ON THE

DYSENTERIES OF INDIA

With a chapter on
Secondary Streptococcal Infections and Sprue.

BY

HUGH W. ACTON, LIEUT.-COL., I.M.S.,

Professor of Pathology and Bacteriology,

Calcutta School of Tropical Medicine and Hygiene,

AND

R. KNOWLES, LIEUT.-COL., I.M.S.,

Professor of Protozoology.

Calcutta School of Tropical Medicine and Hygiene.

'And it was so, that the father of Publius lay sick of fever and dysentery.'—Acts, XXVIII, 8. (R. V.).

CALCUTTA :

THACKER, SPINK & CO.

1928

CONTENTS.

			Page.
Chapter	I.	Dysentery in India. Morbidity and Mortality. Seasonal Incidence. The term 'dysentery.' Causation. Relative Frequencies	1
,,	II.	Acute and Subacute Bacillary Dysentery; Ætiology, Pathology and Symptoms. Acute and Subacute Amœbic Dysentery; Ætiology, Pathology and Symptoms. Balantidial Dysentery. Mixed Infections	23
,,	III.	The Diagnosis of Dysentery. Use of the Sigmoidoscope. Laboratory Examination of Dysenteric Stools. The Morphology of *Entamœba histolytica* and of *Balantidium coli* ..	43
,,	IV.	The Bacteriology of Bacillary Dysentery	64
,,	V.	The Treatment of Acute Bacillary and of Acute Amœbic Dysentery	89
,,	VI.	Chronic Bacillary Dysentery and the Bacillary Carrier ..	109
,,	VII.	Chronic Amœbiasis and the *Entamœba histolytica* Carrier. (Appendix. Table. The Morphology of the Human Entamœbæ)	124
,,	VIII.	Streptococcal Infections Secondary to Bacillary Dysentery. Sprue. The Asthenic Diarrhœa of Indians	143
,,	IX.	Prophylaxis against Dysentery	154
References		.. ..	163
Index ..		.. ..	171

ON THE

DYSENTERIES OF INDIA

With a chapter on

Secondary Streptococcal Infections and Sprue.

ON THE

DYSENTERIES OF INDIA

With a chapter on
Secondary Streptococcal Infections and Sprue.

BY

HUGH W. ACTON, LIEUT.-COL., I.M.S.,

Professor of Pathology and Bacteriology,

Calcutta School of Tropical Medicine and Hygiene,

AND

R. KNOWLES, LIEUT.-COL., I.M.S.,

Professor of Protozoology.

Calcutta School of Tropical Medicine and Hygiene.

'And it was so, that the father of Publius lay sick of fever and dysentery.'—Acts, XXVIII, 8. (R. V.).

CALCUTTA :

THACKER, SPINK & CO.

1928

Printed by Thacker's Press & Directories, Ltd., 6, Mangoe Lane, Calcutta and Published by J. Chaplin, of Thacker, Spink & Co., 3, Esplanade, Calcutta.

To

LEONARD ROGERS,

A pioneer in the study of the Dysenteries of India and the founder of the Calcutta School of Tropical Medicine and Hygiene,

This Book is Dedicated.

PREFACE

Our experience of teaching Indian post-graduate students during the last seven years is that there is hardly any subject about which they are so ignorant as that of dysentery. It is clear that the tremendous advances in our knowledge of the subject which have resulted from the work of the War and post-War years have not as yet been generally incorporated in the teaching of medicine in India, and the old and erroneous belief that most of the dysentery of India is of amœbic origin is still generally held.

In order to try and present to the medical profession in this country a general *résumé* of the present-day knowledge of the subject, accordingly, we published a small paper-covered brochure on it in 1924. The edition of this was exhausted early in 1927. In October 1927, the junior author was asked to deliver the Burdwan Lectures early in 1928 at the Ronaldshay Medical School, Burdwan, Bengal, and chose 'the dysenteries of India' as his subject. The preparation of these lectures afforded us a most welcome opportunity to entirely re-write our previous publication, and to expand it into the present volume. We trust that in the present volume we have succeeded in presenting to the medical practitioner in India a comprehensive yet brief account of the subject in all its phases.

Frankly, this book is a compilation, and chiefly taken from other sources. We have borrowed very largely and extensively, and desire to make the fullest acknowledgment of having done so. Amongst other sources we have borrowed from Manson-Bahr and Marrian Perry's article on bacillary dysentery in Byam and Archibald's *Practice of Medicine in the Tropics ;* from Dobell and Low's articles on amœbiasis and on balantidiosis in the same volume ; from Manson-Bahr's very fine article on sprue in Vol. III of the same work ; from Dobell's *Amœbæ living in Man ;* from Fletcher and Jepps' *Dysentery in the Federated Malay*

States ; from Andrewes' account of bacillary dysentery, and that of amœbic dysentery by Dobell and Harvey in *History of the Great War, Medical Services, Pathology ;* from Manson-Bahr's article on dysentery in *History of the Great War, Medical Services, Diseases of the War.* To these and to other authors from whom we have borrowed, we owe an apology ; we trust that they will realize that our motive has been the desire to quote from authoritative and unimpeachable sources, for there has been far too much erroneous teaching on the subject in the past in India.

If we have committed piracy frankly in the text, we have done even worse with regard to the illustrations. It may surprise our readers that, working as we are in Calcutta, we have been unable to provide original illustrations to this book. But the patients admitted to the Carmichael Hospital for Tropical Diseases attached to the Calcutta School of Tropical Medicine are for the most part middle class Bengalis ; deaths from dysentery are very rare indeed among them, and post-mortem examinations impossible to secure, owing to the refusal of relatives. Major G. Shanks, I.M.S., very kindly placed at our disposal the collection in the Pathological Museum of the Calcutta Medical College, but, on going through it, we found that much of the material was old, preserved in spirit, and somewhat shrunken, whilst some of it was wrongly labelled, owing to the erroneous views as to the great prevalence of amœbic dysentery which formerly prevailed.

Accordingly, we again had resort to the best sources of which we knew. We owe a debt of gratitude to the firm of Johann Ambrosius Barth of Leipzig for their very generous permission to reproduce the figures in Plates I and II, which are taken from the splendid *Atlas Tropischer Darmkrankheiten* by Dr. Gustav Baermann and Dr. Otto Eckersdorff, published by them in 1913. In reproducing these plates we have had to reduce the originals very considerably. Above all we are indebted to Dr. William Fletcher, M.D. (Camb.), formerly of the Institute for Medical Research, Kuala Lumpur, and now Secretary to the Colonial Medical Research Committee, for his immeasurable kindness in permitting us to reproduce illustrations from the splendid plates by himself and Miss Jepps in *Dysentery in the Federated Malay States*, published in 1924 ; also to Dr. A. Neave Kingsbury, Director of the Kuala Lumpur

Institute for his permission as Director of that Institute to borrow from its publications. Also to Messrs. John Bale, Sons and Danielsson for the loan of blocks. Further, our most grateful thanks in the same matter are also due to Mr. Clifford Dobell, F.R.S., Protistologist to the Medical Research Council, National Institute for Medical Research, Hampstead, London, and to Messrs. Baillière, Tindall & Cox. Our thanks are also due to Mr. E. H. W. Flemming, Assistant Radiologist, Carmichael Hospital for Tropical Diseases, Calcutta, for six of the skiagrams herein reproduced.

In studying the literature on the dysenteries of India, it is surprising to note that almost all the work done on this subject has been that of individual and isolated workers, notably Timothy Lewis and D. D. Cunningham in the very early days, more recently Sir Leonard Rogers, F.R.S. and Lieut.-Col. J. Cunningham, I.M.S. Although dysentery is the third most important cause of mortality in India, yet the disease has never been the subject of any organised research commission. It is probably this fact which is chiefly responsible for the backward state of knowledge of the subject by the medical profession in India. If the publication of the present volume does anything to help our brother medical men in India, we shall be only too gratified.

CALCUTTA SCHOOL OF TROPICAL MEDICINE & HYGIENE.
1st March, 1928.

H. W. A.
R. K.

CONTENTS.

			Page.
Chapter	I.	Dysentery in India. Morbidity and Mortality. Seasonal Incidence. The term 'dysentery.' Causation. Relative Frequencies	1
,,	II.	Acute and Subacute Bacillary Dysentery; Ætiology, Pathology and Symptoms. Acute and Subacute Amœbic Dysentery; Ætiology, Pathology and Symptoms. Balantidial Dysentery. Mixed Infections	23
,,	III.	The Diagnosis of Dysentery. Use of the Sigmoidoscope. Laboratory Examination of Dysenteric Stools. The Morphology of *Entamœba histolytica* and of *Balantidium coli* ..	43
,,	IV.	The Bacteriology of Bacillary Dysentery	64
,,	V.	The Treatment of Acute Bacillary and of Acute Amœbic Dysentery	89
,,	VI.	Chronic Bacillary Dysentery and the Bacillary Carrier ..	109
,,	VII.	Chronic Amœbiasis and the *Entamœba histolytica* Carrier. (Appendix. Table. The Morphology of the Human Entamœbæ)	124
,,	VIII.	Streptococcal Infections Secondary to Bacillary Dysentery. Sprue. The Asthenic Diarrhœa of Indians	143
,,	IX.	Prophylaxis against Dysentery	154
References		.. ..	163
Index ..		.. ..	171

COLOUR PLATES.

				Page.
Plate	I.	The lesions of acute bacillary and acute amœbic dysentery ..	*facing*	26
„	II.	The lesions of amœbic dysentery	„	36
„	III.	The microscopic appearances of the stool in amœbic dysentery and in bacillary dysentery respectively ..	„	50
„	IV.	Cysts of the chief intestinal protozoa of man as seen in a saline emulsion	„	132
„	V.	Cysts of the chief intestinal protozoa of man as seen in an iodine emulsion	„	134

ILLUSTRATIONS.

			Page.
Fig.	1.	Admissions for dysentery for six years, British and Indian armies and jails	14
„	2.	Rainfall; admissions and deaths from dysentery and diarrhœa, Rangoon, 1927	15
„	3.	Bacillary dysentery. Shiga's bacillus. Destruction of mucous membrane	28
„	4.	Acute bacillary dysentery. Shiga's bacillus. Ascending colon with black necrosis	
„	5.	Diphtheroid membrane in bacillary dysentery	
„	6.	Necrosis of mucous membrane. Infection with Flexner's bacillus	
„	7.	Amœbic dysentery. Dyak's hair sloughs and ulcers in transverse colon	37
„	8.	Amœbic dysentery. Incipient and advanced lesions ..	
„	9.	Amœbic dysentery. Sea-anemone ulcers ..	
„	10.	Amœbic dysentery. Seaweed sloughs. Ascending colon ..	
„	11.	Amœbic dysentery. Small ulcers in rectum and anus ..	
„	12.	The distribution of amœbic lesions in the appendix, colon and rectum	38
„	13.	Charcot-Leyden crystals	52
„	14.	Vegetative *Entamœba histolytica* in fresh state	

		PAGE.
FIG. 15.	*Entamœba histolytica*	57
,, 16.	*Balantidium coli:* vegetative form and cyst	61
,, 17.	Chronic bacillary dysentery. Flexner's bacillus	111
,, 18.	Subacute bacillary dysentery. Flexner's bacillus	
,, 19.	Subacute bacillary dysentery. Flexner's bacillus	
,, 20.	Chronic bacillary dysentery. Flexner's bacillus	
,, 21.	Bacillary carrier. Ascending colon with retention cysts ..	
FIGS. 22, 23, 24.	Chronic bacillary dysentery. Flexner's bacillus. Skiagrams after a barium meal	117
FIG. 25.	Chronic relapsing amœbic dysentery. Skiagram after a barium meal	125
,, 26.	Severe amœbiasis. Skiagram after a barium meal ..	
,, 27.	Slight amœbic infection of colon. Skiagram after a barium meal	
,, 28.	Amœbic dysentery. Thinning and ballooning of colon ..	130
,, 29.	Chronic amœbic dysentery; chronic ulceration of colon ..	
,, 30.	Amœbic dysentery. Healing ulcers in the rectum ..	
,, 31.	Mixed bacillary and amœbic dysentery. Descending colon ..	
FIGS. 32, 33.	Sprue. Intestinal skiagrams after a barium meal ..	148

CHAPTER I.

Dysentery in India. Morbidity and Mortality. Seasonal Incidence. The term 'dysentery.' Causation. Relative Frequencies.

PERHAPS in no field of therapeutics in India to-day is treatment more random and less satisfactory than in the treatment of dysentery—a problem which constantly faces the medical practitioner in India, and whose solution cannot as yet be said to be entirely satisfactory. Yet the years of the Great War and the post-war years have seen so many additions to our knowledge of the subject that it is time that these lessons were incorporated in the general body of medical practice in India. That such knowledge has not yet been properly appreciated in India is shown by the almost universal and entirely erroneous use of emetine in cases of bacillary dysentery in India—a line of treatment which may inflict irreparable damage upon the patient's cardiac mechanism, but which cannot alleviate his symptoms.

The Morbidity and Mortality due to Dysentery in India.

The amount of morbidity and mortality due to dysentery in India is a fact which we do not think that the medical profession in this country has as yet fully realised. In order to arrive at some approximation to the true state of affairs we have analysed the figures given in the last six available *Annual Reports of the Public Health Commissioner with the Government of India.*

Table I shows the admissions and deaths per mille for the six years 1919–1924 from dysentery, colitis and diarrhœa in (*a*) the British Army in India; (*b*) the Indian Army; (*c*) the jail population in India (including the Andamans); and (*d*) the general civilian population (death rate only). It will be seen at once from this table how important are these diseases as a cause of morbidity; the admission rate is 40·6 per mille for the British Army, rises to 46·5 per mille for the Indian Army, and in jails accounts for the very high

TABLE I.

Combined dysentery, colitis and diarrhœa. Admissions and deaths per mille.

Year.	British Army.		Indian Army.		Jails.		Civilian Population.
	Admissions.	Deaths.	Admissions.	Deaths.	Admissions.	Deaths.	Deaths.
1910–1914 ..	33·3	0·22	33·5	0·14	..	..	....
1915	44·6	0·33	50·8	0·46	..	..	....
1916	48·5	0·55	50·1	0·40	..	..	....
1917	50·1	0·32	47·6	0·46	..	..	....
1918	49·2	0·30	58·4	0·45	..	..	....
1919	55·5	0·28	65·9	0·30	..	..	1·22
1920	48·9	0·18	49·1	0·18	89·0	3·03	0·92
1921	42·4	0·15	54·7	0·38	88·6	2·41	0·95
1922	22·9	0·10	38·2	0·28	92·8	4·09	0·74
1923	24·8	0·13	33·2	0·17	77·6	2·45	0·77
1924	26·4	0·14	30·0	0·04	68·4	1·95	0·95
Averages ..	40·6	0·25	46·5	0·28	83·3	2·79	0·93

admission rate of 83·3 per mille. Mortality is relatively less important, the figures being 0·25 per mille for the British Army, 0·28 per mille for the Indian Army, but reaching the high figure of 2·79 per mille for the jail population. In the civilian population the figure is at a fairly constant level of about 1 per mille.

Table II shows the relative importance of dysentery as a cause of death when compared with other diseases in India. If we take the figures for the different groups respectively, the mortality from malaria per mille in the British Army works out at 0·48, that from respiratory diseases at 0·89, that from dysentery and diarrhœa at 0·16, that from cholera at 0·10, whilst the figure for plague—0·01—is insignificant. In other words in the British Army in India dysentery is the third most important cause of deaths, and of greater importance than cholera. In the Indian Army the figures are closely parallel, with the exception of deaths from respiratory diseases– chiefly pneumonia, which is of very great importance in this community. The death rates are : from respiratory diseases 4·02 per mille, from

malaria 0·55, from dysentery and diarrhœa 0·17, from cholera 0·15, and from plague 0·10.

TABLE II.

Relative Mortality per mille from different diseases.

	European Army.	Indian Army.	Jails.	Civil Population.	REMARKS.
I. Malaria.					
1919	0·74	0·54	1·06	* 22·93	* 'Fevers' (excluding plague).
1920	0·42	0·46	1·11	* 20·68	....
1921	0·75	0·60	0·88	* 19·72	....
1922	0·43	0·58	1·00	* 15·28	....
1923	0·27	0·69	1·01	* 15·35	....
1924	0·24	0·44	1·18	* 16·69	....
Averages ..	0·48	0·55	1·04	* 18·44	....
II. Respiratory diseases (including pulmonary tuberculosis, pneumonia and other).					
1919	1·40	5·27	7·66	1 47	....
1920	0·96	5·11	7·26	1·40	....
1921	1·13	4·61	7·21	1·38	....
1922	0·77	3·37	6·73	1 20	....
1923	0·43	2·70	6·33	1·23	....
1924	0·68	3·05	6·73	1·38	....
Averages ..	0·89	4·02	6·99	1·34	....

TABLE II.—*Contd.*

	European Army.	Indian Army.	Jails.	Civil Population.	REMARKS.
III. Dysentery and Diarrhœa.	(Dysentery only.) No diarrhœa recorded.				
1919	0·28	0·19	6·05	1·22	....
1920	0·16	0·13	3·20	0·92	....
1921	0·15	0·31	2·41	0·95	....
1922	0·08	0·21	4·51	0·74	....
1923	0·13	0·13	2·45	0·77	....
1924	0·14	0·04	1·95	0·95	....
Averages ..	0·16	0·17	3·43	0·92	....
IV. Cholera.					
1919	0·19	0·34	1·21	2·43	....
1920	0	0·02	0·15	0·55	....
1921	0·39	0·46	0·49	1·87	....
1922	0·02	0·03	0·48	0·50	....
1923	0	0·01	0·05	0·30	....
1924	0	0·02	0·11	1·22	....
Averages ..	0·10	0·15	0·41	1·14	....

TABLE II.—*Concld.*

	European Army.	Indian Army.	Jails.	Civil Population.	REMARKS.
V. Plague.					
1919	0	0·09	0·04	0·31	....
1920	0	0·08	0·01	0·42	....
1921	0·01	0·05	0·05	0·29	....
1922	0·03	0·08	0·05	0·32	....
1923	0	0·13	0·02	0·95	....
1924	0·02	0·17	0·01	1·50	....
Averages ..	0·01	0·10	0·03	0·63	....

In the jail population, despite every possible sanitary measure, careful supervision and skilled medical attendance, dysentery becomes a problem of paramount importance, being the second most important cause of death among this population. The figures are : for respiratory diseases 6·99, for dysentery and diarrhœa 3·43, for malaria 1·04, for cholera 0·41, and for plague 0·03. The very high figure for dysentery and diarrhœa in this community is probably due to conditions of crowding, and to dysentery carriers among the jail cooks. It not infrequently happens that a given prisoner appears to be weakly, when he is actually a chronic dysentery carrier. He is taken off all heavy labour and put into the cooks' gang for light work, and this may lead to an outbreak of epidemic dysentery in the jail concerned.

In the general civilian population, dysentery for all-India is nearly as important a cause of death as cholera. The figures are : for ' fevers '—it being impossible on the records to separate the mortality from malaria from that due to other fevers—18·44 per mille, from respiratory diseases 1·34—a figure which is probably well below the actual, from cholera 1·14, from dysentery and diarrhœa 0·92, and from plague 0·63.

In Table II the combined figures for dysentery and diarrhœa are given, since in the returns for the civilian population it is impossible to sort out the returns for diarrhœa from those for dysentery. In the British Army in India, the Indian Army, and the jail population, who are all under skilled medical supervision, however, the returns are given separately, and the figures are fairly reliable with regard to the different incidence for the two complaints. These returns are analysed in Table III.

Table III.

Dysentery versus Diarrhœa. Admission and Death Rates per Mille.

	EUROPEAN ARMY.				INDIAN ARMY.				JAILS.			
	Dysentery.		Diarrhœa.		Dysentery.		Diarrhœa.		Dysentery.		Diarrhœa.	
	Admissions.	Deaths.	Admissions.	Deaths.	Admissions.	Deaths.	Admissions.	Deaths.	Admissions.	Deaths.	Admissions.	Deaths.
1919	14·2	0·28	31·1	0	10·5	0·18	20·6	0·01	77·8	4·76	54·1	1·29
1920	10·1	0·16	32·5	0	6·1	0·12	14·9	0·01	50·5	2·56	38·5	0·67
1921	12·1	0·15	26·2	0	13·7	0·30	20·5	0·01	49·9	1·91	38·7	0·50
1922	9·5	0·08	10·8	0	8·5	0·18	15·7	0·03	57·8	4·09	35·0	0·42
1923	13·2	0·13	8·2	0	7·3	0·13	13·6	0	48·6	2·08	29·0	0·37
1924	11·4	0·14	11·0	0	6·5	0·04	12·2	0	41·2	1·68	27·2	0·27
Averages	11·7	0·16	19·8	0	8·8	0·16	16·2	0·01	54·3	2·85	37·1	0·59

A study of Table III shows that in the British and Indian armies admissions for diarrhœa are roughly about double those for dysentery: 19·8 per mille as against 11·7 for the British Army, 16·2 per mille as against 8·8 for the Indian Army. In jails, however, dysentery becomes a much more important cause of sickness than diarrhœa, the admission figures being 54·3 per mille for dysentery as against 37·1 for diarrhœa. On the other hand—except in the jails—the mortality from diarrhœa, as might have been expected, is a very small one. There was no death from diarrhœa in the British Army during the years 1919–1924, whilst in the Indian Army the death rate from diarrhœa during these years averaged only 0·01 per mille—a quite insignificant figure. In jails, however, the death rates are very high, that for dysentery 2·85 per mille, and that for diarrhœa 0·59—an unexpectedly high figure. It will be seen at once from a general study of Table III that diarrhœa, whilst a very general cause of sickness, is unimportant as a cause of mortality; on the other hand, dysentery, whilst less prevalent than diarrhœa, is responsible for almost the whole of the mortality due to both causes. Further, many cases of severe diarrhœa are in reality due to dysenteric infections—infections with the bacillus of Flexner or with *Entamœba histolytica*, chiefly.

