severe type is not common. Hemorrhage and perforation do not occur, as Peyer's patches are not ulcerated. Secondary anemia is common. Relapses similar to those of typhoid fever have been reported.

Such cases are generally classified as mild typhoid fever or fever of unknown etiology, wherever laboratory methods of diagnosis are not used. Cases have been studied in detail by Coleman and Hastings, and Cabot and Crabtree, all of whom have determined by blood culture or agglutination reactions that the disease is a separate entity from typhoid fever.

McWilliams has described a form of colon bacillus septicemia with hemorrhagic purpura occurring in infants, which is very fatal.

(2) *Local Inflammations.*—(*a*) *Urinary Tract.*—Colon bacilli may be excreted in the urine in large numbers, without the production of symptoms or of pathological changes in the urinary tract. This was first demonstrated by T. Rovsing and has been confirmed by other investigators. The condition occurs in association with constipation, diarrheal attacks, typhoid fever, scarlatina, measles and diphtheria and after abdominal operations. Bassler found the condition in 19 of 191 hospital cases examined. Colon bacilluria may be the first manifestation of a urinary tract infection. It also occurs almost constantly in colon bacillus bacteriemia with abscess formation in other parts of the body.

Cystitis, pyelitis, pyelonephritis and pyonephrosis are the usual results of colon infection of the urinary tract. More rarely it causes urethritis, epididymo-orchitis, prostatitis and periurethral abscess.

In view of the fact that the kidney, the renal pelvis and the bladder are involved simultaneously, it is impossible to separate pyelonephritis, pyelitis, and cystitis into definite clinical entities. Indeed the symptoms themselves are generally confused and are frequently misleading. According to Phelps, the symptoms of infection in the urinary tract fall into five groups: (1) symptoms general in character; (2) symptoms referable to the nervous system; (3) to the pulmonary system; (4) to the gastro-intestinal system; and (5) to the urinary system. Thompson adds the group of uremic symptoms.

Urinary tract infection with general symptoms usually occurs in infants. The child is pale and restless and loses weight. The onset is usually gradual, although it may be sudden at times. The fever is irregular in type and is liable to recur after longer or shorter intervals of quiescence. Chills are characteristic of colon infections at this age.

The type with predominant nervous symptoms is seen in infants and young children. Delirium, convulsions and coma occur, or there may be symptoms of meningeal irritation. C. R. Box has observed children who are shy, nervous and dull and suffer from headaches and incontinence of urine. The tongue is coated and the bowels irregular. There is colon bacilluria. The symptoms disappear with the cure of the colon bacillus infection.

The pulmonary symptoms are caused by referred pain or diaphragmatic irritation. They include rapid respiration and pain in the lower thorax.

Symptoms referable to the gastro-intestinal tract occur most frequently in children. There are vomiting, abdominal pain, diarrhea or constipation. There is abdominal distention and the spleen or kidneys may be palpable. The course is recurrent. The illness may be manifested by attacks of indigestion or periodic vomiting.

Cases with urinary tract symptoms occur in older children and adults. Culver, Herrold and Phifer present a careful analysis of the symptoms presented by 116 patients.

Pain, chills and fever and frequent painful micturition are the three characteristic symptoms of upper urinary tract infection. Pain occurs in about 90 per cent. of the cases. In most instances it is in the lower back on one or both sides, and varies in intensity from a dull ache to an acute pain. It may radiate to the pelvis or thigh or to the neck. It may occur in the abdomen simulating acute appendicitis or renal colic, or it may be in the bladder region only. Chills and fever and frequent painful micturition are found in about one-half of the cases. Constipation, headache, vomiting, hematuria, loss of weight and incontinence of urine are less often observed, but may be the only symptoms of which the patient complains.

Cases with uremic symptoms simulate acute nephritis. Any age may be affected. There are semicoma, anuria, general edema, ascites, ambly-

opia, vomiting and headache. Optic neuritis is frequent. The blood pressure may or may not be raised. Thompson states that "sudden onset with early delirium, then coma but not convulsions, fever and uncontrollable vomiting are pathognomonic symptoms of colon bacillus renal infection." He also believes that many patients with chronic interstitial nephritis eventually suffer from this infection which is the exciting cause of intercurrent urèmic attacks.

Colon infection of the kidneys and pelvis may show every grade of severity. It may be so mild in character that the patient goes about his daily occupation for months; or it may be rapidly fulminating, with chills, high fever, abdominal pain, delirium, severe toxemia and prostration. This latter condition has been termed *unilateral septic infarction* by Brewer, who first described the disease as a clinical entity. It is designated *focal suppurative nephritis* by Keyes.

The duration of colon infection of the urinary tract is variable. While certain cases promptly recover, the greater number become chronic. Other cases may clear up temporarily both as to symptoms and urinary findings, and later relapse. Others still continue to have symptoms of little or moderate severity associated with occasional periodic exacerbations.

Acute or chronic urethritis, epididymo-orchitis and prostatitis are caused by the colon bacillus in rare instances. Endometritis and pelvic inflammations due to this organism are occasionally observed.

(*b*) *Appendix.*—H. A. Kelly states that the colon bacillus has been found in 86 per cent. of the cases operated upon at the Johns Hopkins Hospital, generally associated with other organisms, especially the streptococcus and staphylococcus. He noted that the cases due to the colon bacillus alone were milder and that the disease was limited to tissues of the appendix region, while the cases of mixed infection showed extensive and severe peritonitis. The colon bacillus rapidly overgrows the streptococcus and the staphylococcus, and for this reason may be found alone even when it is a secondary invader. H. C. Low has reported the bacteriology of 100 cases of appendicitis. The colon bacillus was present in pure culture in 8, and with cocci in 74. The streptococcus was present in pure culture in 2. In cases of three days' duration or less the colon bacillus was found in 62 per cent. and the streptococcus in 81 per cent. In cases of two to three weeks' duration the colon bacillus was present in 87 per cent., and the streptococcus in 55 per cent. The colon bacillus alone was found in only one acute case of less than three days' duration. Low also noted that the colon bacillus alone causes a less severe disease than the streptococcus alone or than a mixed infection. Metastatic abscesses due to the colon bacillus may follow appendicitis.

(*c*) *Biliary Tract.*—A. O. J. Kelly, studying in Deaver's clinic, found the colon bacillus alone in 28.33 per cent. of 240 cases of cholecystitis, and associated with staphylococcus in 0.85 per cent. of the cases. Cholangitis, liver abscess and subphrenic abscess may be due to the colon bacillus.

(*d*) *Peritoneum.*—Dudgeon and Sargent conclude that the colon

bacillus causes the largest number of fatalities in peritonitis. Its virulence varies, and while it is less virulent than the streptococcus it occurs more frequently. Flexner, in 56 cases of peritonitis due to bowel infection, found the colon bacillus in pure culture in 8, and associated with other organisms in 35—a total of 43 cases. J. C. Briscoe reports three chronic cases in which caseating peritoneal masses due to the colon bacillus were operated upon.

(e) *Organs Other Than the Kidney, Liver, Bile Ducts, Appendix and Peritoneum.*—In rare instances the colon bacillus invades organs other than the kidney, liver, bile ducts, appendix and peritoneum. Lobular pneumonia, pleuritis, empyema and multiple abscesses of the lung have been observed. Endocarditis and pericarditis are reported. Meningitis may follow acute enteritis or otitis media. Brain abscess and myelitis are sometimes due to the colon bacillus. The organism may be found in otitis media or mastoiditis, tonsillitis or empyema of the nasal accessory sinuses. In the extremities, periostitis, suppurative arthritis and infections in lacerated wounds have been reported. Cutaneous abscesses of infants, herpes of the lips and mucous membrane of the mouth, and septic onychia have been due to this organism. It may be found in the wounds of abdominal and other operations, and was first observed outside of the digestive tract by Tavel in the wound of an operation on the thyroid gland.

(3) *Bacteriemia with Local Abscess Formation.*—Blood stream infection is associated with localized inflammation in many cases. It may precede or follow the local infection. Recognition of this condition has been delayed, owing to the difficulty in isolating the colon bacillus from the blood.

Jacob, studying colon bacillus bacteriemia, found that local abscesses resulted in 22.5 per cent. of the reported cases and in 1 of 13 cases of his own. Of the 8 cases taken from the records of the Massachusetts General Hospital, 2 showed evidence of local areas of inflammation. Enright and Bahr observed 15 cases of colon bacillus pyemia. The patients were debilitated Turks in an army hospital in the near East, and the condition followed tuberculosis, dysentery or pellagra. The organism was recovered from the blood in 2 cases only. Of these cases, 9 died, and at autopsy the bacilli were demonstrated in the kidneys, liver, spleen and lymph-nodes—sometimes with abscess formation, at other times in the venous circulation or in the interstitial tissue without inflammatory reaction. Coleman and Hastings in their 3 cases of colon bacillus septicemia found clinical evidence of acute cholecystitis in 1 of them. The most convincing studies have been made by Cabot and Crabtree. By taking blood cultures during or shortly after a chill they found them positive in 12 of 32 cases of pyelonephritis. They cite one case in detail—a patient with enlarged prostate and residual urine, who was being treated by inlying catheter. On the eighth day there occurred burning micturition followed in two hours by a rigor. The urine at this time showed no microscopical evidence of infection, although the blood culture was positive. The following day pus and bacilli appeared in