From a general study of Tables I, II and III, the conclusion is inevitable that dysentery is a most important cause of both morbidity and mortality in India. In order of importance in the mortality rate of India malaria clearly comes first and foremost; respiratory diseases, including pneumonia and pulmonary tuberculosis second; whilst cholera and dysentery are almost equally placed for the third and fourth places, and both are much more important for all-India than plague.

Even this conclusion, however, does not represent the true state of affairs, for dysentery is often a terminal fatal infection in persons suffering from chronic malarial cachexia, kala-azar, pulmonary tuberculosis or other devitalising diseases, and such deaths are returned as due to the primary disease, whereas the real factor which kills is the secondary dysentery. From Table II we obtain a general dysentery death rate for the civilian population of 0·93 per mille. On a general population of 320 millions, this would represent approximately 297,600 deaths a year from dysentery in India. It is probably not an exaggeration to state that dysentery kills from 300,000 to 350,000 persons a year in India. Yet the disease has never been the subject of any organised Commission of enquiry in India, and since the days of Timothy Lewis and D. D. Cunningham in Calcutta in 1870-71 the research work carried out on the dysenteries of India has always been that of isolated and individual workers. There has long existed a large anti-plague organisation in India, whilst at present an adequate organisation against malaria in India is being gradually built up. The question of cholera has been taken in hand; yet respiratory diseases and dysentery are Indian problems of at least as great importance to India as cholera and plague. And the neglect

of the subject of dysentery in India is responsible for the want of knowledge with regard to the disease among the general medical profession in this country.

Dysentery and the Social Strata.

If dysentery is a very important factor in the general mortality in India, it is of even greater importance in the general morbidity rate. And here there becomes clear a very close relationship between the mortality due to dysentery and the social status of the patients concerned.

Since the opening of the Carmichael Hospital for Tropical Diseases in Calcutta in 1921, the European private 'cabins' in that institution have been filled by a long series of well-to-do European patients suffering from chronic and relapsing dysentery—usually due to an infection with the bacillus of Flexner, more rarely to chronic amœbic infection. Chronic and relapsing dysentery we believe to be a matter of very serious concern to the large European business firms in Calcutta. Very few deaths occur among the European community of Calcutta from dysentery, but the disease causes a tremendous amount of sickness in that community; it is responsible for much invalidism and for repeated and often prolonged absences from duty. Our experience of the last six years leads us to believe that chronic dysenteric infection is a very important cause of sickness among the general European community in India.

The figures in Table III afford a means of measuring the relative case mortality from dysentery in different communities. Thus for the British Army in India, where conditions of housing, diet and sanitation are all good, the admission rate is 11·7 per mille from dysentery, and the death rate 0·16, giving a case mortality rate of 1·4 per cent. In the Indian Army, where conditions are good, but perhaps not quite so good as in the British Army, the figures are: admission rate 8·8 per mille, mortality rate 0·16, case mortality 1·8 per cent. In jails where in general sanitary and dieting conditions are good, but where the population is drawn from a low social class, and where crowding is prevalent, the figures are: admission rate 54·3 per mille, mortality rate 2·85, case mortality 5·3 per cent. It is clear that in jails dysentery is much more prevalent, is much more fatal, and is a far greater cause of mortality than it is among the British and Indian armies in India. Conditions for the general civilian population are probably intermediate between those for the Army and the jail population respectively.

A very instructive study of the relationship of poverty and similar factors to the mortality from dysentery is that given by Fletcher and Jepps (1924) from the Kuala Lumpur Institute for Medical Research. Malaya is a country of immigrants, and whilst the indigenous Malay is comparatively free from dysentery, the immigrant Tamil and Chinese labourers suffer from it very severely. 'Poverty is the chief factor in the prevalence of fatal dysentery in the Malay States, and one of the principal causes of poverty is malaria. Numbers of the Tamils who died of

dysentery at the District Hospital had left the rubber estates where they had been employed, because of malaria. Subsequently they had wandered about the country, living on what they could get from begging, until they developed dysentery as a result of want and exposure, and either found their way to a government hospital or were sent to the home for decrepit Indians by the Controller of Labour.....When dysentery is added to privation or disease, recovery is a still more difficult matter and if a man's large intestine has been damaged to such an extent that there is little or no mucous membrane remaining, complete recovery is impossible.....Even when sufficient food can be obtained, the whole digestive apparatus is in such a weakened state that a return to normal diet means disaster and it is not uncommon for a hearty meal to bring on a fatal relapse.' The average weight of healthy Tamil labourers was just under 112 lb., whilst the average weight of 105 adult Tamils who died from bacillary dysentery was only 76 lb., or 69 per cent of their normal weight.

The same authors record that during three consecutive years there were only 2 deaths from dysentery amongst a population of some 5,000 Europeans living in the Malay States. Among the general population for the same period there was an average of 40 deaths from dysentery. At the General Hospital in Kuala Lumpur a small fee is charged for admission to the third class wards, and here the mortality amongst 1,678 dysentery patients admitted during five years was 17 per cent; on the other hand in the District Hospital in the same town where the patients are in poorer circumstances and pay nothing, the case mortality from dysentery during the same year was no less than 36 per cent.

The Seasonal Incidence of Dysentery.

With regard to the geographical incidence of dysentery in India but little needs to be said. The disease is prevalent all over the peninsula, in every city, town, village and hamlet. Possibly its incidence in hill stations is less than in the plains, but the very common hill diarrhœa which is so prevalent in hill stations—in our experience—is due to infection with the bacillus of Flexner. The junior author has seen cases of acute Shiga bacillus infection in Shillong, but they were all of very acute type and accompanied by the passage of an enormous number of stools containing blood and mucus.

It is a well known fact that the incidence of dysentery in India is much greater during the rainy season than at any other time of the year. This is well brought out in Table IV and Fig. 1. These show the admissions for dysentery (only and exclusive of diarrhœa) for the British Army in India, the Indian Army and the jail population month by month for the six years 1919–24, the figures, which are combined together, being taken from the *Annual Reports of the Public Health Commissioner with the Government of India*. (The figures for the general civilian population, of course, are not available.)

TABLE IV.

Dysentery. Admissions by Months. Army and Jails. 1919–1924.

1919.

Month.	British Army.	Indian Army.	Jails.	TOTALS.
January	64	199	627	890
February	61	132	612	805
March	48	162	695	902
April	59	221	834	905
May	80	181	802	1,063
June	68	203	867	1,138
July	90	207	1,276	1,573
August	99	249	1,088	1,436
September	93	260	823	1,178
October	57	227	800	1,084
November	57	229	811	1,097
December	26	134	707	867

1920.

Month.	British Army.	Indian Army.	Jails.	TOTALS.
January	20	69	505	594
February	28	101	376	505
March	29	63	404	496
April	29	83	394	506
May	50	95	419	564
June	73	62	489	624
July	73	185	657	915
August	84	158	748	990
September	71	156	602	829
October	60	139	509	708
November	26	125	454	605
December	35	84	433	552

TABLE IV.—*Contd.*

1921.

Month.	British Army.	Indian Army.	Jails.	TOTALS.
January	27	73	386	486
February	25	62	279	366
March	32	92	367	491
April	49	142	378	569
May	77	150	408	635
June	61	124	436	621
July	83	198	639	920
August	105	473	919	1,497
September	87	400	742	1,229
October	55	293	556	904
November	65	268	529	862
December	43	133	437	613

1922.

Month.	British Army.	Indian Army.	Jails.	TOTALS.
January	29	70	836	935
February	41	46	506	593
March	36	54	597	687
April	45	66	484	595
May	39	117	577	733
June	39	66	627	732
July	74	116	831	1,021
August	80	146	783	1,009
September	65	191	644	900
October	45	165	597	807
November	45	116	565	726
December	35	107	499	641

TABLE IV.—*Concld.*

1923.

Month.	British Army.	Indian Army.	Jails.	TOTALS.
January	24	64	384	472
February	34	46	330	410
March	31	32	401	464
April	49	66	413	528
May	43	118	445	606
June	58	71	653	782
July	81	60	638	779
August	167	156	777	1,100
September	126	148	709	983
October	86	106	611	803
November	85	104	494	684
December	47	79	411	537

1924.

Month.	British Army.	Indian Army.	Jails.	TOTALS.
January	41	62	395	498
February	20	25	266	311
March	52	52	278	382
April	35	76	372	483
May	52	49	413	514
June	47	46	440	533
July	59	99	620	778
August	86	116	599	801
September	93	98	530	721
October	71	86	507	664
November	77	86	456	619
December	36	86	350	472

Fig. 1 shows in each graph, without exception, a very steep rise in incidence during the monsoon period—July to October—with a peak which is in July in 1919, and in August in 1920, 1921, 1922, 1923 and 1924. A curious feature of these graphs is the apparent tendency for the total incidence to be greater in alternate years; but the very high incidence of dysentery in 1919 may perhaps be associated with the return of dysentery carriers from the war areas after the termination of the Great War.

We believe that four chief factors are concerned in these graphs: viz. (*a*) a more or less constant level of new infections with *Entamœba histolytica* all the year round. It is possible that amœbic infections may be more prevalent during the hot weather when the infective cysts may be blown about and disseminated by dust, but, taking our general laboratory findings in Calcutta, we are accustomed to find amœbic infections at all seasons of the year. (*b*) A more or less constant level of fresh infections with the bacillus of Flexner during the period November to June; during which period we have isolated this bacillus in cases observed in all these months. (*c*) A sudden and marked increase in the number of fresh Flexner bacillus infections during the period of the monsoon, which is the chief—if not the only—factor causing the steep rise of the curve in July to October. These infections are presumably water-borne; and the rise is shown alike in the figures for the British Army, the Indian Army and the jail population. (*d*) In some of the graphs, especially in that for 1922, a smaller peak is shown during the cold weather in January. This rise is confined to the jail figures and is not shown in the figures for the British and Indian armies. It is probably due to small epidemics due to the bacillus of Shiga in the jail population during the cold weather.

That there is a close association between rainfall and the incidence of dysentery is a fact which has long been known. Thus Sir Leonard Rogers (1921), on investigating the statistics for jails in India, concludes as follows: 'The minimum dysentery season occurs in the late cold weather months of January and February, in relationship to the minimum temperature of the year, and is commonly followed by a slight increase in the early hot weather month of March with the rise of the mean monthly temperature to between 72° and 78°F., succeeded by a slight fall during the very hot months of May and June, during which the mean temperature reaches to from 94° to 96°F. The main increase in the prevalence of dysentery always closely follows the onset of the heavy monsoon rains late in June, and thus usually begins in July, when the mean temperature has again fallen to about 80° to 82°F., and reaches its maximum in August and September. This marked monsoon rise is only absent in the extreme North-West Frontier of India, owing to the rain-bearing currents not penetrating as far as this area. Lastly, the curve steadily declines with the cessation of the rains late in October and the fall of the temperature to its minimum. Further, in years of excessive rainfall the dysentery curve is also unusually high and vice versa. The above data relate to all forms of dysentery

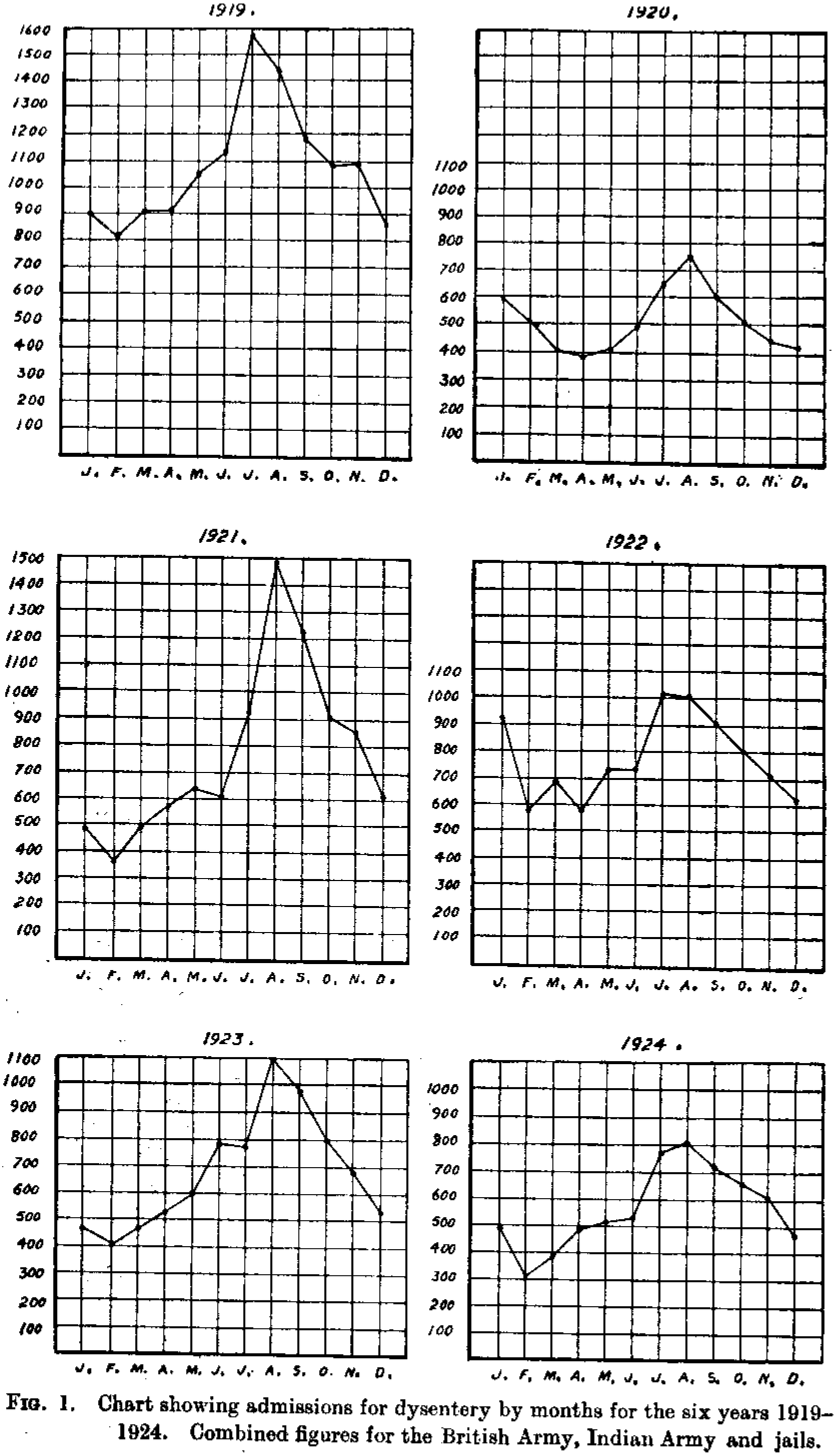


FIG. 1. Chart showing admissions for dysentery by months for the six years 1919–1924. Combined figures for the British Army, Indian Army and jails.

combined, no extensive separate figures being at present available regarding the incidence of the different types.'

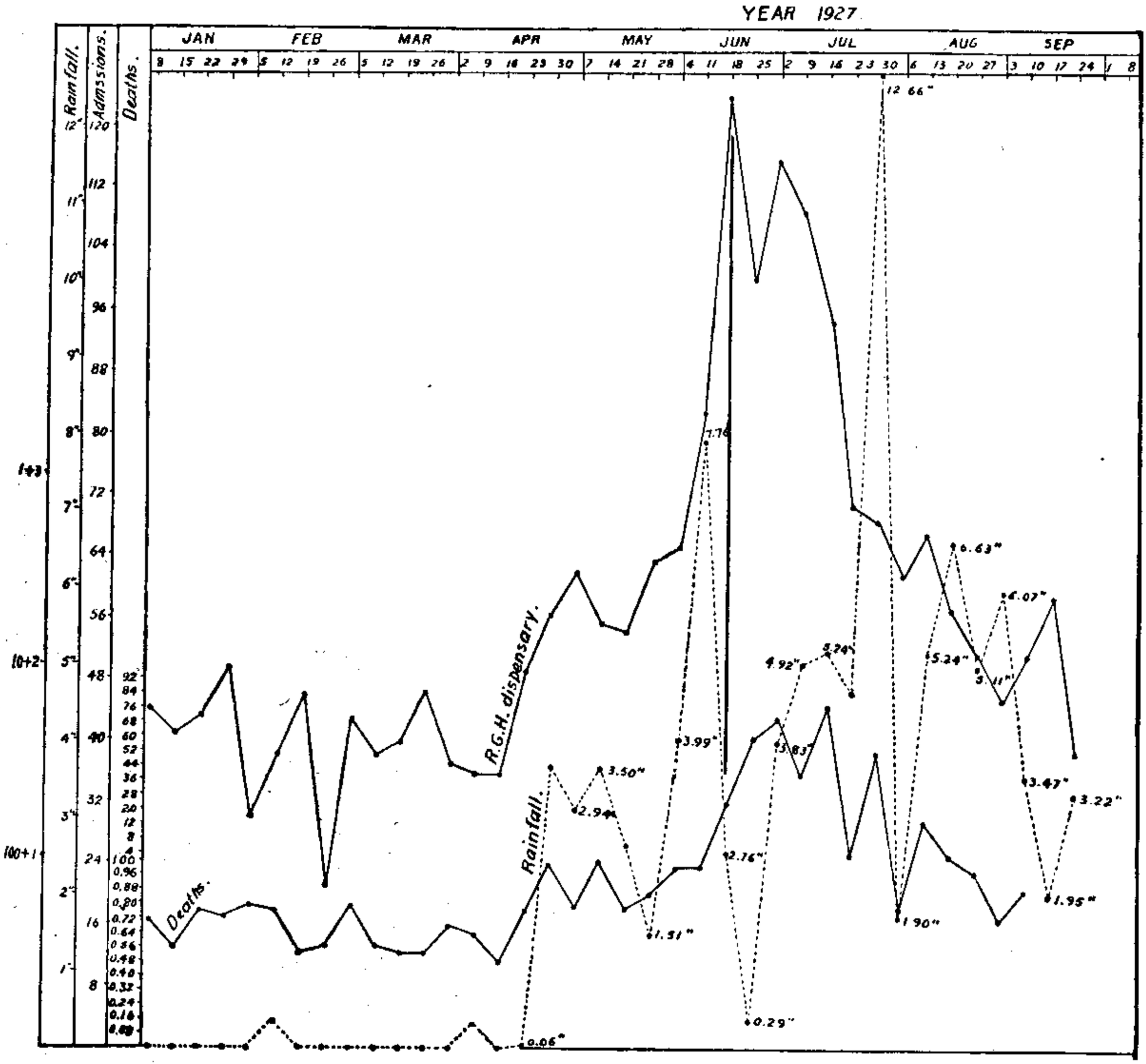


FIG. 2. Chart showing rainfall in inches, Rangoon, and admissions and deaths from dysentery and diarrhœa, Rangoon General Hospital, 1927. (Original kindly lent by Lieut.-Col. J. Morison, I.M.S.) The vertical line on June 18th represents the introduction of chlorination of the water-supply.

A very striking example of the association of rainfall with dysentery and diarrhœa is shown in Fig. 2, for which we are indebted to Lt.-Col. J. Morison, I.M.S.

This shows (*a*) the weekly rainfall in inches; (*b*) the total number of admissions per week from diarrhœa and dysentery to the Rangoon General Hospital; and (*c*) the weekly deaths from diarrhœa and dysentery in the same institution for the year 1927. A study of the portion of the chart up to June the 18th shows that every time a heavy fall of rain occurred there was a marked rise in the admissions for diarrhœa and dysentery about a week later. On June the 18th chlorination of the water-supply was introduced, with the result that the downpour of rain on July 30th was *not* followed by the usual rise in diarrhœa and dysentery, and that—in place of the usual high peak of incidence in August—the admission rate was rapidly declining in that month. The same chart also shows how the curve for death rates tends to follow the general trend of the curve for admissions at an interval of seven to ten days later, each rise in the incidence of admissions being followed by a rise in the death rate a week to ten days later.

A word may perhaps be said with regard to the age incidence of the dysenteries. In young infants entero-colitis is frequently due to the *Bacillus proteus*, in which infection the stools are frequently very offensive. At a slightly later age the summer diarrhœa of infants is usually due to Morgan's bacillus; or sometimes an infection with the *Bacillus pyocyaneus* is associated with diarrhœa and the passage of green and slimy stools containing much pus. Dysentery in childhood is almost invariably of bacillary origin, and this point is one to be especially noted in connection with the infectivity of the condition. A mother who is nursing a child suffering from a Flexner bacillus infection and at the same time preparing the household food may easily carry the infection from one member of the household to another. We have never seen amœbic dysentery in young children, and we cannot too strongly condemn the practice of treating dysentery in children by the administration of emetine; these cases are almost always—if not always—of bacillary origin.

The term 'Dysentery'.

The term 'dysentery' is not the name of a disease, but of a symptom-complex, such as asthma or bronchitis. The condition is one in which there is the passage of frequent stools containing blood and mucus, accompanied by pain and tenesmus. It is important to note the words 'mucus' and 'tenesmus' in this definition, since the mere presence of blood alone in the stool is insufficient to establish the diagnosis of dysentery. Dysentery in India is usually of bacillary origin, sometimes of amœbic origin, more rarely due to a mixed infection with the *Bacillus dysenteriæ* and *Entamœba histolytica*, and sometimes—but still more rarely—due to an infection with *Balantidium coli*. There are certain other conditions, however, which we have known to be mistaken for dysentery, and they may briefly be considered here.

They are as follows:—

(1) Internal hæmorrhoids. In this condition bleeding and pain during defæcation are characteristic. The fæces are usually formed, whilst the blood

spurts over them in a characteristic manner, and is of a bright arterial colour. Digital examination of the rectum is sufficient to exclude this source of error.

(2) A polypus of the rectum, situated low down, may give rise to tenesmus with the passage of blood and mucus. Again, digital examination of the rectum—which should be a routine matter in all cases of dysentery—will discover the presence of a pedunculated tumour.

(3) Malignant disease of the rectum is not infrequently treated as chronic bacillary dysentery. The growth is generally of the fungating variety and associated with alternating periods of constipation and diarrhœa. The patient usually shows severe debility, whilst the stools, which may contain blood and mucus, are usually very offensive. Again, digital or sigmoidoscopical examination of the rectum will differentiate the condition from dysentery, whilst the general appearance of the patient may lead to the suspicion of malignant disease.

(4) Syphilitic stricture of the sigmoid flexure or rectum is not uncommon during the tertiary period of syphilis ; it appears to occur more frequently in women than in men, and is accompanied by marked induration of the gut wall with the formation of ulcers which bleed and suppurate easily. Digital or sigmoidoscopical examination is here again of value, whilst the Wassermann test may be made. In one patient—an elderly Hindu female—weeks of treatment of what was apparently a chronic bacillary dysentery (but in which no causative organism had been isolated) were followed by no alleviation of the symptoms. The Wassermann test, however, turned out to be strongly positive, and a course of treatment with novarsenobillon led to rapid cure.

(5) Intussusception may occasion difficulty in diagnosis, especially in young children ; in fact acute intussusception may occur as a complication in a young child suffering from acute bacillary dysentery. The sudden onset of the pain, together with the development of the characteristic tumour and signs of intestinal obstruction, should be sufficient to suggest intussusception.

(6) Tubercular enteritis is a relatively common disease in India, and usually affects the small intestine and cæcum. As a rule the stools are profuse and loose, with much mucus, but little or no blood, and very offensive. The state of emaciation of the patient, the evidence of tuberculosis in the lungs or elsewhere, or the demonstration of acid-fast bacilli in the stools by the antiformin method should clear up the diagnosis. On the other hand a secondary and usually fatal infection with the *Bacillus dysenteriæ* or the *Bacillus pyocyaneus* is not uncommon in tubercular enteritis.

(7) Severe ankylostomiasis is rare in India, but may lead to the passage of mucus in the stool accompanied by slight melæna. The anæmic state of the patient is characteristic, whilst large numbers of the characteristic ova will be found on microscopical examination of the stools.

(8) Mass infestation with *Ascaris lumbricoides* may perhaps be accompanied by diarrhœa and a muco-sanguineous discharge, especially in children. Again, the characteristic ova will at once be found on examination of the stools. Even in cases of true dysentery, *Ascaris* infection may be a complicating factor and will then require adequate treatment.

(9) *Giardia intestinalis*, we believe, is never a cause of dysentery, whilst the infection is frequently present in persons who are in excellent health and passing normal stools. The evidence for pathogenicity on the part of this organism is exceedingly scanty, though perhaps it may be responsible for diarrhœa, especially in children. The characteristic cysts will be recognised on examination of the stools.

(10) The characteristic dysentery of kala-azar is usually—almost always, in fact—due to a secondary infection with the bacillus of Flexner, and is of the nature of a true bacillary dysentery, supervening in a patient whose resistance to infection has been lowered by the primary disease.

(11) Acute intestinal symptoms may develop in malaria, especially in malignant tertian malaria. These may be associated with diarrhœa and melæna, but never with tenesmus. The condition is really of embolic origin, the capillaries of the intestine being blocked by red blood corpuscles filled with parasite schizonts. This leads to multiple capillary hæmorrhages and the presence of traces of blood in the stools. The characteristic rigors and vomiting and blood examination will lead to the true diagnosis; malaria parasites have even been found in the red blood corpuscles in such stools on appropriate staining.

(12) Cholera may occasionally simulate acute bacillary dysentery, though it is far more common for a hyperacute Shiga bacillus infection to be mistaken for cholera. On microscopic examination of the stools in cholera abundant columnar epithelial cells are found, whilst pus cells and blood are absent, and the whole cytological picture is different from that in acute bacillary dysentery.

(13) Ptomaine poisoning, or infections with the *Bacillus enteritidis* or *Bacillus ærtrycke* may give rise to symptoms suggestive of acute bacillary dysentery, but the short duration of the disease, the vomiting and the absence of blood from the stools should differentiate these states from acute bacillary dysentery. A developed *B. enteriditis* or *B. ærtrycke* infection resembles paratyphoid fever far more than it resembles dysentery.

(14) An infrequent, but very curious condition, is membranous colitis. It usually occurs in elderly women, and is associated with the passage of large membranous casts of the mucous membrane of the colon. We have seen a few of these cases, but have not known the symptoms to be associated either with tenesmus or the passage of blood. On microscopical examination the cast is found to consist of fibrin, in the meshes of which lie innumerable pus cells. We have never been able to isolate the *Bacillus dysenteriæ* from such casts or to discover *Entamœba histolytica* infection in such patients.

We shall deal later with the very important question of the secondary infections in amœbic and bacillary dysentery, but sufficient has already been said to emphasise the importance of the clinical examination of the patient in all cases of suspected dysentery, including digital or sigmoidoscopical examination of the rectum, as well as the microscopic and laboratory examination of the stools.

The Causes of Dysentery in India.

Of the causative agents of dysentery in India we can at once eliminate schistosomiasis, since *Schistosoma mansoni* is not indigenous in India. *Fasciolopsis buski* is said to be very rarely a cause of dysentery, but, although this parasite does very occasionally occur in India (e.g., S. M. Lal, 1923 and Chandler, 1928, p. 731) it is sufficiently rare to constitute an exceptional curiosity. Infection with this parasite is more usually associated with severe anæmia and chronic diarrhœa than with dysentery. *Balantidium coli* infection of man occurs in India, but must be considered a very rare cause of dysentery in this country. Sinton (1923) has recorded symptomless infection with this parasite in a Pathan prisoner in Lahore jail; whilst we have frequently found *Balantidium coli* infection in pigs and monkeys (*Macacus rhesus*) in Calcutta, and one of the sweepers at the School of Tropical Medicine in Calcutta has contracted a symptomless infection with this parasite, presumably as a result of cleaning out the cages of infected monkeys. Ramsay (1923) considers *Balantidium coli* to be a common parasite of pigs, and even of cattle, in Cachar, Assam, and that man may not infrequently be infected in this area. Hermitte, Sen Gupta and Biswas (1926) record four cases of the infection in man from Moheema, Assam, three of them associated with dysenteric symptoms; they found that stovarsol was almost a specific cure for this infection. Major Shanks, I.M.S., informs us that a fatal case of balantidial dysentery occurred in the Medical College Hospital, Calcutta, in 1926. It is clear therefore that infection with *Balantidium coli* may be a very occasional cause of dysentery in India; also the infection seems to occur most commonly in the tea gardens of Assam, where the association of the tea coolies with pigs is closer than that of man with pigs elsewhere in India. On the other hand, although we have encountered *Balantidium* infection in man in Mesopotamia without symptoms, yet, during many years of work in India, we have not encountered the infection in man—with the solitary exception of the sweeper referred to, and the infection must be a rare one in this country. Free-living ciliate protozoa not infrequently come to contaminate fæces or the saline used in making up emulsions of fæces for examination, and are apt to be mistaken for *Balantidium coli* by the inexperienced laboratory worker. In one case of supposed balantidial dysentery referred to us the protozoon present was not a *Balantidium*, but a free-living *Chilodon* accidentally present in the stool from extraneous sources.

To all intents and purposes the dysenteries of India are due to infection with the *Bacillus dysenteriæ*, or with *Entamœba histolytica*, or—sometimes—with both *Bacillus dysenteriæ* and *Entamœba histolytica* in the same patient. And, of these two causes, infection with the *Bacillus dysenteriæ* is very much the more important, for, as we shall show later, although intestinal infection with *Entamœba histolytica* is quite common in man in India, it is only occasionally that this parasite is the actual cause of dysentery.

The term 'dysentery' indeed is a bad one, and one that we should like to see abolished, for the condition present in infections with *Bacillus dysenteriæ* and *Entamœba histolytica* is rather of the general nature of a colitis, invariably associated with the passage of more or less mucus in the stools, but only sometimes with tenesmus and the passage of blood.

Relative Frequencies.

Up to about 1916 it was commonly believed that most of the dysentery in Asiatic countries was of amœbic origin. With the onset of the Great War, however, dysentery became a most important problem, especially for the British Empire, which had armies fighting on many Eastern fronts. The pioneer work of Ledingham (1920) in Mesopotamia however, the admirable study of dysentery in Egypt and the Mediterranean theatres of war by Wenyon and O'Connor (1917), and above all the splendid work of Dobell in London and Southampton, which resulted in the publication in 1919 of his memoir *The Amœbæ Living in Man*, and in 1921 of Dobell and O'Connor's *Intestinal Protozoa of Man* soon showed that this view was an entirely erroneous one. Throughout Mesopotamia and India, probably throughout the East in general, bacillary dysentery is about five or six times as common as is amœbic dysentery. Thus Dobell and Harvey (1923) record that of a series of cases from different theatres of war in hospital with clinical symptoms of acute dysentery only 6·1 per cent showed motile *Entamœba histolytica*, the remaining 93·9 per cent being judged to be bacillary, either from the microscopical appearances of the cellular exudate in the stool, or by the isolation of the specific dysentery bacilli. Wenyon and O'Connor (loc. cit.) are recorded in the same memoir as having found bacillary dysentery to be sixteen times as common as amœbic in troops in Egypt during the period January to August, 1916. Anderson (1921), on an analysis of figures for troops from different fronts, considers that over 90 per cent of dysentery cases were of bacillary origin. Mackie (1922) considers that the majority of dysentery cases in Mesopotamia were of bacillary origin; whilst Cunningham (1923) found 86 per cent of cases of dysentery in the jails of Eastern Bengal to be of bacillary origin, and that much the same proportion held for Moplah prisoners examined in the Madras Presidency. In the general annual reports by the Public Health Commissioner with the Government of India it is impossible to differentiate the figures for bacillary dysentery from those for amœbic dysentery, but our

experience during the last seven years in Calcutta is that bacillary dysentery is at least five or six times as common among the civilian population of Bengal as is amœbic dysentery.

Whenever and wherever an experienced laboratory worker enters the field his findings are the same. Thus Fletcher and Jepps (1924) on an analysis of the causes of dysentery among 983 patients at the District Hospital, Kuala Lumpur, record the following findings :—

	Per cent
Bacillary dysentery proved ; *B. dysenteriæ* isolated	65
,, ,, suspected ; cell exudate characteristic	22
Amœbic dysentery proved ; *E. histolytica* present	20
,, ,, suspected from character of the cellular exudate ..	1
Cause not ascertained ; doubtful	2

In other words, bacillary dysentery constituted no less than 87 per cent of the cases. A very interesting paper in the same connection is one by Manifold (1926) on dysentery as studied among British troops in Poona. Prior to his taking over charge of the laboratory there, during 1924 of 92 cases of dysentery examined, 84 had been recorded as of amœbic origin and only 8 as being of bacillary origin. Of the first 129 cases admitted after Major Manifold's taking over the laboratory in 1925, no less than 117 proved to be of bacillary origin and only 12 of amœbic origin. The figures for 1924, he states, were completely erroneous, and the mistake was due chiefly to mistaking macrophages in bacillary dysentery stools for vegetative *Entamœba histolytica.*

The Superintendent of the Central Jail, Alipore, has kindly sent us the figures of that jail for the last three years, and they are as follows :

	Amœbic dysentery.	Bacillary dysentery.	Colitis without dysentery.
1924	15 cases	14 cases	0
1925	17 ,,	27 ,,	23
1926	23 ,,	40 ,,	66
TOTAL ..	55	81	89

An even more recent record is that by Wats, Loganandan and Conquest (1928). Their findings among British and Indian troops in the Secunderabad Command were as follows :—

Total number of cases with mucus or mucus and blood ..	404
B. dysenteriæ isolated from	178 or 44·1 per cent.
Entamœba histolytica found in	43 or 10·6 per cent.
Exudate typical of bacillary dysentery, but *B. dysenteriæ* not isolated	101 or 25·2 per cent.
Exudate indefinite ; no organism isolated	82 or 20·3 per cent.

Thus, in this series, bacillary dysentery accounted for 69·3 per cent of the admissions, and these authors remark that 'the medical officer who uses emetine or allied drugs without laboratory diagnosis would be wrong in nearly nine cases out of ten.' *

Further, whilst we cannot definitely establish any seasonal variation in the types of dysentery met with in India, yet there appears to be a definite difference in the geographical distribution of the two infections. Amœbic dysentery is relatively frequent in wind-swept dry regions, where the infective cysts are blown on to foodstuffs by hot and arid winds, whilst bacillary dysentery is relatively more common under communal and city conditions, where the population is more closely crowded and where the infection consequently spreads more easily, and especially so where water-supplies may come to be contaminated. Further, whilst bacillary dysentery—and especially that due to Shiga's bacillus—is frequently epidemic, amœbic dysentery is never epidemic, but always endemic.

We wish that we could bring home to the medical profession in India the much greater prevalence of bacillary than of amœbic dysentery, for therapy—if it is to be successful—must be based on a correct knowledge of the facts.

---

* Still further evidence on the same subject has been published by Manifold and de Monte, whilst this volume was in press. The station of Poona is notorious for the great prevalence of intestinal troubles there during the rains, a condition locally referred to as 'Poona-itis'. These workers have shown that 'Poona-itis' is almost always due to infection with the bacillus of Flexner. Important findings in their memoir are that the bacillus of Flexner far more often causes diarrhœa than true dysentery, and the great importance of flies as carriers.

REFERENCE.

MANIFOLD, J. A. and DE MONTE, A. J. (1928). Report on an investigation of dysentery and diarrhœa in Poona. *Indian Journ. Med. Res.*, Vol. XV, No. 3, p. 601.

CHAPTER II.

Acute and Subacute Bacillary Dysentery; Ætiology, Pathology, and Symptoms. Acute and Subacute Amœbic Dysentery; Ætiology, Pathology, and Symptoms. Balantidial Dysentery. Mixed Infections.

INTO the pathology and symptomatology of acute bacillary dysentery it is not necessary for us to enter in much detail, since these subjects are very well dealt with in the text-books of tropical medicine.

Of *predisposing causes* one may mention fatigue, chills, errors in drink and diet, and especially any cause likely to cause irritation of the intestinal canal. A very good example of the latter is an account of a severe epidemic due to Shiga's bacillus among Moplah prisoners at Bellary, given by Lopez (1926). The prisoners were under very good conditions of housing, food, and latrine accommodation, and flies were relatively few. But most of the prisoners when admitted were in a much debilitated condition, and an epidemic of Shiga bacillus dysentery set in with 520 cases, of which 40 or 7·7 per cent proved fatal. The only predisposing cause that could be ascertained was the very high proportion of sulphates in the drinking water supply, and when this was changed in October 1925 the epidemic ceased completely. Children under the age of five years appear to be especially liable to bacillary dysentery, whilst small outbreaks due to Shiga's bacillus appear to be prevalent in Indian jails during the cold weather, and bacillary dysentery is especially prevalent in asylums and mental hospitals. Owing to the insanitary habits of lunatics, when bacillary dysentery occurs in an asylum the latrines are very apt to become fouled, and the infection to become epidemic.

Infection is usually acquired by *contagion*, by fæcal contamination of cooking utensils, dishes and food or water, and the more crowded the community the more likely is the disease to become epidemic. A good example of infection from an infected water-supply is one given by Fletcher and Jepps (1924): a small epidemic due to Shiga's bacillus occurred in a remote village in the Federated Malay States and caused 69 cases with 17 deaths; the water-supply was from a shallow well which was found to be infected. It is stated by Manson-Bahr (1925) that the bacillus of Shiga will survive for three weeks in such a water-supply; direct sunlight, however,

is lethal to it. Chronic bacillary carriers are always a most important source of small epidemics. Thus Stitt (1922) quotes an instance of a small epidemic of Shiga type recorded by Friedmann: an infected soldier returned to barracks after furlough, and this resulted in 86 cases in the man's regiment, 49 of which belonged to his own squadron; the epidemic was only finally suppressed by the enforcement of the most rigid rules with regard to washing the hands after leaving the latrine. Mild and unrecognised cases are also important factors in the spread of epidemics.

The rôle of flies as disseminators of bacillary dysentery may possibly be of some importance. Thus Manson-Bahr (1914) records having isolated the bacillus of Shiga from the gut of house-flies in the Fiji Islands; and the same author (1922) records that in Egypt during the really hot weather both dysentery and house-flies are rare, but directly the flies increase during the cooler autumn months there is a proportionate rise in the incidence of bacillary dysentery. It has been proved experimentally that dysentery bacilli can survive for five days in the intestine of the house-fly.

We shall deal with the bacteriology of the dysentery bacilli later, but we may here quote certain figures as to the relative incidence of Shiga and Flexner infections respectively. There is no doubt that Flexner infections preponderate overwhelmingly over Shiga infections. Infection with the bacillus of Flexner tends to be endemic and to persist all the year round, with a rise to a maximum peak during the rains; whilst Shiga infections tend to occur in small and localised epidemics, and are apparently most prevalent during the cold weather. Manson-Bahr (1922) records that during the Great War Shiga infection was recorded from all theatres of war; that it accounted for about half the number of cases in the Eastern theatres; but that in France and Belgium it was responsible for only 15 per cent of the cases of dysentery. Fletcher and Jepps (1924) isolated Shiga's bacillus in only 31 or 3 per cent of their series of 983 cases. Manifold (1926) isolated it in only 15 out of his series of 117 cases of bacillary dysentery. Fletcher and Jepps remark that infections with Flexner's bacillus were eighteen times as common as infections with Shiga's bacillus; in common with all other authorities, however, they stress the importance of Shiga infections as a cause of mortality.

Wats, Loganandan and Conquest (1928) record that of 178 stools from which dysentery bacilli were cultivated, the distribution of the species of bacilli concerned was as follows:—

Total number with *B. dysenteriæ*	..	178
Flexner's bacillus isolated in	..	147 or 82·6 per cent.
Shiga's bacillus isolated in	..	22 or 12·4 per cent.
Schmitz's bacillus isolated in	..	9 or 5·0 per cent.

In brief, we would place the causative organisms of dysentery in India in the following order of importance :—

1. The bacillus of Flexner, on account of its universal prevalence.
2. The bacillus of Shiga, on account of its virulence.
3. *Entamœba histolytica.*
4. *Balantidium coli.*

Acute Bacillary Dysentery. Pathology.

We shall deal with the bacteriology and serology of the *Bacillus dysenteriæ* later in a separate chapter ; it is sufficient here to state that the dysentery bacilli are divided into two main groups : the non-mannite fermentors or Shiga-Kruse group, and the mannite fermentors or Flexner-Strong group. The former are especially associated with acute, epidemic bacillary dysentery, the latter with endemic, sporadic and subacute or chronic bacillary dysentery.

In mild cases the earliest lesions in bacillary dysentery seem to originate in the solitary lymphoid follicles of the large intestine, which become hyperæmic and swollen, and then ulcerate. From this origin ' snail-like ' ulcerations are produced which spread across the bowel wall, especially along the free edges of the transverse folds of mucous membrane. Along with this there is generalized catarrhal inflammation of the whole mucous membrane and hypersecretion of much ropy mucus. In hyperacute cases the chief change is in the intestinal mucosa, but there are abundant signs throughout the body of widespread and acute toxæmia. Very acute inflammation of the whole of the mucosa of the large intestine sets in, and, if life be sufficiently prolonged, this ends in gangrene or colliquative necrosis of the whole of the mucosa of the colon. The disease tends especially to attack the rectum and pelvic colon, but may affect the whole of the colon, and even the lower part of the ileum. On opening the abdomen paralytic distension of the large intestine is often observed ; the mucosa is bright red and acutely inflamed ; there may even be plum-coloured patches. The lumen of the gut is occupied by viscid blood-stained mucus, or even with pure blood and serous fluid. A general lymphoid peritonitis is not infrequently present in the peritoneal cavity with deposition of lymph flocculi on the peritoneal surface, whilst the mesentery is often œdematous. The mesenteric glands are inflamed, the right side of the heart engorged, the liver usually enlarged and congested with consequent parenchymatous changes. The gall-bladder usually contains scanty and viscid amber-coloured bile. The spleen is generally dark on section, engorged and slightly diffluent. In very acute cases death may occur within 56 hours from the onset of first symptoms.