the urine. They quote Kowitz, who found that certain infants suffering from diarrhea showed first colon bacilli in the blood and then albumin, bacteria and pus, in sequence, in the urine.

The onset of the septicopyemia type of the disease is generally with chill followed by high fever. The symptoms are more serious than those of either of the uncomplicated infections spoken of above. The accompanying local disease may be manifest or it may remain obscure for many days. The temperature curve is extremely irregular, with wide daily swing and chills. It may be intermittent, remittent or relapsing in character. The course of this type of the disease is long, extending over many weeks.

(4) *Secondary Implantation of the Colon Bacillus upon a Tissue Already Damaged.*—In appendicitis, peritonitis, cholecystitis and urinary tract infections, the colon bacillus is associated with other organisms in many cases. Even when it is obtained in pure culture it is quite probable that it has overgrown the original organism.

(5) *Terminal Infections.*—Flexner has made a careful investigation of the terminal infections of heart disease and chronic nephritis—patients in whom no infection had existed until shortly before death. There were 222 cases studied. Colon bacillus appeared alone in 2 cases of general infection, and in combination with other organisms in 4. It appeared alone in 24 cases showing local infection of the various organs, and 41 times in combination with other organisms. In all, the colon bacillus invaded the blood stream or tissues in 71 of 222 cases.

The organisms were found by culture or stained section in all of the viscera and also in the peritoneum, pericardium, endocardium and pleura. It was found that they may cause a definite lesion of the tissues in which they lodge or they may be present without local reaction. Flexner believes that the bacillus wanders through the intestinal wall wherever a small lesion such as ecchymosis, erosion or ulcer exists. They are found in distant viscera almost without exception if a serious lesion of the intestine is present.

PHYSICAL FINDINGS.—*Bacteriemia.*—The patient has the appearance of mild typhoid fever. The tongue is coated and tremulous. A rose rash similar to the rash of typhoid fever is present upon the abdomen. Tympanites occurs and the spleen is enlarged.

Local Inflammations and Septicopyemia.—The local inflammations and septicopyemia present the physical signs typical of inflammation of the organs involved.

In urinary tract involvement the patient may appear well or he may present varying degrees of toxemia and prostration. On palpation, moderate or severe tenderness is found, most frequently in either costovertebral angle, also in the flanks, along the course of the ureter or in any part of the abdomen. The kidney infected may be palpable and tender. The liver and spleen may be felt.

Terminal Invasion.—The terminal invasion of the body by the colon bacillus is rarely accompanied by physical signs other than unexplained fever.

Fever.—The temperature curve of colon bacillus bacteriemia is similar to that of typhoid fever: it is rarely as high; it reaches the maximum in three or four days, and declines to normal in about two weeks. The fever curve of pyemia shows wide daily variations of an intermittent or remittent type. Enright and Bahr report cases in which the curve was of the relapsing type with pyrexia of 5 to 7 days, and remissions of 7 to 10 days.

Chills.—Chills occur at irregular intervals. Chills in infants and children are frequently due to this type of infection.

Laboratory Findings.—A moderate anemia of the secondary type is common in the prolonged, severe infections.

There is generally leukocytosis if the infection is localized. The septicemias more often show leukopenia.

The colon bacillus can always be recovered from the blood in the septicemic type of the disease and frequently in cases of pyemia. Cabot and Crabtree have shown that it can be recovered from the blood in cases of pyelonephritis if the culture is made during or shortly after a chill.

Urine.—Colon bacilluria occurs in a large proportion of the cases of septicemia or pyemia.

In urinary tract infections the urine may appear normal or show only a few bacilli or pus cells during the first forty-eight hours of the disease. This finding is the result if the infected kidney fails to excrete or if the urinary flow is blocked by calculus or other obstruction.

When the infection has become established the urine is obviously turbid, due to pus; or it may show a haze or shimmering, due to bacilli. In the latter case filtration through ordinary filter paper or sedimentation does not affect the haze. The urine is commonly acid, although faint alkaline reactions may occur. Ammoniacal decomposition is never present because the colon bacillus cannot decompose urea. The specific gravity is high—a surprising contrast to the pale color of the specimen. Obvious hematuria is not common, being recorded in only 12 per cent. of the cases by Culver, Herrold and Phifer. Albumin is generally present. The sediment shows bacilli and pus cells. Red blood-cells may be present, and casts indicate renal involvement.

The culture of the urine may be positive for colon bacillus even with a microscopically clear urine. The organism is generally present in turbid urines but it is possible to have a negative culture in these cases.

Tissues, Sputum, Peritoneal Fluid, Pleural Exudate, Cerebrospinal Fluid.—The colon bacillus can be grown from the infected tissues and from sputum, peritoneal fluid, pleural exudate and cerebrospinal fluid.

Special Examinations.—The only special examinations applicable in colon bacillus infections are those employed by urologists in determining the nature and extent of damage to the kidneys and urinary tract. *The phenolsulphonephthalein test* of Rowntree and Geraghty shows noticeable diminution in the output of the dye when pyelonephritis exists. It may give inaccurate results in this disease where the changes are frequently unilateral. The determination of the nonprotein nitrogen,

urea or creatinin of the blood is valuable in determining the combined function of the kidneys.

Cystoscopic examination is rarely indicated in the acute state of the disease, but is valuable in the chronic types to determine the seat of the infection and the extent of damage to the kidneys. It is of the utmost importance in making the differential diagnosis and in detecting associated conditions. The *x*-ray is employed for the same purpose, especially in pyelography.

Diagnosis.—The diagnosis is established by the recovery of the colon bacillus. The organism may be found in the blood, in exudates, in pus and in the tissues. It is found in the urine in kidney and bladder infections and in many localized infections remote from the urinary tract.

Serum agglutination does not have the important diagnostic significance in colon bacillus infections that it has in typhoid fever. The test is unreliable because of group reactions and the variable reactions given by the different strains. Using the homologous organism, Coleman and Hastings found that the reaction may occur in dilution of 1-100 in septicemia and that it disappears during convalescence. Dudgeon found that a positive reaction with the homologous organism was rare in cases of renal and peritoneal infection. W. J. Stone states that a positive reaction in a dilution of 1-40 is indicative of colon infection.

DIFFERENTIAL DIAGNOSIS.—Colon bacillus bacteriemia is to be differentiated from *typhoid and paratyphoid fevers.* The symptoms of the three diseases are practically the same, and differential diagnosis can be made only by the isolation and identification of the infecting organism from the blood by the methods given in the section on laboratory diagnosis in the chapter on Typhoid Fever.

The diagnosis of urinary tract infection presents several features. It is necessary to determine the location and severity of the disease process, to recognize the condition when the characteristic symptoms are absent, and to differentiate it from other diseases of the genito-urinary tract and from diseases of the abdomen. Fever, abdominal or renal pain and frequent painful micturition are the characteristic symptoms. Pyuria is the one pathognomonic sign. In the severe types it is impossible to define the disease as being limited to the bladder, renal pelvis or kidney, since all are more or less involved. *Cystitis* may exist as an entity for a few days, but if persistent, infection elsewhere in the tract is certain. *Pyelitis* should be the diagnosis if the disease is mild and subacute, if pain and costovertebral tenderness are absent, if the excretion of dyes is not diminished, and if the outline of the renal pelvis is normal. *Pyelonephritis* should be the diagnosis if pain and tenderness are present, if the dye excretion is diminished, and if the course has been chronic. *Pyonephrosis* presents the same signs and symptoms as pyelonephritis. The toxemia and sepsis are, however, more severe, the kidney is more readily palpable and the urinary pus is thicker than in pyelonephritis. *Suppurative nephritis* is indicated by the sudden onset of high fever, severe sepsis and toxemia, delirium and vomiting, in addition to the other symptoms and signs of a urinary tract infection.

In infants and children the characteristic urinary symptoms may be absent, the disease manifesting itself only by fever of a remittent or continued type, or by fever with gastro-intestinal or nervous symptoms. The detection of pus and bacilli in the urine will clear up the diagnosis.

In the differentiation of colon bacillus infections from *other diseases of the genito-urinary* system the *x*-ray, the cystoscope and the chemical and bacteriological examination of the urine from each kidney must be employed. *Renal tuberculosis* or *urinary calculus* are the conditions most liable to cause error.