In less acute cases the signs of generalized toxæmia are slighter. The mucosa of the colon is of a rosy plum colour, and stippled with numerous submucous hæmorrhages. The gut wall is œdematous and consequently thicker than normal.

Plate I.

The lesions of acute dysentery.

[Figures reproduced, reduced in size, from Baermann and Eckwesdorff (1913), *Atlas Tropischer Darmkrankheiten*, by kind permission of Johann Ambrosius Barth, Leipzig.]

Fig. 1. Acute Shiga bacillus dysentery. Death on the 6th day. Leucocytes 16,000 per c.mm. Agglutination + 1 : 60. A, descending colon; B, sigmoid flexure.

„ 2. Shiga bacillus infection; 3 months' duration. Hæmoglobin 30 per cent. Leucocytes 10,500 per c.mm. Agglutination + 1 : 40. Death from mesenteric thrombosis.

„ 3. Mixed infection. Stools full of motile *Entamœba histolytica.* Agglutination + 1 : 80 to Shiga's bacillus. Leucocytes 15,000 per c.mm. Temperature 96·5°F. Died the day after admission.

„ 4. Gangrenous amœbic dysentery. Descending colon. Perforation, localized peritonitis, and diffuse hepatitis. Leucocytes 16,600 per c.mm. Death on the 6th day.

Plate I.

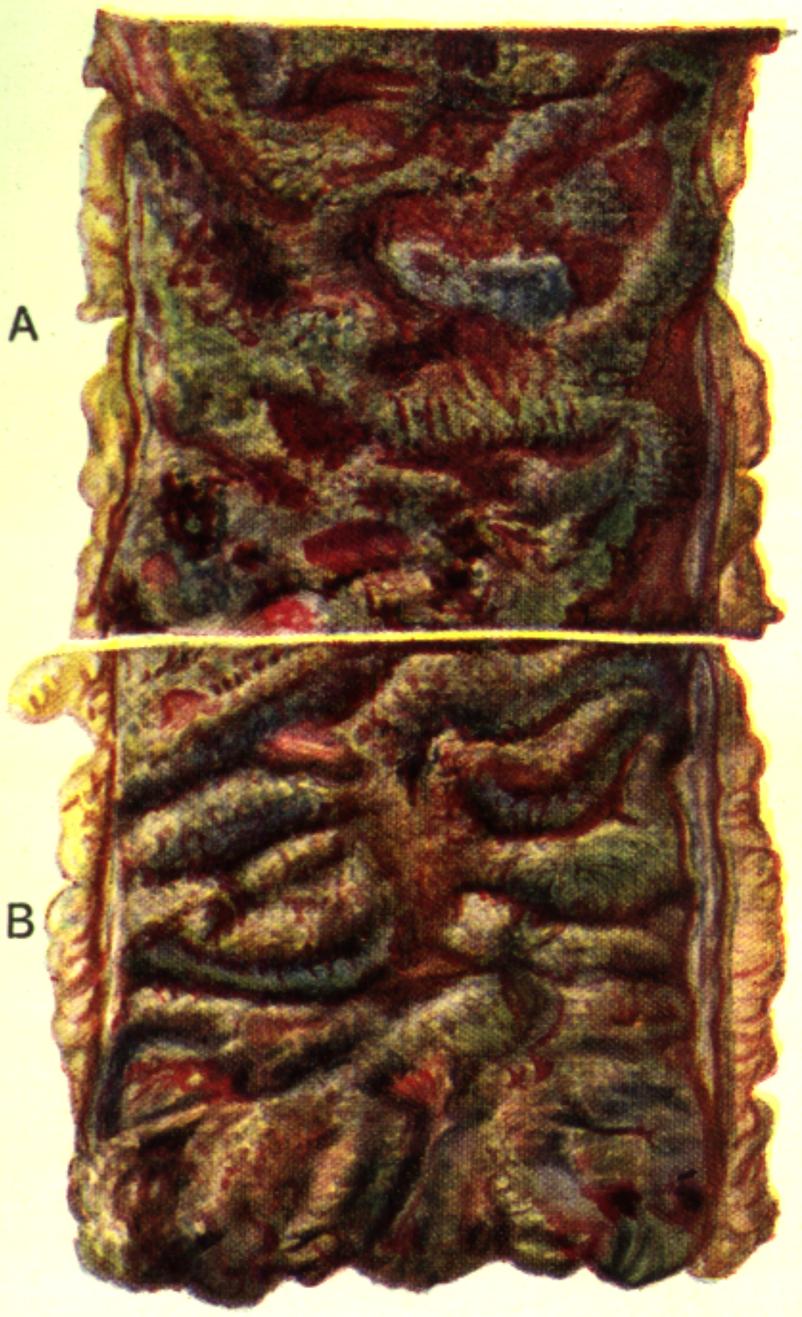


Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

If the patient survives for a week or longer, this stage of acute hæmorrhagic infiltration of the gut wall passes into a state of colliquative necrosis of the mucosa. The large gut, especially the sigmoid flexure and rectum, is narrowed down into a contracted elastic tube. The mucous membrane is converted into an olive-green—or sometimes blackish—substance, rigid to the touch, and often honey-combed or fenestrated. In acute Shiga infections the mucous membrane of the whole of the colon may be necrosed and blackish-green, from the ileo-cæcal valve to the anus, whilst there may be acute, patchy membranous inflammation of the last foot of the small intestine. The intestinal contents consist of dark grey fluid containing blood, or of fluid bile containing necrotic sloughs. Occasionally the necrosis may have a patchy distribution in the descending and pelvic colon, or be confined to the hepatic and splenic flexures.

Should the patient survive such a state of affairs, which he rarely does, the necrosed mucous membrane is exfoliated in much the same manner as a diphtheritic membrane, exposing a raw, bleeding, granulated surface underneath. In such cases death may occur in the third or fourth week of the disease. At autopsy the body is found to show great emaciation, the subcutaneous fat has completely disappeared and the tissues appear as if drained of fluid. All fat has disappeared from the omentum, and the abdominal viscera are considerably wasted. The mesenteric glands are hard and fibrous. Should the patient survive, the gut passes into a condition where fibrosis of the raw surface competes with attempts at regeneration of the mucous membrane from islands of mucosa which have escaped unscathed. Where the necrosis is more limited, exfoliation of necrosed membrane leads to the formation of ulcers of irregular outline, usually of oval or quadrilateral shape, and communicating with one another by submucous sinuses. This condition may involve the whole of the large intestine, and lead to a characteristic rat-eaten appearance. The ulcers of bacillary dysentery may be distinguished from those of amœbic dysentery by the fact that they tend to run transversely to the longitudinal axis of the gut. In subacute Flexner infections the mucosa may appear granular and resemble the skin of a toad, the œdematous mucous membrane being divided by cracks, fissures and ulcers into knobs and bosses like those on a toad's back. On repair of such a gut the colon may be contracted down to a narrow fibrous tube, with the mucous membrane converted into a glazed surface with fibrotic scars; or the colon—and especially the transverse colon—may become sacculated, portions distended with gas or intestinal contents alternating with fibrous constricting bands. Plastic peritonitis may lead to the matting together of coils of large and small intestine and omentum.

Where less extensive damage has taken place, the mucous surface resembles reddish plush, and the formation of granulation tissue may occur as a generalized condition throughout the mucosa of the colon, or in scattered portions in the lower part of the large bowel and may end in polypus formation. Diaphanous

areas of fibrosed bowel may occur at the hepatic and splenic flexures. General hypertrophy of the bowel wall, such as is observed in chronic amœbic dysentery, does not occur.

The ulceration in bacillary dysentery usually does not extend deeper than the submucous coat, but very occasionally it may involve the muscular and even peritoneal coats. Manson-Bahr (1922) records that in a series of over 300 autopsies on bacillary dysentery cases ante-mortem perforation of the transverse colon with generalized peritonitis was found in 3 instances. This however is a very rare complication of bacillary dysentery. The ulcers are generally roughly ovoid in shape, their bases consisting of grey and yellow tenacious sloughs.

Turning to the histo-pathology of the diseased tissues, in the most acute phase the mucous membrane is infiltrated with lymphocytes and round plasma cells, the capillaries are engorged and there are numerous capillary hæmorrhages in the submucosa. The goblet cells show great secretory activity, whilst the lymphoid follicles beneath the muscularis mucosæ are intensely inflamed. In the necrotic stage the whole mucosa has undergone coagulation necrosis and is converted into a structureless layer in which only polymorphonuclear leucocytes with disintegrated nuclei can be distinguished with difficulty. The submucosa is thickened to twice or three times its normal thickness, owing to œdema and hæmorrhage. The œdema is most intense amongst the connective tissue fibres and lymphatic channels immediately adjacent to the muscular coats. In the vascular and lymphatic capillaries numbers of large endothelial macrophages can be distinguished throughout the section. These are large cells, from 15 to 20 μ in diameter, and appear to be derived from the capillary endothelium. They often contain ingested red blood corpuscles and leucocytes, and when voided in the stools are liable to be mistaken for vegetative forms of *Entamœba histolytica*. The fibres of the circular and longitudinal muscular coats stain badly and appear to be affected by the general toxic processes. In the stage of exfoliation of the necrosed mucosa, the dead mucosa is seen towards the lumen of the gut, whilst beneath it the muscularis mucosa has become converted into a mass of granulation tissue and the submucosa has become the site of newly-formed capillaries. In the stage of repair proliferation of the columnar epithelium of the crypts of Lieberkühn is seen, together with abundant formation of granulation tissue. The submucosa is œdematous and contains much collagenous fibre and fibroblasts.

Dysentery bacilli have occasionally been recovered from the inflamed mesenteric glands at autopsy, but never from the bile or blood-stream. During life, however, they may very rarely indeed invade the blood-stream. Thus Manson-Bahr (1922) records that Wilson during the war in France recovered Shiga's bacillus in 3 instances in blood cultures from 88 acute cases, and also obtained Shiga's bacillus 3 times and Flexner's bacillus 8 times in cultures of the urine of 1,113 cases.

FIG. 3. Destruction of mucous membrane. Bacillary dysentery. Infection with Shiga's bacillus. The mucous membrane was almost entirely destroyed and hung in shreds. Patient died on 32nd day of the disease. In some parts of the intestine only the serous coat was left intact. The cæcum was like a thin walled balloon.

(After Fletcher and Jepps, 1924.)

FIG. 4. Acute bacillary dysentery. Ascending colon with black necrosis. Infection with Shiga's bacillus. The patient was taken ill in the surgical ward of the hospital, and died on the 9th day. There was an acute, patchy, membranous inflammation of the lowest 12 inches of the ileum. The mucous membrane of the large intestine was necrosed and blackish-green from the ileo-cæcal valve to the anus.
(After Fletcher and Jepps, 1924.)

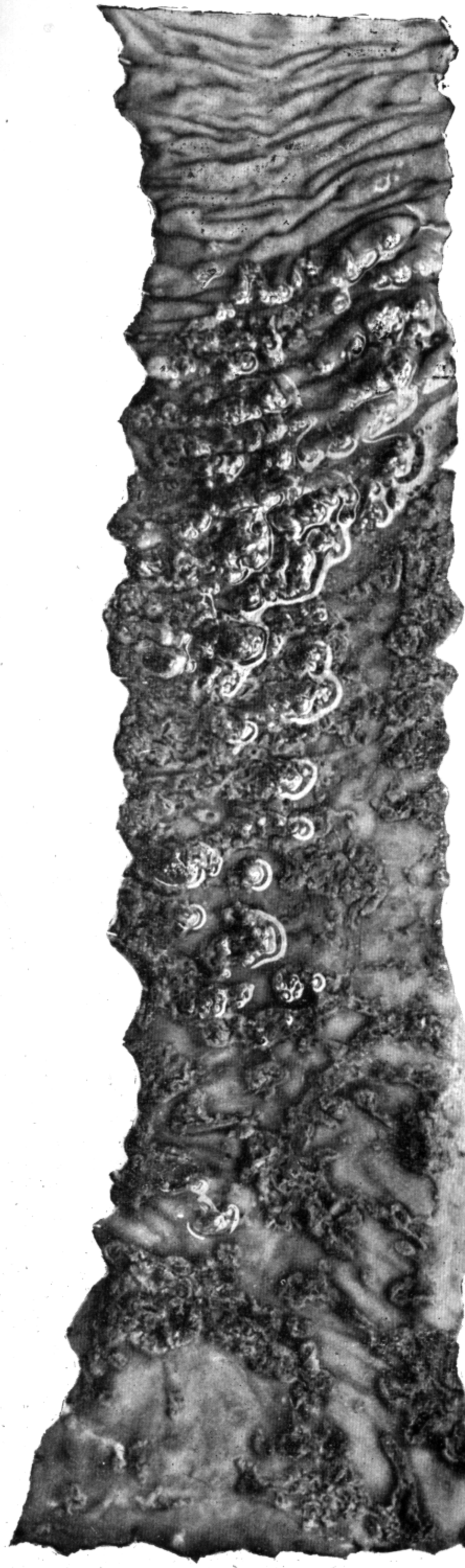


FIG. 5. Diphtheroid membrane in bacillary dysentery. Dysentery contracted in hospital. Patient died on the 9th day.
(After Fletcher and Jepps, 1924.)

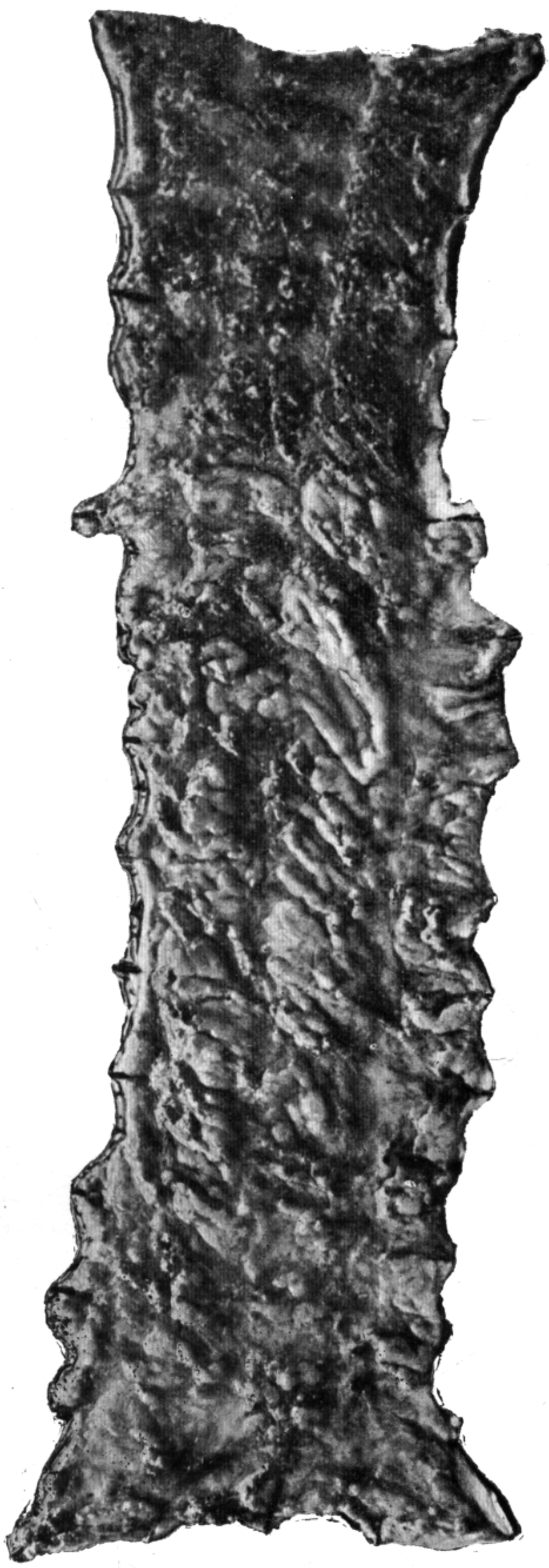


FIG. 6. Necrosis of mucous membrane. Infection with Flexner's bacillus. Acute inflammation of the large intestine, especially the ascending and transverse colon. Death on the 10th day.
(After Fletcher and Jepps, 1924.)

Acute Bacillary Dysentery. Symptomatology.

Bacillary dysentery may be of any grade of severity, from a mild diarrhœa of a few days' duration to a fulminating choleraic attack with a fatal result within two or three days of onset. The incubation period appears to be short, about 2 to 6 days as a rule. The onset—in contra-distinction to what occurs in amœbic dysentery—is usually sudden; there is at first general abdominal discomfort, followed by an initial diarrhœa, accompanied by violent and painful intestinal peristalsis. As a rule the diarrhœa continues for a day or two before blood appears in the stools.

On the other hand, in fulminating cases the onset of the disease is dramatic in its suddenness. These may be divided into two types—the choleraic and the gangrenous. In the choleraic form the onset is frequently accompanied by vomiting; collapse sets in early, with all its concomitant symptoms; the temperature is subnormal; the tongue dry and glazed, the skin cold and clammy, and the patient may even complain of cramps. There is usually an initial watery diarrhœa, which is soon replaced by dark-red mucus containing a large proportion of blood, or it may be serum alone. It is hardly necessary to emphasize the close clinical resemblance which these cases bear to cases of true cholera. The gangrenous form of the disease commences suddenly with a rigor, headache, vomiting and other evidences of a severe toxæmia. The face is flushed, the pulse rapid and bounding. The abdominal pain and tenesmus are very severe, but as the toxæmia deepens, these wear off. It is very important to note this point, for in such patients, with pyrexia and insensitiveness to abdominal pain, the prognosis is apt to be very bad. The stools at first resemble 'meat-washings,' but towards the end are composed of dark-grey offensive fluid, containing much blood. In these cases the necrosis of the mucosa is so excessive that the goblet cells are all destroyed; hence mucus does not appear in the stools in such cases.

Fever is present in all cases of bacillary dysentery (with the exception of those of choleraic type); generally it is of a low type, 99° to 100°F., but in acute attacks the temperature may rise to 103°F. or so at night. The fever is of intermittent character and accompanied by drowsiness and headache.

Generalized griping abdominal pains are very characteristic of the disease, together with generalized pain and tenderness over the whole abdomen. The tenesmus indicates intense inflammation near the anal orifice, and the more intense this inflammation and the nearer the anus its site, the more severe will be the tenesmus. Early in the disease the recti muscles are rigid, but later—especially in fatal cases—the abdomen becomes quite lax, and the pain appears to be no longer felt, the patient being overwhelmed by toxæmia. The sigmoid colon is generally very tender on palpation, and if contracted by spasm can be rolled like an elastic cord under the examining hand. The transverse colon and cæcum are rarely affected to the same degree, and are less often palpable.

The number of the stools passed during the 24 hours varies enormously according to the severity of the disease, and their number and character may be taken as a guide to prognosis and treatment. They may only number 3 or 4 in the day, or there may be up to 50 stools a day, or they may be so incessant that the patient is almost continuously on the bed-pan. In cases running a favourable course, after an initial diarrhœa, they consist of gelatinous blood-stained mucus resembling red currant jelly or pink frog's spawn ; they are of such tenacity that the stool adheres to the bed-pan and can only be detached from it with difficulty. They are characteristically odourless, or may have a faint smell of spermin. After three or four days in such cases the stools become more purulent, contain less blood, and are of a yellowish colour. Next the bile-pigments make their appearance, together with grey fæcal matter, whilst finally, the appearance of pasty yellow stools indicates that convalescence has begun. In some mild Flexner cases the stools may be fæcal from the beginning, but with a glairy coating of mucus. In many Flexner bacillus infections the stools are diarrhœic and offensive, containing mucus, but little or no blood.

In fulminating bacillary dysentery the stools contain a large proportion of dark blood and resemble 'meat-washings', whilst they have a musty odour. There may be dark blood-stained clots mixed with green bile-stained mucus or the stool may consist of a very foul dark liquid containing much altered blood, without obvious traces of mucus. When necrosis of the mucosa has taken place the stools may be choleraic in character and contain sloughs of the dead exfoliated mucosa. In hyperacute cases the stools may consist only of pure blood or of serous exudate.

The blood changes are not characteristic in bacillary dysentery. In about a quarter of the cases there is moderate leucocytosis. The urine in severe cases is concentrated, of high specific gravity, about 1,030, dark coloured, and contains abundant urates. The tongue is usually clean, but in acute cases may be coated with a thick yellow fur.

Acute Amœbic Dysentery. Ætiology and Pathology.

Acute amœbic dysentery is due to invasion of the mucous membrane of the colon by *Entamœba histolytica*, but is actually an unusual—and not a common—complication of amœbiasis. The morphology of this parasite will be described later, but it is to be noted that in only some ten per cent of persons infected with *E. histolytica* is there sufficient ulceration of the colon mucosa to give rise to symptoms of dysentery.

Infection is acquired by the patient swallowing the infective cysts of the parasite. The resistance of the cysts of *E. histolytica* is extraordinary. They are killed by complete desiccation, but will withstand anything short of it for a prolonged period of time. Yorke and Adams (1926*a*) have recently made a special study

of the viability of the cyst of *E. histolytica*. They find that normal fæces contain a substance which tends to kill off the cysts, but when the passed fæces are diluted with water the cysts survive. The cysts commence to die off rapidly in fæces kept at either 0°C. or 16° to 20°C., and are all dead in 3 or 4 days' time. Washed suspensions of cysts however may show viable cysts up to a period of three weeks. At 45°C. the cysts survive for 30 minutes, but are killed in 5 minutes at a temperature of 50°C. They are remarkably resistant to emetine and yatren and to relatively high concentrations of hydrochloric acid and chlorine. Chlorine in strengths far in excess of that used for bacteriological sterilization of water-supplies has no effect on them.

The following chemicals were found to be lethal to the cysts in the strengths stated, both at 37°F. and at laboratory temperature :

Mercuric perchloride at	1 :	2,500.
Formaldehyde	0·5	per cent.
Carbolic acid	1 :	100.
Lysol	1 :	100.
'Milton'	2·5	per cent.
Potassium permanganate inactive at	1 :	100.

Yatren ; no effect in 5 per cent solution.

Emetine hydrochloride ; no effect in 5 per cent solution.

Transmission occurs from man to man by the contaminative method. Usually in the tropics infection is acquired from a 'carrier', i.e., an apparently healthy person who harbours *E. histolytica* in his colon, passes the infective cysts in his fæces, and has to do with the handling of foodstuffs. Water-supplies and fresh vegetables may also come to be infected, whilst the cysts may perhaps be blown about in dust and settle on foodstuffs. A fall of rain may wash sewage into wells and water-supplies and thus pollute them with the infective cysts. Tanks, rivers and ponds are frequent sources of infection. Wenyon and O'Connor (1916, 1917) have stressed the importance of flies as carriers and disseminators of the infection ; they will feed readily on fæces containing cysts of *E. histolytica*, and the cysts will pass intact through their intestine and be deposited in their fæces on foodstuffs, etc. Or a fly, by first visiting the latrine and then the dinner table, may convey the cysts on its spongy feet from fæces to foodstuffs. In general, however, it is the human carrier who is chiefly responsible for the carrying of the infection. If a medical officer in charge of a regimental mess or other hostel institution has a number of cases of amœbic dysentery frequently occurring, examination of the fæces of all cooks or mess servants concerned who have to do with handling the food will soon show the presence of one or more active carriers, responsible for the occurrence.

The incidence of *E. histolytica* infections is now known to be world-wide. Dobell (1921) gives the percentage of infection among 3,146 persons examined in the

United Kingdom as being from 7 to 10 per cent. Boeck and Stiles (1923) examined the fæces of 8,029 persons in America, including both those who had stayed at home and those who had been abroad, and found from 8 to 10 per cent infected. Wenyon and O'Connor (1917) in Alexandria found 5 per cent of healthy British troops infected, 10 per cent of regimental cooks—a most dangerous state of affairs—and 14 per cent of apparently healthy jail prisoners. In Calcutta, during a year's routine examination of hospital patients, 24 persons were found parasitised out of 233 examined; and we may conclude that in general some 10 per cent of humanity is parasitised with this entamœba; also that in the tropics the figure is probably higher—some 15 per cent or so.

The senior author, when attached to No. 12 Indian General Hospital in Mesopotamia in August-December 1916, examined the stools of the whole personnel of the hospital—112 persons—and found that 6 per cent of them were *E. histolytica* carriers. In September 1918, the personnel had risen to 300 in all by the addition of new drafts, but most of the old personnel were still present. The stools of these 300 persons were now examined, and a carrier incidence of 20 per cent was discovered. These findings show how the carrier incidence steadily rises in a community of individuals constantly exposed to amœbic infection.

Kofoid, Swezy and Boyers (1925) record as high an incidence as 53·7 per cent on examining 367 employees of mixed races of the United Fruit Co., in America, but this figure refers to a rather low grade population. The more often and the more carefully stools are examined in the tropics, the higher becomes the incidence of *E. histolytica* infection, and a general figure of 15 per cent for the tropics is probably not too high.

That man contracts the infection by swallowing the infective cysts was first experimentally demonstrated by Walker and Sellards (1913) in the Philippines. They selected 20 jail prisoners in whom, on repeated preliminary examination of their stools, no protozoa had been found. They were placed on a fully cooked diet, with nothing but distilled water to drink, in order to exclude all natural channels of infection. They were then fed with capsules containing cysts of *E. histolytica*, collected from the fæces. Eighteen out of the 20 became parasitised with *E. histolytica* in periods varying from 1 to 44 days, the average being 9 days, and 4 of these persons went on to develop amœbic dysentery at 20, 57, 87 and 95 days respectively after the infective feed (average 65 days).

It is possible that the dog may play some part in the dissemination of amœbic dysentery in India, for pariah dogs frequently feed on fæces, and Ware (1916) has recorded what was apparently spontaneous amœbic dysentery in a pack of foxhounds in India. Nine dogs became infected, of which one died and the other eight were cured by the administration of emetine. No worker has yet discovered encystation of *E. histolytica* in the dog, but the possible rôle of this animal as a disseminator of amœbic infection deserves further investigation. Certain authors

claim that the rat may harbour *E. histolytica*, and Lynch (1915) claims to have successfully infected this animal experimentally. Brug (1919) states that wild rats in Java—*Mus rattus*—harbour *E. histolytica* in Nature, but a natural entamœba of the rat, *Entamœba muris*, is of very common occurrence, and somewhat simulates *E. histolytica*, though it forms an 8-nucleate cyst, such cysts often containing chromatoid bars. Kessel (1923) states that rats may be freed from their natural amœbic infection by feeding them with stale bread soaked in a saturated solution of magnesium sulphate, and claims that in such rats, freed from their natural infection, he has established *E. histolytica* infection. Kessel (1923*a*) regards the rat—*Rattus norvegicus*—as a natural reservoir of *E. histolytica* and a probable disseminator of the disease from man to man. The rat is a common inhabitant of drains and sewers, but it is a clean feeder, and it is very doubtful whether it can play the part attributed to it as a disseminator of amœbic infection.

The cyst wall of *E. histolytica* is insoluble in gastric juice, but soluble in trypsin (Ujihara, 1914). Hence, when the infective cysts are swallowed, presumably they pass through the stomach unchanged, and excyst, either in the small or the large intestine. Sellards and Theiler (1924) have shown that experimental excystation of *E. histolytica* can be produced in the rectum of the kitten, and their work has been confirmed by Knowles (1925) and Hoare (1926). Hence it is probable that in man the site of excystation of the cyst is the large—rather than the small—intestine. The actual process of excystation has been especially studied by Yorke and Adams (1926). In the formed stool of the carrier there are found cysts at all stages of development: 1-nucleate, 2-nucleate, and adult 4-nucleate. In culture these cysts often develop into the mature state and excyst; the cyst wall dissolves and from within it a mass of protoplasm containing 4 nuclei emerges, the nuclei being clustered together at the anterior pole. From this, four little uninucleate amœbulæ are budded off in turn. Sometimes, however, the nuclei multiply until 8, 16, or even more are present in a cluster at the anterior pole, and a similar large number of uninucleate amœbulæ are budded off in turn. Presumably a similar process takes place in the human colon, and the little amœbulæ creep by pseudopodial movement to the mucosa of the colon which they invade, finally settling in the submucous layer, where they multiply by binary fission.

Amœbic infection may occur at any age, although it is distinctly uncommon in young children as compared with adults. The infection, when once acquired may, and probably does, persist in most untreated cases for the rest of life (Dobell and Low, 1922, p. 1349). All races and both sexes are liable to infection, and in Calcutta at least we consider the infection to be quite as common in male Europeans as in Indian males.

Once the amœbæ are liberated from the cysts they first attack the mucous membrane of the gut. They may attack the mucosa directly at any point on its surface, or may pass down the crypts of Lieberkühn and make their entry into the

tissues through these. *E. histolytica* secretes a powerful proteolytic ferment and feeds upon pre-digested tissue juice, this leading to dissolution of the tissues, and in sections of infected gut the amœbæ are seen lying in clusters in little pools of dissolved tissue between the mucosa and the submucous coat. The amœbæ divide by binary fission and, as they multiply, they tend to wander laterally in the plane between the mucous and submucous coats. As they constantly come in contact with fresh living tissue, they attack, dissolve, and destroy it. They are thus found in close relationship to the living cells, and with a variable quantity of necrotic tissue in their train.

The degree of ulceration produced by *E. histolytica* varies very widely. Within recent months a certain amount of evidence has come forward indeed to show that occasionally—but only occasionally—*E. histolytica* may live in the lumen of the gut and feed upon bacteria. This however is not its normal habitat, which is in the deepest layers of the colon mucosa, where it feeds upon dissolved tissue juice and, sometimes, red blood corpuscles. Even in the apparently healthy carrier ulceration of the gut is present, often indeed to a surprising extent—even in the absence of symptoms. The ulceration may be superficial, and not extending through the muscularis mucosa, or it may be so deep as to cause a perforation into the peritoneal cavity. It may be localized as solitary ulcers, varying in size from those just visible with a hand lens to conspicuous crater-like cavities several centimetres in diameter. On the other hand, it may be diffuse, and spread over areas of all sizes. A serpiginous type of ulceration is not uncommon and adjacent ulcers—originally discrete—frequently become confluent. A common type of ulcer, and one which is generally regarded as typical, is one in which the amœbæ have penetrated the mucous membrane, leaving a breach of variable size at the point of entry, and have then spread laterally in the submucous layer, where they give rise to a pocket of necrosed tissue extending beneath the mucosa and passing downwards to a variable depth. Such undermining of the mucosa is common and gives rise to ulcers with an overhanging margin, and filled with necrotic tissue which often projects in shreds and tufts into the lumen of the gut. In vertical section the ulcers have the shape of a flask. Deep ulcers often have swollen or raised edges, and are surrounded by punctate hæmorrhages. The smallest ulcers may only appear to the naked eye as tiny hyperæmic patches. All types of ulceration may be seen in different parts of the gut simultaneously.

When the ulceration is not sufficiently severe to give rise to symptoms we refer to the patient as an *Entamœba histolytica* 'carrier,' and it is clear that such a carrier is a danger both to himself and to others. He passes cysts of *E. histolytica* in his stools and may thus infect other persons, whilst if at any time his resistance to the infection is lowered, the ulceration may become severe and the patient develop amœbic dysentery. Exactly why infection with *E. histolytica* should give rise to amœbic dysentery in one person, but in nine others to no symptoms at all,

it is difficult to say, and a study of the problem is badly wanted. The ideal relationship between parasite and host from the point of view of both is that of balanced mutual toleration, and this is nearly but not quite reached in the 'healthy' *E. histolytica* carrier. Presumably what causes the carrier to go down with amœbic dysentery is a sudden or gradual lowering of resistance in the mucosa of his colon. In this connection the work of Sellards and Leiva (1923*a*) is of great interest; they have shown that under conditions of stasis in the colon, with the gut contents very fluid, infection of kittens occurs when cysts are administered into the lumen of the colon. Possibly the same two factors—intestinal stasis and a fluid condition of the contents of the colon—are operative in man. Further, the presence of hæmolytic streptococci may be of importance. As shown by Knowles, Napier and Das Gupta (1923), and Acton and Knowles (1924) the stool in amœbic dysentery is usually markedly acid in reaction, and the following findings for the pH of stools may be quoted.

	Number of observations.	pH findings; mean and standard deviation.
E. histolytica present and actively motile	25	6·35 ± 0·299
E. histolytica present, vegetative phase, dead or dying ..	22	7·00 ± 1·112
E. histolytica cysts present	51	7·24 ± 0·253
Charcot Leyden crystals present, no amœbæ seen ..	54	6·96 ± 0·291
Bacillary dysentery, proved as such on culture ..	23	8·11 ± 0·168

Observations during 1925 at the Calcutta School of Tropical Medicine have shown that practically every sweeper at the School is a 'healthy' carrier of *E. histolytica*, but free from symptoms. In the case of these sweepers on repeated culture of the stool no hæmolytic strains of streptococci have been isolated. On culture of the stools of acute amœbic dysentery on a modified Conradi-Drigalski medium, however, hæmolytic streptococci are very frequently isolated, whilst the same often happens in the case of the carrier with minor symptoms. Non-hæmolytic streptococci are of normal occurrence in healthy stools, but these streptococcal strains in acute amœbic dysentery are of hæmolytic type and correspond to the *Streptococcus anginosus* type of Andrewes. It is possible that what happens in the transition from the healthy carrier state to that of amœbic dysentery is that hæmolytic streptococci invade the small amœbic ulcers, produce lactic acid, and that this acid environment proves favourable for the rapid growth and multiplication of *E. histolytica*. It is to be noted, however, that Boeck and Drbohlav (1925)

Plate II.

The lesions of amœbic dysentery.

[Figures reproduced, reduced in size, from Baermann and Eckwesdorff (1913), *Atlas Tropischer Darmkrankheiten*, by kind permission of Johann Ambrosius Barth, Leipzig.]

Fig. 1. Amœbic dysentery; acute gangrenous necrosis. Transverse colon. Stools watery brown, offensive, and incessant. Temperature subnormal. Leucocytes 21,600 per c.mm. Ileum also affected in lower part. *Entamœba histolytica* found post-mortem in enormous numbers. Death on the 6th day.

„ 2. Acute amœbic dysentery, supervening after lobar pneumonia. Cæcum and ascending colon. Leucocytes 13,600 per c.mm. Temperature 102·9°F. Acute necrosis and sloughs.

„ 3. Recurrent subacute amœbic dysentery. A, cæcum and ascending colon; B, descending colon. Miliary abscesses in the right lobe of the liver, and thrombosis of the right external iliac vein. Stools 5 to 10 a day.

„ 4. Mild, chronic amœbiasis of the cæcum and ascending colon. Patient died from tuberculosis of the lungs, ileum and mesentery. *Entamœba histolytica* present in sections of the ulcers. Stools diarrhœic.

PLATE II.

FIG. 1.

FIG. 2.

A

B

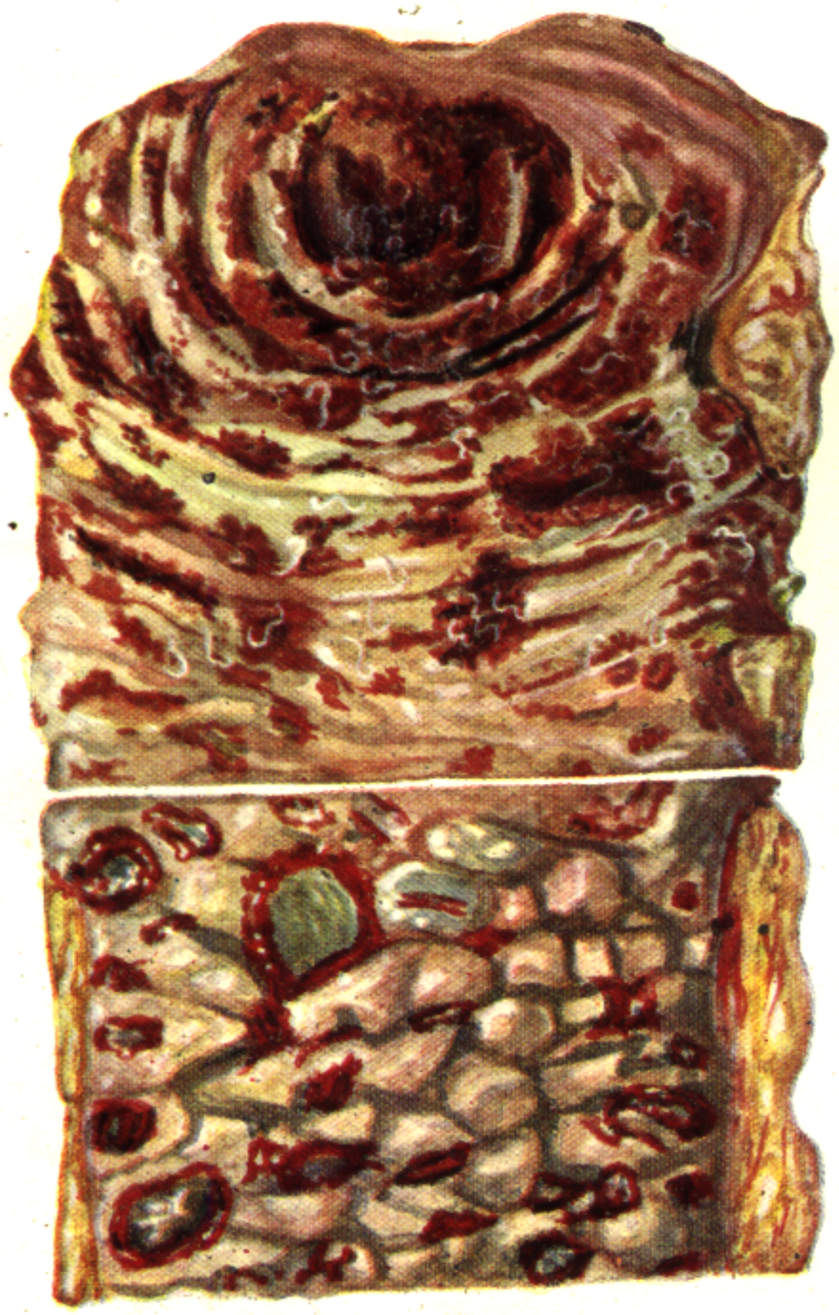


FIG. 3.

FIG. 4.

FIG. 7. Amœbic dysentery. Dyak's hair sloughs. Amœbic ulcers in the transverse colon, with frayed margins and black hairy sloughs. Patient had suffered from repeated attacks of dysentery. He died two days after admission to hospital with amœbic ulcers from the ileo-cæcal valve to the anus.
(After Fletcher and Jepps, 1924.)

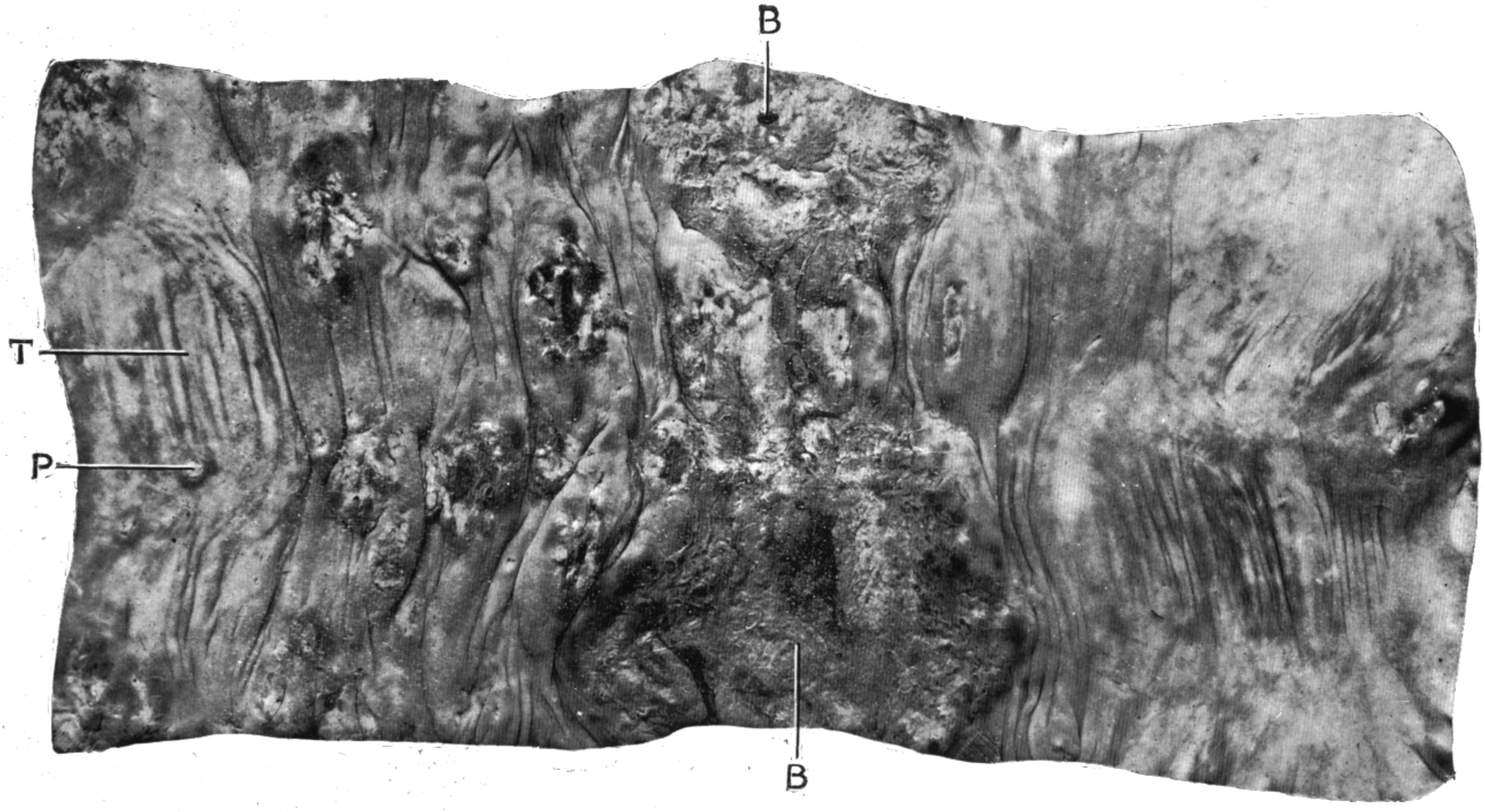


FIG. 8. Amœbic dysentery. Incipient and advanced lesions. Two large ulcers with hairy, black sloughs marked B. Several small ulcers. Minute papular lesions, marked P. Thinning and ballooning of the colon between the ulcers at T. History of dysentery for 10 days. Died on the day of admission to hospital.
(After Fletcher and Jepps, 1924.)