The diagnosis of *infections of the urinary tract by organisms other than the colon bacillus* is determined by culture of the urine. Certain clinical differences are observed. Streptococcus and staphylococcus infections follow tonsillitis, carbuncles or osteomyelitis, and they cause *alkaline urine* because of ammoniacal decomposition of urea. Colon infections follow intestinal diseases and cause *acid urine*. In the *coccus infections of the kidney* the pus does not appear until twenty-four to forty-eight hours after the onset, and the phthalein output is normal for several days; while in colon infections the pus is found within the first twenty-four hours and the phthalein output is diminished at once.

Rare cases of pyelonephritis present the clinical syndrome of uremia with anuria, edema and nervous symptoms. The renal function tests show great diminution, and there is an increase in the blood nitrogen. The blood-pressure is lower in pyelonephritis than in uremia. In pyelonephritis, pus and bacilli are the prominent elements in the urine while in uremia casts and blood-cells predominate.

Pyelonephritis or suppurative nephritis may simulate acute abdominal inflammation. In the latter the pain is abdominal instead of renal, vomiting is present and tenderness and muscle spasm can be found. Confusion is more liable to arise in the case of children than in adults. The finding of pus or bacilli in the urine should make the diagnosis clear, though it is to be remembered that both conditions may exist.

A large percentage of colon infections accompany or follow *pregnancy* and *confinement*. They are admitted to the hospital, diagnosed as "puerperal fever." Sepsis, particularly puerperal sepsis, should be considered in the differential diagnosis.

The diagnosis of *appendicitis, cholecystitis, peritonitis and other local infections which may be due to the colon bacillus* is considered in the various chapters devoted to the consideration of these diseases.

Tuberculosis, malaria, influenza and relapsing fever are to be differentiated from the pyemic type of colon bacillus infection. *Tuberculosis* is distinguished by the pulmonary findings, the low white blood-cell count and the demonstration of tubercle bacilli in the sputum. *Malaria* is differentiated by the presence of the plasmodium in the blood. *Influenza* is a disease of short duration and ends quickly. *Relapsing fever* is diagnosticated by finding the spirillum in the blood stream. None of these diseases is characterized by pyuria or bacilluria which frequently occur

in colon bacillus pyemia. The colon bacillus should be isolated if possible.

The occurrence of the colon bacillus as a secondary invader is determined only by recovery of the organism by culture. It is rarely detected as a terminal invader.

Complications and Sequelæ.—Aside from extension of the infection by the blood stream, by the lymphatics, or by continuity, complications do not occur.

Association with Other Diseases.—Colon bacillus infection is almost always associated with certain other diseases. These are enumerated in the section on Etiology.

Pathology.—The lesions caused by the colon bacillus vary from a mild inflammatory reaction to abscess formation. Microscopically there is an exudate of lymphocytes or polymorphonuclear leukocytes with serum and eosinophile cells, and the organism can usually be seen in the stained section. The process terminates in sclerosis or scar tissue. According to Mallory, the lesions in general are mild, though acute and intense reactions may occur.

The lesions of the kidney have been fully described by Cabot and Crabtree. In the pelvis the mucous membrane is reddened, granular and dull. Microscopically the mucosa is thickened and the submucosa is infiltrated. Bacilli can be found in the submucosa. Simple pyelonephritis shows a kidney which is slightly enlarged. The capsule is thickened but strips easily and the cut surface is pale. Microscopically the tubules are dilated and hyaline degeneration is present. There is lymphocytic or polymorphonuclear infiltration of the interstitial tissue. The glomeruli are not damaged unless they are situated in the center of an infected area. The process begins in the pyramids and spreads toward the cortex and pelvis. When the infection is more severe the cortex is mottled and the medullary portion shows many yellowish-red or opaque pinhead-sized areas from which bands and streaks extend toward the pyramids. These areas are seen microscopically to be the centers of degeneration and necrosis. True abscess formation in the kidney due to the colon bacillus alone is rarely, if ever, observed. In cases of long duration the pelvis and calices are much dilated, and contain dirty purulent urine or, in the case of pyonephrosis, a thick ropy pus. The kidney tissue is diminished in amount and shows areas of scar tissue.

In the liver cholangitis and abscesses result from colon bacillus infection. Microscopically exudation of serum and polymorphonuclear leukocytes with necrosis are seen in the tissues surrounding the ducts. Cirrhosis confined to the periphery of the lobules follows the inflammation.