FIG. 9. Amœbic dysentery. Sea-anemone ulcers. Sigmoid flexure. Ulcers with raised margins and white sloughy bases.
(After Fletcher and Jepps, 1924.)

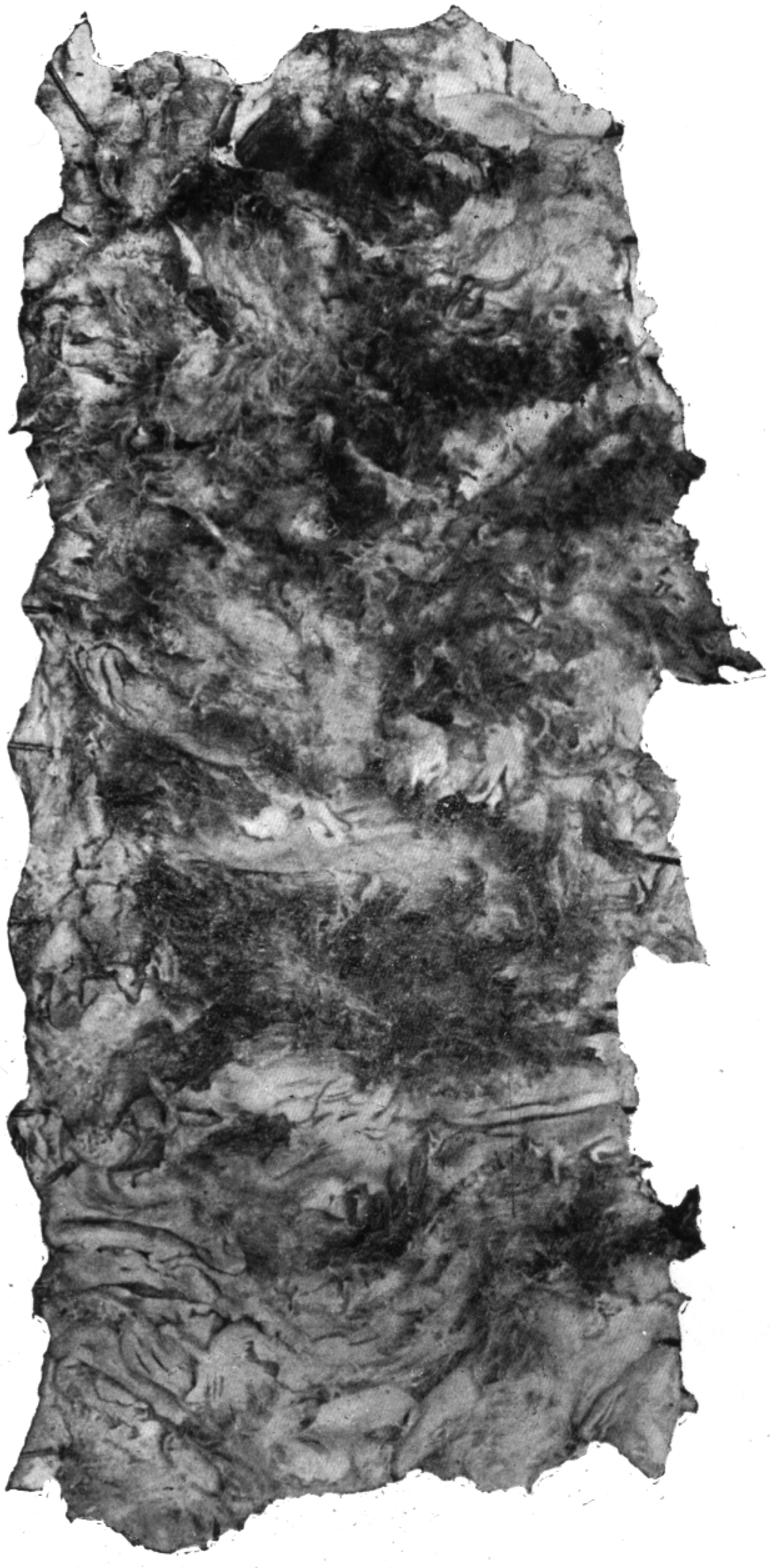


FIG. 10. Amœbic dysentery. Seaweed sloughs. Ascending colon. The whole of the mucous membrane covered with stringy, black sloughs like seaweed. History of 14 days' illness, but it must have been of longer duration. There were firm adhesions to the pancreas, and two perforations in the transverse colon.

(After Fletcher and Jepps, 1924.)

FIG. 11. Amœbic dysentery. Small ulcers in the rectum and anus. The ulcers in the rectum are never very large. Their bases are formed by yellow or white sloughs. The stringy, black sloughs are found higher up the intestine.

(After Fletcher and Jepps, 1924.)

record that the pH of their culture medium for *E. histolytica* is from 7·2 to 7·8, and that the amœbæ grew well at this pH. This fact would rather tend to throw doubt upon this 'acid environment' view. Further investigation is wanted on the whole subject, for if we could only obtain a clear understanding of why *E. histolytica* should prove pathogenic to some persons, but not to others, we should be in a position to much improve our treatment of amœbic dysentery.

Whatever the case, with the onset of amœbic dysentery the ulceration which was present in the carrier state now becomes much more extensive. The characteristic lesion of amœbic dysentery is an exuberant ulcer. The border of the ulcer is raised, rounded, and frayed at the edge, whilst attached to its base is a shaggy black slough—the 'Dyak's hair sloughs' as Fletcher and Jepps (1924) term them. The lesion commences from beneath the surface of the mucous membrane, attacks it from below, pushes it up and breaks through, whereas bacillary dysentery, on the contrary, begins as a catarrhal inflammation of the surface, succeeded by colliquative necrosis. In a moderately severe case the whole surface of portions of the colon may be covered with 'sea-anemone' ulcers with rounded, raised margins and white sloughy bases. From other ulcers long hairy black sloughs hang into the lumen of the gut, or the whole surface of the colon may be covered with stringy black sloughs looking like seaweed. In the rectum the ulcers tend to be smaller and fewer in number than in the cæcum and ascending colon.

The invasion of the mucous membrane by the entamœbæ is accompanied by reaction on the part of the tissues, leading to the characteristic ulceration. The capillary vessels at first show stasis, then thrombosis. Exudate is poured out from them giving rise to œdema, followed by coagulation necrosis. There is a certain degree of round celled infiltration, but not suppuration; if suppuration be present, it indicates a secondary infection. The necrotic tissue in the cavity of the ulcer consists of a coagulum containing cells in all stages of disintegration, broken down nuclei and fragmented endothelial cells. In acute cases the sloughs are dark in colour, and have been compared to old black cobwebs. Stools containing such sloughs are usually very offensive.

Whereas in bacillary dysentery the part of the colon most usually attacked is the rectum and pelvic colon, in amœbic dysentery the lesions are most numerous in the cæcum and ascending colon, where the ulcers may be so numerous as to cover the whole surface with hairy-looking sloughs like a tangle of seaweed. When ulcers do occur in the rectum, they are usually small, and with but little sloughing. Clark (1924) has shown that the infection especially tends to become localized at the flexures of the colon. In 186 fatal cases of amœbic dysentery examined post-mortem the distribution of the lesions was as follows:—(*a*) scattered throughout the colon in 113 cases (61 per cent); (*b*) isolated areas alone involved, 63 cases (34 per cent), chiefly in the cæcum, ascending colon, iliac colon, rectum, and hepatic flexure in that order of frequency; (*c*) in 10 cases (5 per cent) no ulcers, but only

scars were found; these were cases of secondary amœbiasis with infection of other organs. Stasis, he emphasizes, is of great importance in intestinal amœbiasis, and it is at the sites where stasis is greatest that there is a special tendency for the amœbæ to invade the gut wall. The appendix was involved in 41 per cent of the cases, and the lower end of the ileum or the ileo-cæcal valve in 5 per cent. Figure 12 is taken from his paper.

In convalescent cases, after the amœbæ have been killed off, either by treatment or by the natural powers of resistance of the body, the sloughs separate and granulation tissue appears at the base of the ulcer. Fibrous tissue is gradually

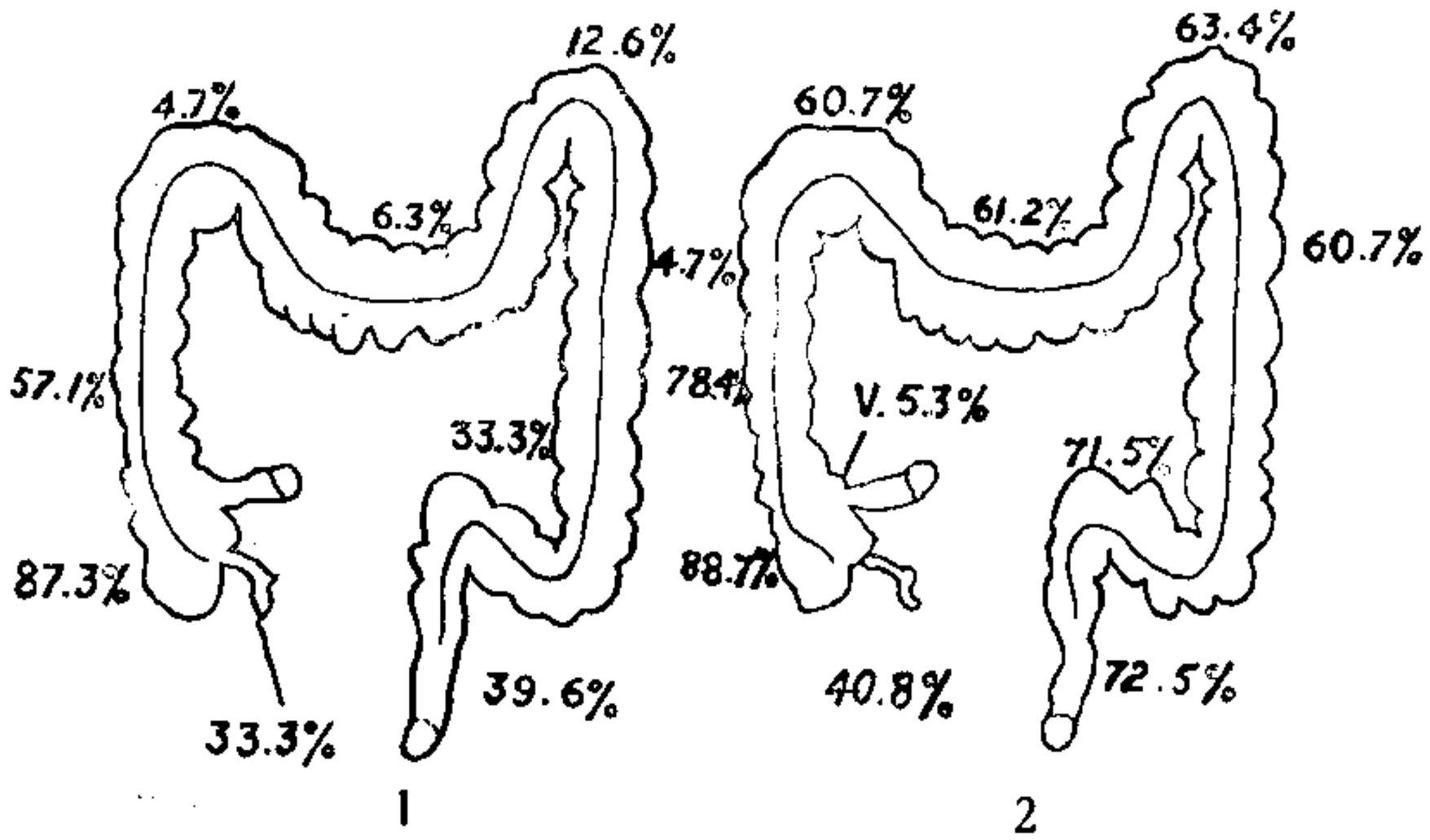


FIG. 12. The distribution of amœbic lesions in the appendix, colon and rectum. (After Clark, 1924.)

1. Shows the regional distribution of lesions in 63 cases examined post-mortem, where only one or few ulcers were present. This shows the sites where primary infection of the gut is most liable to occur.
2. Shows the regional distribution of the lesions in a total of 186 fatal cases examined post-mortem.

formed and contracts, giving rise to a characteristic parchment-like scar, often of a slatey colour. Fletcher and Jepps (1924) describe the healed ulcers after amœbic dysentery as 'strong, smooth, depressed, inconspicuous cicatrices. The scars of bacillary dysentery, on the contrary, are always pigmented, and are often so friable that they break down readily under slight pressure.'

Amœbic Dysentery. Symptomatology.

The mode of onset of amœbic dysentery differs very markedly from that of bacillary dysentery. In bacillary dysentery the onset is usually sudden, and the

patient, rendered ill by the toxæmia present, takes to bed. In amœbic dysentery—in our experience—the onset is usually gradual and progressive, and the patient, although incommoded, tries to carry on his work. Very frequently amœbic dysentery begins as a mild diarrhœa, which gradually develops into dysentery in the course of a few days. Even severe and ultimately fatal cases may begin in this mild fashion. There is considerable abdominal discomfort, but not the marked abdominal pain of bacillary dysentery; tenderness on pressure is usually elicited over the cæcum and transverse colon. The stools in acute amœbic dysentery are usually small, dark, tarry in colour and offensive. They are larger than those in bacillary dysentery, are always fæculent, and are much fewer in number than in bacillary dysentery; they may number only three or four during the 24 hours and seldom exceed twelve. Fever is not present as a rule, except in severe cases or when hepatitis accompanies the dysentery. Tenesmus and straining as a rule are much less marked than is the case in bacillary dysentery, as the rectum is much less frequently involved. The stools contain much dark and altered blood and have an offensive odour. In consistence and appearance they have been compared to anchovy sauce. Blood-streaked mucus is present and occurs as flecks scattered throughout the fæcal mass. In most cases the cæcum and ascending colon are thickened and palpable, and in old standing and chronic cases the markedly thickened cæcum may be mistaken for an appendicular abscess; progressive emaciation is often a marked feature of the disease.

In fulminant and gangrenous cases the onset may be sudden, or the condition may be reached progressively after beginning with mild symptoms. In such cases there may be numerous stools—up to 20 or so a day—and the stools may contain much blood or be hæmorrhagic. If the ulceration is near the hepatic flexure the stool may be small, black and tarry and there may be severe epigastric pain. If the gangrene becomes extensive the gut may become paralysed and the passage of stools may cease. The stools in these severe cases are full of the characteristic black cobweb-like sloughs, and as Rogers (1921) points out, these may be detected by freely diluting the stool in a large vessel with water. There may be severe abdominal pain and all the signs of early peritonitis. Leucocytosis up to 25,000 per c.mm. may be present in the early phases of gangrenous amœbic dysentery, but is not characteristic of milder cases. The cæcum and ascending colon are definitely palpable as an elongated sausage-like mass, and if the intestine is greatly thickened without being tender in an acute case, gangrene is usually present and the prognosis bad.

Death may ensue from exhaustion, intestinal hæmorrhage, perforation, peritonitis or complicating liver abscess. Perforation may be sudden, with all the signs of acute peritonitis, and in such cases laparotomy is usually of no avail owing to the gangrenous condition of the gut. More commonly post-cæcal or post-colic

perforation may occur, leading to abscess formation behind the peritoneum, and such cases may very closely simulate appendicular abscess.

Cases which partially recover are very apt to become cases of chronic amœbic colitis. This condition will be dealt with in more detail later, but in the meantime we may quote the following passage from Sir Leonard Rogers (1921):

'Cases in which the bowel symptoms have persisted for a month or more may be considered for purposes of description to be chronic, although any hard and fast line must be artificial, but necessary for purposes of clinical classification. There are few diseases which so frequently pass into a chronic and intractable stage as amœbic colitis, the ulceration continuing for months or even for years, fresh portions of the mucous membrane becoming involved as the earlier attacked parts heal, extreme organic change of the bowel wall eventually resulting. The symptoms also vary greatly in accordance with the activity or quiescence of the bowel disease, any degree from an acute gangrenous exacerbation down to mere slight irregularity of the bowels being met with, whilst for weeks or even months the disease may be practically in abeyance, once more to light up suddenly as a fairly severe attack of dysentery.'

'By this time the patient will have become emaciated, and anæmia of considerable degree will be evident from the pallor of the mucous membranes. The muscles will be greatly atrophied and the strength proportionately reduced. The stools, although less frequent than in the earlier stages, are yet sufficiently numerous and painful to be a cause of constant suffering to the patient, whose condition is altogether a most pitiable one, and if no relief is afforded by treatment he gradually sinks into extreme asthenia, and, worn out by his sufferings, eventually finds a happy release in death.'

Rogers further gives an analysis of the duration of the condition in 30 such cases. Of these 5 had lasted for 1 month, 12 from 1 to 3 months, 7 from 3 to 6 months, 4 from 6 to 12 months, and 2 for over a year.

Balantidial Dysentery.

Balantidial dysentery is so rare in India that we have had no personal experience of it. The following general outline is taken from Dobell and Low (1922*a*):

'Invasion of the tissues of the large intestine by *Balantidium coli* gives rise to a chronic catarrhal condition and ulceration. The ulcers are usually blackish to the naked eye, and recent ones are generally irregularly shaped with undermined edges. Between the ulcers the mucosa is reddened and hæmorrhagic. In distribution, conformation and appearance generally, the ulcers resemble, both macroscopically and microscopically, those produced by *E. histolytica*. Histologically, the principal changes are catarrh of the mucosa, necrosis, hypertrophy of

the vessels, hæmorrhages, round-celled infiltration and sometimes infiltration with polymorphonuclear leucocytes. A local eosinophilia has also been described. The parasites usually lie against or in the healthy tissues underlying the ulcers. They occur singly or in groups in the mucosa and submucosa at all depths, in the muscular layers sometimes and in the blood-vessels and lymph spaces.....

'E. L. Walker (1913) believes that *Balantidium coli* can pass through the healthy mucous membrane by pushing aside the cells or rupturing the epithelium, the process not being accompanied by necrosis and ulceration. A diastase and a hæmolysin have been isolated from the parasites (Glaessner, 1908) but not, as yet, a proteolytic ferment, and it seems still doubtful how they actually penetrate and destroy the tissues..... Secondary invasion of the liver or other organs—such as is seen at times in amœbiasis—is not known to occur in balantidiosis.

'Balantidiosis in man is sometimes associated with clinical symptoms, especially diarrhœa and dysentery. Walker found that about 20 per cent of his cases showed intestinal symptoms—the others being comparatively healthy carriers. Severe colic is a common symptom, and tenesmus, loss of appetite, thirst, a dirty tongue and cachexia have also been noted. Sometimes there is nausea or even vomiting. There is typically no pyrexia and the leucocyte count is usually normal, but sometimes a secondary anæmia appears in the later stages.

'When diarrhœa is present, the stools are liquid and alkaline. In more severe dysenteric cases they contain, in addition to mucus, blood and occasionally pus. The abdomen may become swollen. Palpation of the colon often elicits tenderness, and thickening may be felt through the abdominal wall. When the disease has become chronic, general weakness, exhaustion and emaciation are typically observable. Œdema of the feet and ankles has been noted (Strong, 1904)..... General thickening of the wall of the bowel may be met with, and also strictures resulting from cicatricial contraction of old ulcers. In Strong's analysis of reported balantidial cases 25 per cent of the patients gave a history of having either associated with pigs or eaten or prepared fresh sausages, and it appears probable that human beings usually acquire infection with *Balantidium coli* through swallowing food or drink contaminated with pig's fæces containing cysts.'

Mixed Infections.

Mixed infections with both bacillary and amœbic dysentery are by no means uncommon, and Fletcher and Jepps (1924) record them as present in 27 out of their series of 198 cases or 14 per cent. Dysentery bacilli and pathogenic amœbæ were only found together twice in the same specimen of fæces, and from three to

six or more examinations were necessary to discover all cases of mixed infections. In 15 out of these 27 cases the double infection probably existed before the patients were admitted to hospital ; in the other 12 the bacillary infection was apparently contracted whilst the patients were in hospital undergoing treatment for amœbic dysentery. It is to be noted that bacillary dysentery *is frequently contracted in hospital.* Amœbic ulceration may be superimposed on a healing bacillary infection, but this is rare. It is much more common for acute bacillary dysentery to supervene in an intestine which is in a condition of chronic amœbic ulceration.

CHAPTER III.