In the peritoneum the inflammation tends to remain localized and is not of a severe type. Rare cases of chronic peritonitis with dense adhesions and caseating, tubercle-like masses due to the colon bacillus have been observed.

Treatment.—PROPHYLAXIS.—The colon bacillus is one of the organisms that make up the normal intestinal flora. It becomes pathogenic by auto-infection under conditions either of increased virulence of the

organism, or of diminished resistance on the part of the host. The duty of the physician in the prophylaxis of colon bacillus infection is restricted to the recognition of the various general and local conditions that predispose to colon infections, and to anticipate and, if possible, to guard against them. Unfortunately many cases occur without warning and we have no means of preventing them.

Pathological activity of the colon bacillus should be anticipated: (1) in the prolonged fevers, especially typhoid, and in the acute exanthemata; (2) in acute enterocolitis, constipation, ulceration of the colon, intestinal tumors and parasites, hernia, anal fissure and after operations upon the intestines, rectum or anus; (3) in acute urethritis and cystitis, prostatism, urethral stricture, renal and vesical calculus, malformations, tumors, spinal cord disease and other conditions that may cause retention; (4) in pregnancy and after delivery.

Colon invasion of the urinary tract may be prevented in many of the above conditions by the administration from time to time of **urinary antiseptics. Urinalysis at definite intervals** should be made promptly to detect a bacilluria or a pyuria. *Infection by instruments and through open wounds in the region of the genitalia* may be prevented by **strict asepsis and cleanliness. Soiling of the genitalia with bowel contents is especially to be avoided** in female infants and young girls. **Catheterization** should be done **only under the strictest aseptic precautions** and should be **followed by a liberal ingestion of fluids and the administration of urotropin. A prophylactic colon vaccine** should be considered in conditions in which infection is especially to be feared.

TREATMENT OF BACTERIEMIA.—This is similar to the treatment of typhoid fever and does not require separate consideration.

TREATMENT OF LOCAL INFECTIONS.—(1) *Urinary Tract.—General Management.*—**Rest in bed with competent nursing until the urine is free from pus and bacilli** is essential, although it is difficult to keep the patient at rest after symptoms have disappeared. The **room should be kept warm and drafts and chilling of the patient avoided. Hot sponge baths** may be given daily to aid elimination by the skin. The bowels should be kept free with **appropriate cathartics. Calomel** may irritate the kidney and **should be avoided.** *If diarrhea is present* its cause should be sought and proper therapy applied.

Diet.—The protein intake should be low, as in nephritis, and renal irritants avoided. For the average adult 60 to 70 grams (2.12 to 2.47 ounces) of protein per day should be the maximum. The required daily number of calories—40 per kilogram of body weight—may be built up as in the diet for typhoid fever (p. 583) by the addition of carbohydrates and fats. Carbohydrates are of especial value, as they spare protein loss and inhibit the growth of the colon bacillus in the intestinal tract.

In the absence of marked nitrogen retention milk is a suitable food. A liter contains 35 grams (1.23 ounces) of protein and yields 640 calories. It acts as an efficient diuretic. With from one to three pints of milk as a basis the protein and calory requirement may be obtained by the selection of articles with low protein percentage from the table

of foods (Table 7) in the chapter on Typhoid Fever (p. 585). Vegetables and fruits may be added to the diet when the acute stage of the disease has passed.

Symptoms of uremia require the reduction of nitrogen intake to the lowest possible point. Protein should be limited to that contained in one or two pints of milk, or, in severe cases, the low protein diet of Mosenthal for nephritis may be prescribed.

TABLE I

LOW PROTEIN DIET (Mosenthal)

Salt, sugar, and butter may be used as desired, and need not be weighed or measured.

Breakfast: Sherry, 30 c.c.; baked apple or orange; "hominy cornstarch cereal" two-thirds hominy, one-third cornstarch; cream, 15 c.c.

Dinner: Sherry, 30 c.c.; potato, baked or mashed; String beans, cabbage, carrots, lettuce, onions, tomatoes, cucumbers, pickles; fruit cornstarch pudding or fruit tapioca pudding.

Supper: Same as dinner.