The Diagnosis of Dysentery. Use of the Sigmoidoscope. The Laboratory Examination of Dysenteric Stools. The Morphology of *Entamœba histolytica* and of *Balantidium coli.*

In the diagnosis of dysentery, careful clinical examination of the patient should never be omitted, whilst it is advisable to have a four hourly temperature chart kept. If the patient is not carefully examined, such diseases as typhoid fever or tubercular enteritis or syphilitic stricture of the rectum may easily be mistaken for dysentery. On the other hand laboratory examination of the stools is even more necessary than clinical examination of the patient.

The Use of the Sigmoidoscope.

Within recent years the sigmoidoscope has come to be more and more used in the diagnosis of the type of dysentery from which the patient is suffering, whilst its value in excluding conditions which may simulate dysentery is very great. Recent papers which have drawn attention to the use of the sigmoidoscope—especially in connection with chronic and relapsing dysentery in India—are those by Hance (1927) and Gregg (1928) : also one by Manson-Bahr and Gregg (1921). The following are details with regard to its use, chiefly taken from these three accounts.

The patient should first be carefully prepared, or very little will be seen. In chronic cases it is as well to give a mild purgative overnight in order to clear the bowel. The bowel is at the same time repeatedly washed out with warm saline from a rectal tube and large glass funnel, the washing being continued until the returned fluid is quite clear. This should be again repeated the next morning before the examination is made. About 20 to 30 minutes before the examination is made gr. $\frac{1}{4}$ of morphia may be given hypodermically, and a gr. $\frac{1}{30}$ suppository of cocaine inserted into the rectum. With these precautions an anæsthetic is not usually necessary. Examination is best carried out with the patient in the lithotomy position, though Hance especially advocates the knee-elbow posture.

The instrument having been generously lubricated with glycerine is inserted into the anus and the patient directed to breathe deeply with his mouth open. Relaxation being thus obtained, the instrument is passed beyond the sphincters and passed gently onwards, being left more or less to find its own way. During

its passage in the anal canal it will be observed that the sigmoidoscope points first towards the patient's umbilicus and then, on entry into the rectum, changes its direction to adapt itself to the sacral curve. On this change of direction taking place, the obturator is removed, and the eyepiece with illuminating device substituted, the remainder of the passage of the instrument being under direct visual control. If the lubrication has been liberal and the bowel thoroughly emptied, but little use of the bellows is necessary. In this way a thorough and detailed inspection of the rectum and the lower 4 to 6 inches of the sigmoid flexure is possible. In normal healthy persons the bowel wall should be in soft folds which should yield gently as the instrument is advanced in the direction of the lumen. The mucosa should resemble the inside of the cheeks in colour, but be slightly less shiny, and the small blood-vessels are more prominent. On reaching the pelvic colon the wall appears more flexible and the folds smaller and more numerous.

In acute bacillary dysentery the sphincter may be hyper- or hypotonic; the bowel is intensely hyperæmic and instrumentation is painful. The contents of the bowel consist of a uniform mixture of blood and mucus, with which much pus may be incorporated. The surface of the mucosa is dull, and œdematous thickening takes up the folds of the gut so that they become less apparent. There may be large irregular ulcerated areas, but not infrequently the bowel presents a spongy, uniform wall which oozes blood all over on the slightest touch.

In chronic bacillary dysentery the perineal muscles are wasted, the sphincter tone poor, and the anus almost patulous. The mucous membrane may show general injection and hyperæmia, bleeding easily when touched, or there may be irregular ulcers, shallow, with their margins not undermined and their bases showing shreds of muco-pus, of which a film may cover the whole ulcer. Areas of exuberant granulation tissue may mask subjacent ulceration, and the latter may only be revealed on removal of the former with a wool-carrying probe. The folds of the gut may be narrow and scanty. The surface may in one place show anæmia, and in another be hyperæmic and glazed or granular in appearance.

In amœbic dysentery there are frequently accompanying hæmorrhoids, the sphincters are usually normal in tone, and the rectum is thrown into voluminous folds so that the bowel appears redundant. These folds are soft and are easily pushed aside without pain. The contents of the bowel are mixed fæces, mucus and blood. The sheen of the mucosa is of normal colour, and scattered on the bowel wall are ulcers which are usually small, clear cut, oval, circular or diamond-shaped or saucer-shaped. The smallest ulcers are about the size of a pin's head, with the intervening mucous membrane normal in appearance. Sometimes the ulcers crown small elevations in the mucous membrane, in which case they give an appearance resembling minute boils or carbuncles. In more acute cases the ulceration is much more extensive and flame-shaped, and blood-stained mucus may

be observed drifting into the instrument and obscuring the view. Instrumentation is usually painless despite the ulceration.

One of the chief merits of the use of the sigmoidoscope is that not only will it often enable an immediate clinical diagnosis of which type of dysentery is present to be given, but it will enable the observer to get perfectly fresh material for microscopic examination and culture.

The Laboratory Examination of Dysenteric Stools.

If treatment is to be properly applied it is essential that as soon as the patient comes under observation the correct diagnosis of which type of dysentery he is suffering from shall be made. Whilst the general clinical state of the patient and the use of the sigmoidoscope may help to differentiate between bacillary and amœbic dysentery, the examination of the stools in the laboratory alone will enable the physician to say with certainty which type of infection is present.

1. The first essential is that the stool must be a fresh one, free from urine and antiseptics, passed into a dry bed-pan. If possible, the whole stool should be sent for examination. Examination of stale stools is a waste of time. A useful method of obtaining perfectly fresh material is one advocated by Colonel Proctor, I.M.S. If the patient is in the laboratory, suffering from dysentery, a soft rubber catheter can be passed well into the rectum, twisted round several times and withdrawn. There will then be a good deal of blood-stained mucus in the eye of the catheter, sufficient at least for microscopic examination and culture. This ensures obtaining perfectly fresh material. The use of a sigmoidoscope will also ensure obtaining fresh material.

2. First record the macroscopic appearance of the stool. As shown by Cunningham (1923) macroscopic examination of stools is of great value in controlling epidemic and endemic dysentery in such institutions as jails, etc. Daily macroscopic examination of the stools of all inmates will soon enable one to identify those men who are passing blood and mucus, or mucus only, and to segregate them; further, microscopic examination in the case of these men will show what type or types of dysentery are present, and indicate the correct line of treatment.

The stool in bacillary dysentery may vary a good deal in character, especially if the disease has lasted for some days, but typically it is an inoffensive stool, composed almost entirely of bright red blood and mucus, with little or no fæcal matter. In amœbic dysentery the character of the stool may be very varied indeed. It may be simply diarrhœic; it may be semi-formed, with or without adherent traces of blood and mucus; and its colour may vary from deep brown to greyish green. It is often a small stool, dark and tarry in colour. As a rule the blood and mucus—the former of which may be invisible to the naked eye—tend to mingle more intimately with the fæcal matter than in the case of the bacillary stool. Taken all

round, however, an inoffensive stool consisting only of bright red blood and mucus is usually from a case of bacillary dysentery, whilst an offensive stool with adherent or admixed blood and mucus and much fæcal matter is usually from a case of amœbic dysentery.

3. Next test the reaction of the stool. This can be done with red and blue litmus paper and gives useful information. Or the pH can be tested. The stool of bacillary dysentery is usually strongly alkaline in reaction, with a pH of about 8·0; the stool of amœbic dysentery is often markedly acid, with a pH of about 6·1 to 6·6. This point is of importance: in the bacillary stool the red blood corpuscles are unchanged and their hæmoglobin unaltered; in the acid stool of amœbic dysentery, the red blood corpuscles are affected and their hæmoglobin changed to acid hæmatin.

4. Next prepare saline and iodine emulsions of the stool for microscopic examination. The details of technique are as follows:

I. Preparation of the Saline Emulsion:—

(1) Take a perfectly clean slide and cover-slip. (Dirty slides, greasy slides, scratched slides, frosted cover-slips, which medical storekeepers delight to supply, are useless.) The slide and cover-slip must be absolutely clean and not merely half clean. Also the cover-slip should be a thin one—No. 1 or No. 0. Large square cover-slips are best.

(2) The saline to be used must be fresh and not stale. (Stale saline often becomes contaminated with free-living protozoa.) For most purposes normal (i.e., 0·85 per cent) saline is satisfactory, though for motile protozoa a strength of 0·5 per cent is perhaps preferable. Place a small (not large) drop of saline on the centre of the slide.

(3) Pick up a tiny particle of the stool. If the stool is a fluid one this is best done with a capillary pipette. If the stool is formed or semi-formed the point of a wooden toothpick is useful for this purpose (though it should have no antiseptic on it). The writers usually use the point of a scalpel. A platinum loop is unsatisfactory, as it is too flexible.

(4) Very thoroughly emulsify the particle of stool in the saline. Cover with the cover-slip. If there is now too much fluid for satisfactory working, tilt the slide gently, and with a bit of filter-paper applied at the margin of the cover-slip drain away any excess of fluid. If the examination is likely to be a prolonged one, ring the preparation with vaseline.

(5) Everything depends on getting the emulsion right. The mistake usually made is to make the emulsion too thick; this obscures vision and renders accurate observation impossible. It is far better practice to search three or four thin preparations than to attempt the impossible task of examining a thick preparation. If the emulsion has been properly prepared, when the prepared slide is laid on a page of printed matter it should be easy to read the print through it.

(6) With the microscope set vertically, concave mirror, tube length out, condenser racked down, iris perhaps partly closed, and good critical illumination, examine the slide; first a general glance through with the $\frac{2}{3}$rds objective; then with the $\frac{1}{6}$th inch dry objective. Using the mechanical stage, work systematically through the whole of the preparation, stopping to examine minutely every suspicious object. The greenish translucent colour of the protozoa as seen in saline is most characteristic.

If the preparation has been properly made, the oil immersion objective can be used and will give far clearer detail than the dry $\frac{1}{6}$th. (The writers specially advocate the use of a $\frac{1}{7}$th inch 'fluorite' oil immersion objective which gives good working distance, very clear definition, and is far more satisfactory than a dry $\frac{1}{6}$th.)

II. Preparation of the Iodine Emulsion :—

(1) Prepare the following solution :—

Iodine 1 gramme ; potassium iodide 2 grammes ; water 100 c.c. (This solution gradually decolourizes, and it should be used as fresh as possible, e.g., a fresh solution be made every 7 or 10 days.)

(2) Prepare an emulsion of a particle of the fæces in this iodine solution in the same way that the saline emulsion was prepared, taking the same precautions, and making the emulsion thin.

(3) Examine this in the same way as the saline preparation. (A modification of the iodine method which gives very good results is to proceed as follows :—Make a fine emulsion of the stool in the above iodine solution with a pestle and mortar. Centrifuge thoroughly. Throw away the supernatant fluid. Put a small drop of normal saline on a clean slide. With a capillary pipette pick up a tiny particle of the centrifuged deposit and thoroughly emulsify it in the saline. Mount under a cover-slip and examine. By this method cysts are stained with iodine and stand out against the unstained saline background, and details can readily be made out.)

* * * *

The laboratory worker should always prepare and examine *both* saline and iodine preparations. In the saline preparation the vegetative forms will be seen and cysts encountered, whilst in the iodine preparation nuclear structure stands out and the details within the cysts can be made out. Three or four preparations from all suspicious parts of the stool should be examined.

He should also remember that the cysts of the intestinal protozoa are infective if swallowed, and all material used in examining the stool should be transferred to 5 per cent lysol solution after use, including slides, cover-slips, toothpicks, etc.

(4) First, examine the general characters of the cellular exudate in the stool.

The microscopic characters of the exudate in the stool in amœbic dysentery are as follows :—

(*a*) The total cellular exudate is, in general, scanty. A few polymorphonuclear leucocytes, some coarsely granular eosinophile leucocytes and clumps of red corpuscles comprise the picture. *E. histolytica* secretes a powerful proteolytic ferment and this results in semi-digestion of cellular elements. Thus, as well described by Anderson (1921), the chief elements in the field are pyknotic residues, red corpuscles reduced to half or quarter of their original size, polymorphonuclear leucocyte nuclei and nuclear remnants lying free in the fluid. Anderson states that such pyknotic cell remnants comprise 83 per cent of the total leucocytes seen. (*b*) Macrophages may be occasionally present, but they are very scanty in number, and only very rarely seen ; Anderson, in fact, states that they were absent from the stools of five cases very carefully examined. (*c*) A few intestinal epithelial cells are usually present, but in scanty numbers. (*d*) The few polymorphonuclear leucocytes present show marked degeneration ; they present a 'mouse-eaten' appearance due to proteolytic digestion, are shrunken and disintegrated—a process finally going on to the production of pyknotic residues and free nuclear remains. (*e*) The bacterial picture may vary. Sometimes the only extraneous organisms seen are occasional chains of streptococci and scanty yeasts the latter identified as such by their multiplication by budding. Sometimes, however, an amœbic stool may be loaded with bacteria, and in such stools the motile *E. histolytica* die off very rapidly. The degree of bacillary infection in an amœbic stool may indeed exceed that in one due to bacillary dysentery. (*f*) Secondary infections may be present. Of these, infections with hæmolytic streptococci and with Vincent's infection are the most important. In quite a number of cases of amœbic dysentery an infection with Vincent's spirochæte and the fusiform bacillus supervenes, usually as a transient phenomenon, on amœbic ulceration. Spirochætes in general are not at all infrequent in amœbic stools, and if daily examination of the stools be conducted it will frequently be found in amœbic dysentery that at about the 4th or 5th day of the disease the stool swarms with Vincent's infection, and that this infection clears up within another 36 or 48 hours.

The most important change, however, concerns (*g*) the red blood corpuscles. In amœbic dysentery there appears to be a marked change in the erythrocyte membrane, which becomes sticky and agglutinative. As the stool is generally markedly acid, and the hæmoglobin in it is being converted into acid hæmatin, the limiting membrane of the erythrocyte appears to degenerate. The red blood corpuscles tend to appear, not singly or in rouleaux, but agglomerated together into half-fused masses. One may here give a striking instance of this degeneration. In November 1923 the junior writer's attention was called by Dr. B. M. Das Gupta, Assistant Professor of Protozoology at the School, to a most unusual appearance in a fresh

amœbic stool. The stool was full of actively motile *E. histolytica* pushing their way through their environment, as Dobell well describes it 'like slugs moving at express speed.' But in every single microscope field in six consecutive preparations examined there appeared two or three red blood corpuscles which appeared to be motile and which presented exactly the appearance of a Trichomonas with an undulating membrane. If present in only a part of one film, such an anomalous appearance would, of course, suggest an artefact ; but this curious and aberrant appearance was present in every field in the six films examined. Stained preparations were made, and a study of these showed the nature of the artefact present. The stool was full of spirochætes with regular, even curvature—presumably *S. curygyrata*. Owing to the adhesiveness of the red blood corpuscles many of these spirochætes were adherent by either one or both ends, or by their whole length, to the edges of the red blood corpuscles, and their movements gave the curious appearance of an erythrocyte with a marginal undulating membrane.

This adhesive character of the erythrocytes in the amœbic stool is so marked, that, if it be present in a stool which otherwise shows the cellular character of a bacillary dysentery infection, it should arouse the question of the possibility of mixed infection.

Anderson sums up the characters of the acute amœbic stool as showing a very small proportion of polymorphonuclear leucocytes—$7\frac{1}{2}$ per cent in the differential count ; many coarsely granular eosinophile leucocytes—an average of 2 to 5 per cent in the differential count ; an absence or rarity of macrophages ; and a high proportion of pyknotic cell residues.

The microscopic characters of the stool in bacillary dysentery present an entirely different picture. Here the whole microscope field is full of cells. Of these (*a*) some 90 per cent are polymorphonuclear leucocytes. Although degenerated, they present a totally different appearance to that of the scanty polymorphonuclears in the amœbic stool. To quote Anderson (*loc. cit.*) 'they appear to die *en masse*'; their cytoplasm becomes full of refractile fatty globules, the cell outline is well preserved, however, and the nuclei as seen in saline show up as dull greenish masses. There is not here—as in the amœbic stool—partial digestion and marginal disintegration, but rather fatty degeneration and swelling. Many of the polymorphonuclears in a fresh stool, however, are normal. (*b*) Intestinal epithelial cells are fairly numerous ; they are either columnar or squamous, and are usually somewhat swollen, but with clearly visible nuclei. (*c*) Endothelial cells are usually present in some numbers ; like the polymorphonuclears they show similar degenerative changes, being usually vacuolated with breaking down nuclei. (*d*) Macrophages are present in some numbers—about 2 per cent of the differential count according to Anderson. The 'macrophage' is a cell which is in origin either a large hyaline mononuclear leucocyte,

Plate III.

The microscopic appearances of the stool in amœbic and in bacillary dysentery respectively.

Fig. A. Amœbic dysenteric stool. Note the scanty cellular exudate.

(*a*) Motile *Entamœba histolytica*, with pseudopodia and ingested red blood corpuscles.

(*b*) Agglomerated masses of red blood corpuscles, showing their adhesive tendency and change of hæmoglobin to acid hæmatin.

(*c*) Flakes of mucus.

(*d*) Degenerated polymorphonuclear leucocytes, showing 'mouse-eaten' appearance.

(*e*) Lymphocyte.

(*f*) Coarsely granular eosinophile leucocyte.

(*g*) Pyknotic and nuclear residues.

(*h*) Yeasts.

(*i*) Chains of streptococci.

Fig. B. Bacillary dysenteric stool. Note the abundant cellular exudate.

(*a*) Unaltered red blood corpuscles, showing normal dichroic yellow-green colour.

(*b*) Polymorphonuclear leucocytes, many of which show fatty degeneration and refractile dots.

(*c*) 'Ghost cells'; (*vide* text).

(*d*) Degenerated epithelial cells.

(*e*) Macrophages, showing ingested red blood corpuscles, fat droplets, and nuclear remains of ingested leucocytes.

(*f*) Endothelial cells, many degenerating.

(*g*) Scanty non-motile bacilli.

(*h*) Lymphocytes.

PLATE III.

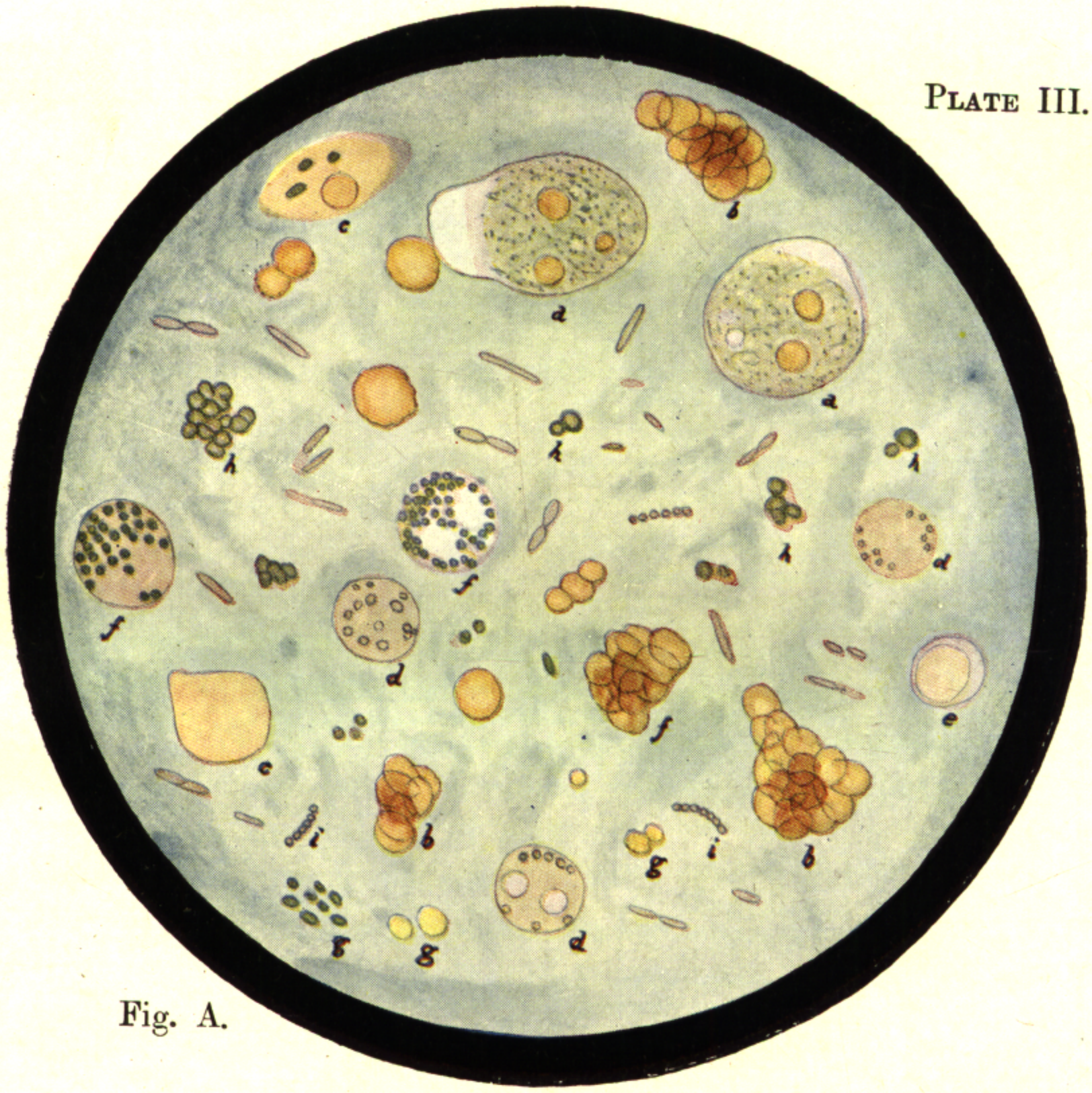


Fig. A.