TABLE II

NITROGEN CONTENT OF FOODS IN LOW PROTEIN DIET

	Nitrogen (per cent.)		Nitrogen (per cent.)
Cereal:		*Fruit:*	
"Hominy cornstarch cereal" two-thirds hominy, one-third cornstarch	0.13	Baked apple	0.04
Cream:	0.41	Orange	0.16
Desserts:		Stewed prunes	0.14
Apple tapioca pudding	0.02	*Vegetables:*	
Blackberry cornstarch pudding	0.05	Cabbage	0.16
Peach tapioca pudding	0.06	Carrots	0.10
Prune cornstarch pudding	0.07	Cucumber pickle	0.10
		Lettuce	0.24
		Onions	0.17
		Potato, baked	0.48
		Potato, mashed	0.40
		String beans	0.23
		Tomatoes	0.23

In anuria, or uremia with water retention, the fluid intake should not exceed 1,500 c.c. in the twenty-four hours. Edema is unusual but, if present, requires a salt-free diet, with restricted fluid intake. Should the stomach be irritable, small meals may be given every two or three hours. Usually the diet can be arranged for three meals a day.

Certain foods are renal irritants and should be rigidly excluded. These include preserved meats, beef tea, meat soups and broths, sauces and condiments, radishes, parsley, onions and asparagus. Tea, coffee

and cocoa in moderation are not harmful. Alcohol in small quantity is not objectionable. Mosenthal finds that an ounce of sherry with each meal does not irritate the kidneys.

(2) *Local Infections Other Than the Urinary Tract.*—The treatment of the local infections other than those of the urinary tract is surgical in a large proportion of the cases. If the infection has become generalized and beyond the reach of surgical methods the symptomatic and supportive treatment as described for typhoid fever is to be employed. (*See* p. 599.) A vaccine may greatly hasten the cure of draining abscesses or sluggish inflammatory conditions not resulting in abscess formation, but will not take the place of surgery when the latter is indicated. Terminal infections are rarely recognized and treatment is of little importance.

LOCAL TREATMENT.—Lavage of the pelvis of the kidney is contraindicated in the acute stage and in chronic cases with impaired renal function and dilated pelvis. It may be of value in cases in which the infection is recent, the renal function normal, and the outline of the pelvis shows no dilatation.

TREATMENT OF SYMPTOMS.—*Pain* of any degree of severity may occur. When mild, **hot-water bottles or hot compresses** will relieve. **Aspirin or phenacetin** may be given at the same time. *In severe pain* **codein or morphin by the mouth or hypodermically** will be necessary. *Painful urination and tenesmus*—serious because they may cause retention—should be promptly relieved. **Potassium citrate or acetate** in doses sufficient to alkalinize the urine will give relief: 20 to 40 grains (1.3 to 2.6 grams), every four hours, well diluted with water, may be given. A vesical sedative—**tincture of belladonna or tincture of hyoscyamus**—may be prescribed with the alkali. **A suppository of extract of belladonna leaves or extract of opium** often acts well. **Oil of santal,** 5 to 10 minims (0.3 to 0.6 c.c.), **in capsule** is a useful sedative for more prolonged administration.

Fever rarely requires symptomatic treatment. **Hydrotherapy** gives the best results. **Phenacetin,** 5 grains (0.324 gram), given every hour for two or three doses during the afternoon, will reduce the temperature and ease the discomfort of the pyrexia. *Headache, vomiting, convulsions and other uremic symptoms* are treated as in acute nephritis.

SPECIFIC THERAPY.—*Vaccines.*—A certain degree of success has resulted from the administration of colon vaccines in urinary infections. Cabot has found that with vaccine treatment the symptoms are improved in about 50 per cent. of the cases, and that results are equally good in both upper and lower urinary tract infections. The bacilluria, however, is not relieved, and relapse is frequent. An autogenous vaccine is to be preferred.

The initial dose should not exceed 25 millions of bacilli; succeeding doses to be increased according to the clinical reaction of the patient, until a maximum dose of 600 to 1,000 million is reached. The injections are given at intervals of five to seven days.

MEDICINAL TREATMENT.—**Hexamethylenamin** is the most efficient

urinary antiseptic and is indicated in colon bacillus infections of the urinary tract, and as a prophylactic in conditions liable to be followed by infection. The drug is not a urinary sedative and should not be relied upon alone in the presence of infection with bladder irritability and tenesmus.

Hexamethylenamin is excreted by the kidney, and either there or in the bladder it is decomposed into ammonia and formaldehyd, the antiseptic action depending upon the latter product. The amount of the drug decomposed in its passage along the urinary tract varies with the individual patient. In about 40 per cent. of the cases no decomposition occurs. Decomposition of hexamethylenamin takes place only in the presence of an acid medium. An *acid urine,* therefore, is essential to the therapeutic action of the drug. In an alkaline urine no decomposition takes place and the remedy is inert.

Burnam's test for formalin should be made in all cases which do not improve under the administration of hexamethylenamin. It is performed as follows:

Add to the urine 3 drops of a 0.5 per cent. aqueous solution of phenylhydrazin hydrochlorid, then 3 drops of a 5 per cent. aqueous solution of sodium nitroprussid, and finally an excess of a saturated aqueous solution of sodium hydroxid. Both the urine and the hydroxid should be warmed to body temperature. If formalin is present in concentrations of 1-20,000 there follows an intense blue color, changing to brown. If there is no liberation of formalin after the administration of larger doses, the drug should be discontinued.

The average dose of hexamethylenamin is 7½ to 10 grains (0.49 to 0.65 gram) three times a day. To get the full effect it may be necessary to administer 30 to 40 grains (1.95 to 2.60 grams) every four hours. It is best given dissolved in an abundance of water. *Acidity of the urine* may be assured by the **simultaneous administration of acid sodium phosphate,** 15 to 20 grains (0.972 to 1.3 grams) three times a day. The drug may be given over long periods. In large doses it may cause frequent and painful micturition and hematuria. If these symptoms occur the remedy should be discontinued and, later, resumed in smaller doses.

Sodium benzoate is an efficient urinary antiseptic in colon bacillus infections. The dose is 5 to 10 grains (0.324 to 0.65 gram) four to six times a day, given in pill or capsule.

The use of the **alkaline diuretics** has been considered. They **should not be given with hexamethylenamin.** The administration of the **alkalis and hexamethylenamin on alternate weeks** has been advised, on the theory that the change in the reaction of the urine inhibits the growth of the bacilli. In our personal experience the plan has not been very satisfactory.

Surgical Indications.—The acute stage of colon bacillus infection of the kidney rarely demands surgical intervention. If the signs and symptoms point to unilateral disease and the toxemia is so severe as to threaten the patient's life, the kidney should be explored. The condition of the unaffected kidney should be determined by cystoscopy. Nephrectomy or

nephrotomy must be decided upon by the surgeon after the kidney has been exposed to view. In chronic pylonephritis with great destruction of tissue, or in pyonephrosis, nephrectomy is the only recourse.

MANAGEMENT OF CONVALESCENCE.—Active treatment should be continued until all signs of disease have disappeared. It is not enough to relieve the symptoms; pyuria and bacilluria should disappear before the patient can be discharged as cured. During convalescence the factors predisposing to recurrence of the infection should be corrected.

Prognosis.—MODE OF DEATH.—The disease terminates by sepsis.

MORTALITY.—In Jacob's series of 39 cases of bacteriemia and septicopyemia 15—or 40 per cent.—died. In Cabot's series of 8 cases taken from the wards of the Massachusetts General Hospital, 25 per cent. died. Enright and Bahr report 9 deaths in 15 cases—a mortality of 60 per cent. Bacteriemia and septicopyemia due to the *Bacillus coli communis* are therefore serious diseases with a high mortality.

The mortality of local infections depends upon the tissue or organ invaded and the virulence of the infection. Primary, uncomplicated colon infection of the urinary tract does not have a high mortality. Appearing as a complication of calculus, prostatic hypertrophy or other pathology, the outlook is serious.

Recovery after infection of the lower urinary tract depends upon the nature of the individual case. Without free drainage of the infected areas the condition tends to become chronic and to persist indefinitely. Re-infections are common. Infections of the pelvis of the kidney are very apt to relapse and become chronic. Renal infections of mild type may recover completely in a few weeks. The more severe lesions, however, heal by scar formation and may leave little renal tissue. Pyonephrosis results in complete destruction of the kidney.

Historical Summary.—The *Bacillus coli* was first cultivated by Emmerich, in 1885, from the feces of cholera patients, and it was cultivated from the feces of healthy infants by Escherich, in 1886. The organism was first observed outside of the intestinal tract by Tavel, who recovered it from the wound of an operation upon the thyroid. During the development of the science of bacteriology the *Bacillus coli* was recovered from various tissues, Rovsing having furnished the most complete early studies on its pathogenicity. The invasion of the blood stream by the *Bacillus coli* was first reported in detail by L. Jacob, in 1909, who observed a series of cases of continued fever and pyemia due to this organism. Except in the case of urinary tract infections, comparatively little study has been devoted to this bacillus as a cause of disease.

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