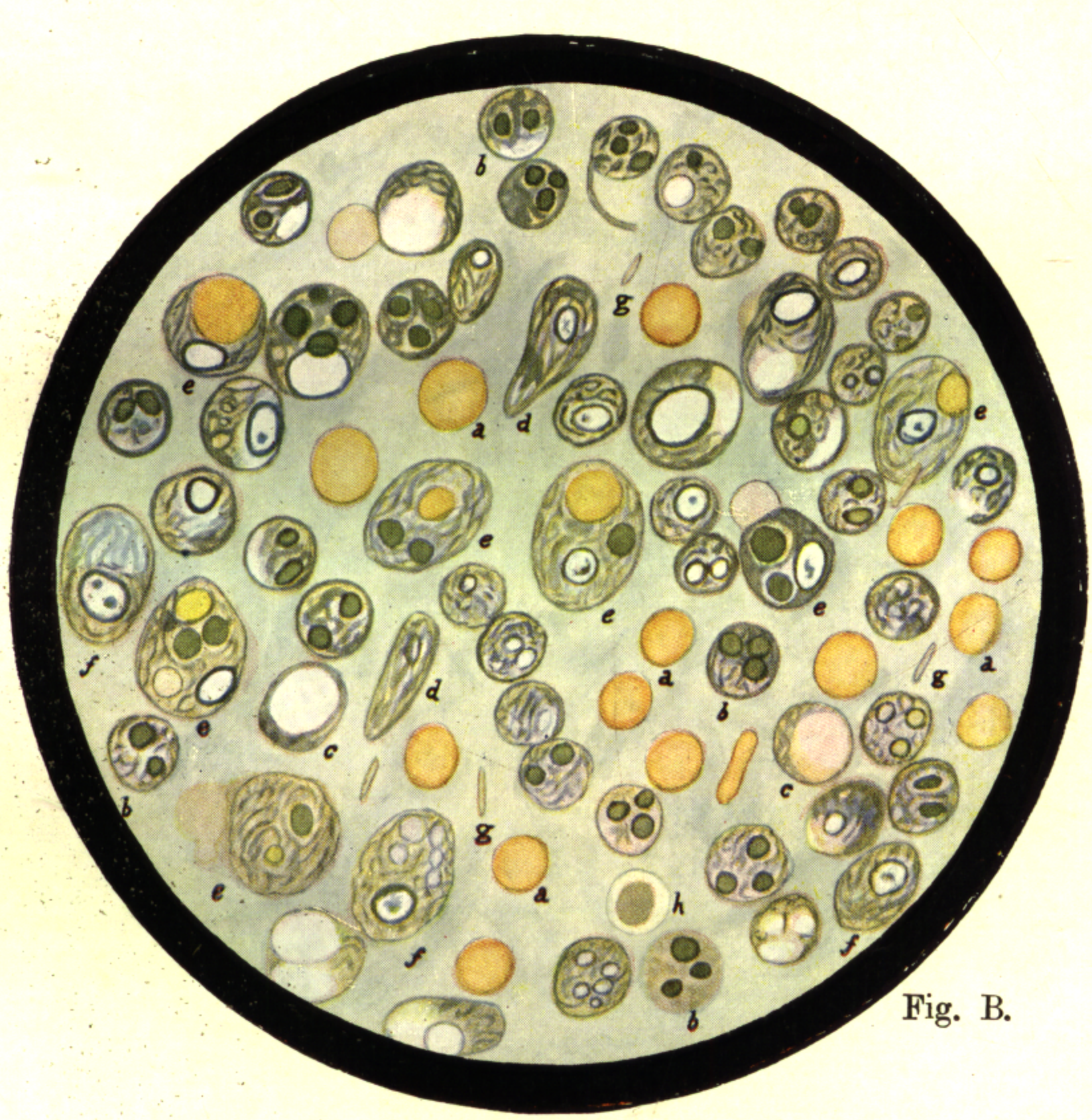


Fig. B.

a detached endothelial cell from the capillaries more usually, or sometimes a wandering plasma cell. They show up very clearly, and can be identified by their large size, prominent nucleus which is usually oval, and the ingested remains of erythrocytes, nuclear remnants of ingested leucocytes, and fatty globules. Many authors speak of these cells as being absolutely non-motile. On the other hand, they could not be phagocytic if they did not possess powers of forming pseudopodia, and they are very sluggishly amœboid. The amœboid activity is, however, so sluggish that prolonged observation under the microscope is necessary to observe the formation of small, knob-like pseudopodia. (*e*) The red blood corpuscles are unaltered ; they show up as isolated cells or in normal rouleaux, and the tendency to adhesion and agglomeration seen in the amœbic stool is here absent. (*f*) 'Ghost cells' are a prominent feature of the exudate, i.e., cells which have lost all structure, but not their outline, and which show a clear, definite cell wall, almost devoid of cell contents—mere shadows of their original selves. Many, if not most, of them are derived from breaking down polymorphonuclear leucocytes. Finally (*g*) the waterways between the cells show a very scanty bacterial content. In the early and acute case, bacteria are extraordinarily scanty ; a few non-motile bacilli are seen in each field on focussing, sometimes in the fluid at a higher level there are scanty clusters of non-motile bacilli of the dysentery group.

Anderson sums up the characters of the bacillary stool as being preponderance of polymorphonuclear leucocytes, absence of eosinophile leucocytes, the presence of prominent macrophages, and absence of pyknotic residues. To these characters we would add absence of any change in the red blood corpuscles, which show their normal dichroic yellow-green colour.

It should be added, however, that the microscopical characters of the bacillary dysentery stool may vary (*a*) with the specific organism concerned—thus in Flexner bacillus infections the stool is not infrequently fæculant and with less cell exudate ; (*b*) with the stage of the disease. Thus Manson-Bahr, Perry and the late Sir Patrick Manson (1922) give the following as the characteristic cell-picture during the stages of a bacillary dysentery case of average severity :—

Stage 1. *First three days of the disease.*—Preponderance of polymorphonuclear leucocytes, fresh red blood corpuscles, macrophages, endothelial cells, intestinal epithelial cells, and calcium phosphate crystals. Few visible micro-organisms.

Stage 2. *Second three days of the disease.*– Disintegrating pus cells, red cells, bile-stained columnar epithelial cells, disintegrating macrophages, and calcium phosphate crystals. Many motile bacilli visible.

Stage 3. *Third three days of the disease.*—Disintegrating red cells, free hæmatoidin crystals, pus cells in an advanced stage of degeneration containing fat particles with active Brownian movement, large numbers of motile bacilli, and often flagellate protozoa, or it may be active *E. coli*.

As the acute attack of dysentery subsides and convalescence sets in, certain changes occur in the character of the cell exudate as seen under the microscope.

In the *amœbic stool*, the most prominent feature is the appearance of Charcot-Leyden crystals (Fig. 13). These are of four types: (*a*) thin, sharply pointed, whetstone-shaped crystals, varying from 5 μ to 50 μ in length; (*b*) short, almost diamond-shaped forms; (*c*) forms similar to the type (*a*), but with the ends truncated; and (*d*) long, acicular forms. In all cases they show up with a green, clear, refractile look, and stain an intense jet-black with iron-hæmatoxylin staining. In iodine preparations they show up badly. Chemically Charcot-Leyden crystals appear to consist of ethyl-imine, and to be a product of tissue digestion by *E. histolytica*. As shown by Acton (1918), and by J. G. Thomson and Robertson (1921), the appearance of Charcot-Leyden crystals in the stool is almost pathognomonic of amœbic infections, and they may persist in the stool long after even cysts of *E. histolytica* have ceased to be found. So characteristic, indeed, of amœbic infection do we regard these crystals that their appearance in an acute dysenteric stool together with that of actively motile *E. histolytica* we regard as evidence of true relapse in amœbic infection—as distinct from re-infection of a previously cured patient.

In the *bacillary dysentery stool*, as the acute symptoms subside, the secondary intestinal protozoal parasites become prominent. Motile, vegetative *Endolimax nana* and *Iodamœba bütschlii* are frequently seen at this stage, whilst such stools often show vegetative *Entamœba coli* in considerable numbers. The two commonest organisms in such stools, however, are *Trichomonas hominis* in its motile, vegetative phase, and *Blastocystis hominis*,— a fungus of high type, and a source of considerable confusion to the laboratory worker,—which often appears in profusion. In the meantime the pH of the stool is rising towards the normal of about 7·2 in the amœbic case, and falling very slightly to about 7·5 to 7·8 in the bacillary case.

In balantidial dysentery, according to Haughwout (1924), the cellular exudate is at first rather like that in an amœbic dysenteric stool: scanty, and with an absence of macrophages and ghost cells. He states that the action of the balantidia on the mucosa of the colon is mechanical, rather than by the production of enzymes, and hence epithelial cells of normal appearance tend to be shed in fair numbers and to appear in the stools. Later on, with reaction occurring in the infected gut, pus cells may appear in considerable numbers; but under such circumstances the worker must be very careful not to mistake *Balantidium coli* in the stools of a patient suffering from bacillary dysentery for balantidial dysentery.

During the later phases of amœbic dysentery, the ulcers may become secondarily infected with streptococci or other pyogenic bacteria. Under these conditions the vegetative forms of *E. histolytica* may be found in a stool which has a rich

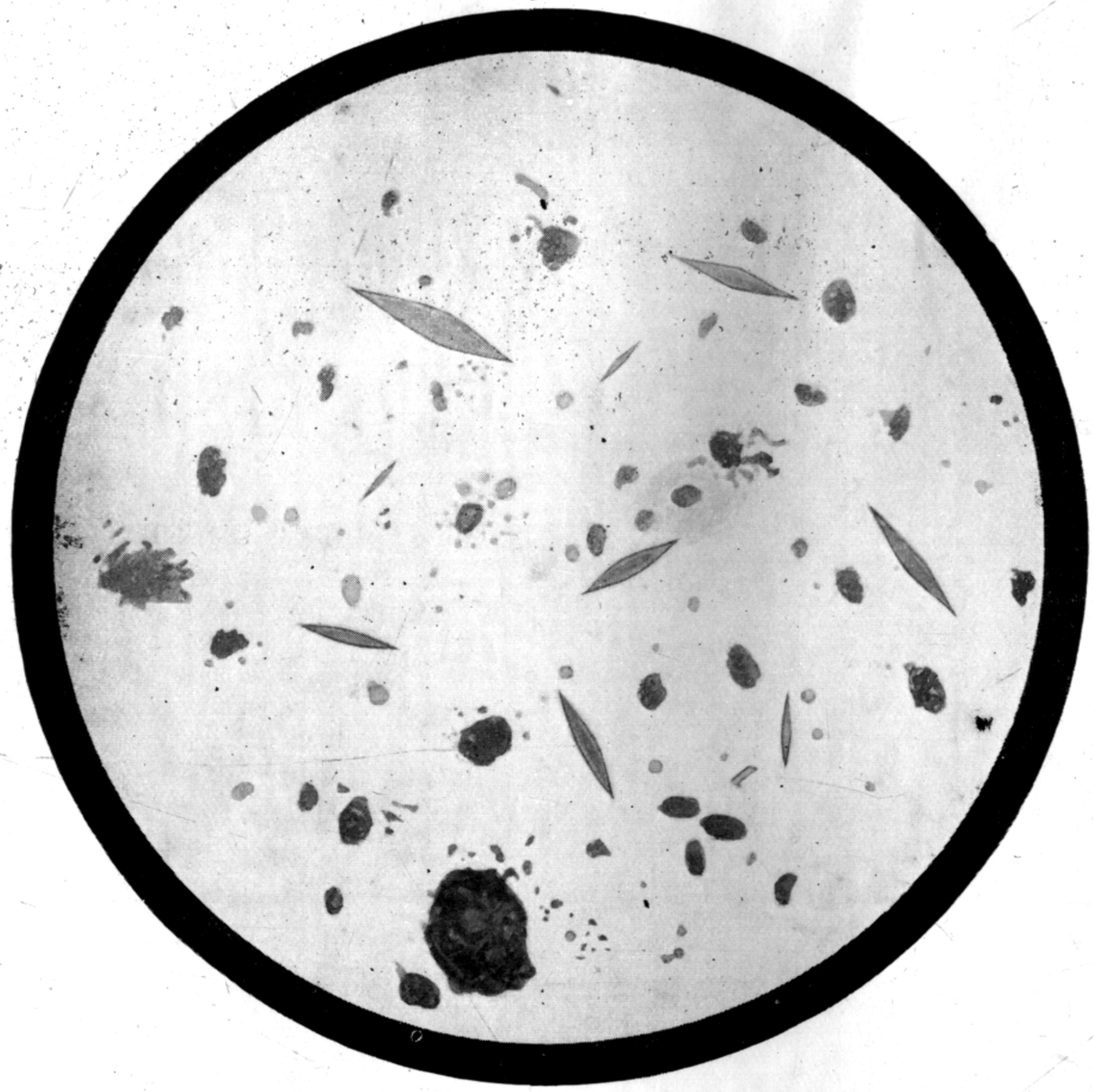


FIG. 13(*a*).

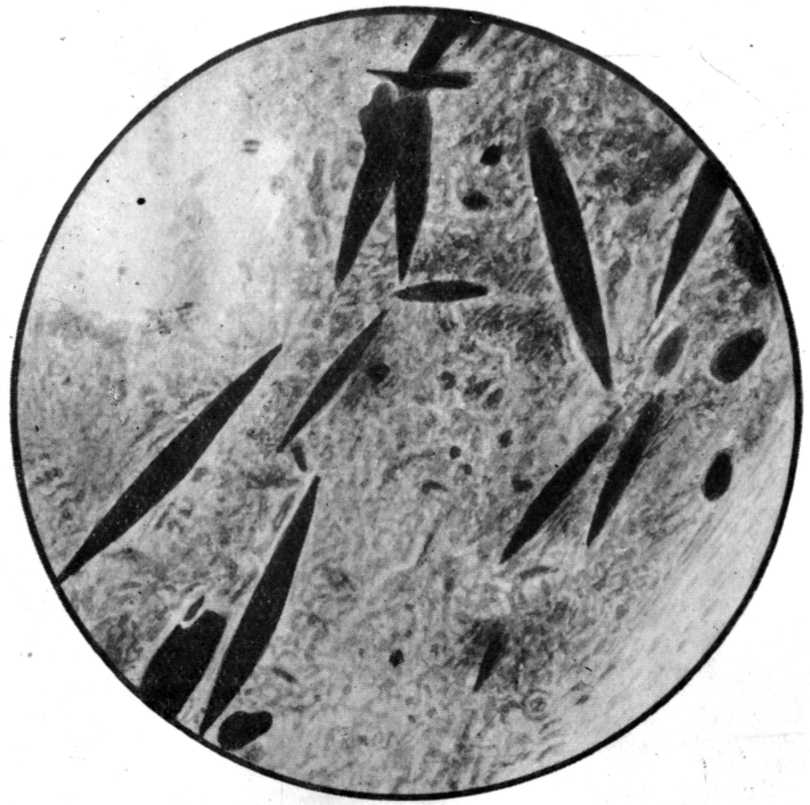


FIG. 13(*b*).

FIG. 13. Charcot-Leyden crystals.

(*a*) Unstained. As seen in saline emulsion. (Original.)

(*b*) As stained by iron-hæmatoxylin. (After J. G. Thomson and Robertson, 1921.)

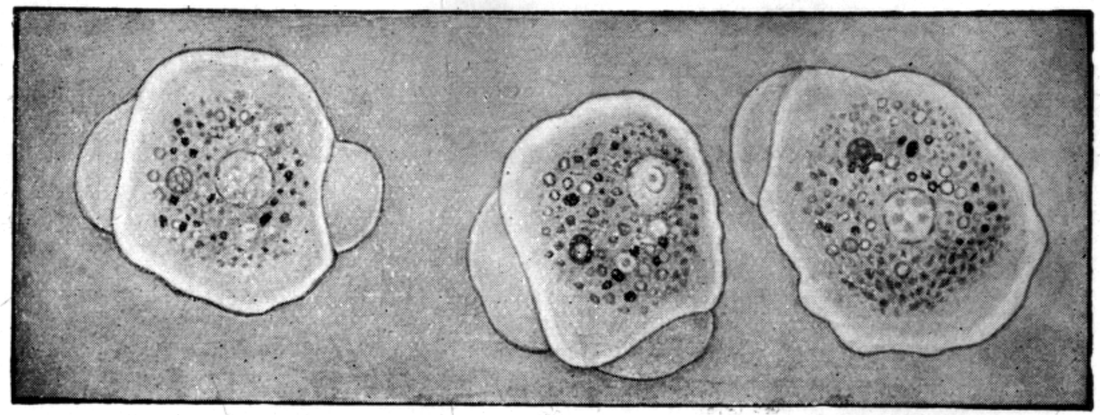


FIG. 14. Vegetative *Entamœba histolytica* (' *Entamœba tetragena* ') in a slightly stale stool as seen in the fresh state. Note that the nucleus is almost invisible, and the large rounded dome-like pseudopodia, consisting of ectoplasm. (From Doflein, 1911, after Hartmann.)

cellular exudate, full of polymorphonuclear leucocytes. Again, the utmost care must be taken to exclude bacillary dysentery.

* * * *

In cases of balantidial and amœbic dysentery careful and thorough examination of the stools will almost always enable the laboratory worker to find the protozoa responsible in their actively motile and vegetative phase; on the other hand, the characters of the cellular exudate in acute bacillary dysentery are so typical that this infection can usually be diagnosed at once from them. Hence the laboratory worker in most instances will be able to send such an immediate report to the waiting physician as 'amœbic dysentery', or 'balantidial dysentery', or 'probable bacillary dysentery', which will enable the appropriate treatment to be instituted at once without waste of time.

Haughwout (1924) sums up the results of his study of the cytodiagnosis of dysenteric stools as follows:—

1. 'The cellular exudate of acute bacillary dysentery is characteristic of that and of no other intestinal disorder. Its distinguishing features are present in the early stages of the onset and offer no difficulties in interpretation.

2. The absence of endothelial macrophages and evidence of toxic necrosis in a leucocytic exudate, no matter how rich, is sufficient to rule out a diagnosis of bacillary dysentery. Such decision, however, should be made only after prolonged search of several carefully made preparations from different portions of the bowel movement.

3. The cellular exudate occurring in protozoal dysentery is mainly of value in estimating the extent of accompanying bacterial infections. No diagnosis of protozoal dysentery should be made except in the presence of organisms in the trophozoite stage of their life-cycle, and under circumstances that make it probable that they, and no other organisms, are the cause of the prevailing *acute* process.

4. Certain non-specific affections of the colon give rise to the production of large masses of mucus. This mucus may contain desquamated epithelial cells in large numbers, as well as leucocytes and cells of uncertain origin. Superficially, such masses may resemble the exudate of bacillary dysentery, but brief study of the cells shows its composition to be so different from that of bacillary dysentery, that it becomes impossible to mistake such an exudate for that of bacillary dysentery.

5. Cellular exudates of other types often present features that lend themselves to analysis and ultimate interpretation in clinical terms.'

* * * *

Having examined the characters of the cellular exudate, the laboratory worker will next concentrate his attention on trying to isolate the organism or organisms responsible for the dysentery. Hence we must next deal with these seriatim. In

the stool of acute amœbic dysentery, he will come across the actively motile vegetative forms of *Entamœba histolytica*—usually in considerable numbers. In the stool of balantidial dysentery there should not be much difficulty in coming across the large free-swimming forms of *Balantidium coli*. In bacillary dysentery cultural methods will be necessary.

The Vegetative Form of Entamœba histolytica.

We may first consider this as seen in a perfectly fresh amœbic dysenteric stool. When rounded up, the vegetative form measures from 18 μ to 40 μ, usually from 20 μ to 30 μ, but is sometimes smaller than 10 μ. One-third of the cytoplasm of the amœba consists of clear, translucent, highly refractile ectoplasm, the remaining two-thirds consisting of finely granular endoplasm, a point which is of considerable value in differentiating it from vegetative *E. coli* (Fig. 14).

The movements of the amœba in the perfectly fresh state are very characteristic. The following description is taken from Dobell (Dobell and O'Connor, 1921) :—'A normal individual, just removed from its host, and examined in a suitable medium and under favourable conditions of temperature, displays astonishing activity. It flows, almost in a straight line, across the field of the microscope in an extended form which suggests a slug moving at express speed. In this condition the anterior end consists of a single large pseudopodium, advancing so rapidly that no sharp line can be seen separating the ectoplasm from the endoplasm. The red corpuscles contained within such an organism flow about and roll round one another with every movement, as though the protoplasm were a mobile liquid.' Thomson and Robertson (1925) give the following description of the movements of *E. histolytica*, as seen in material from culture *in vitro* :—'When actively motile, *E. histolytica* becomes stretched out in a ribbon-shape, with blunt rounded ends. The ectoplasm, while clearly differentiated from the endoplasm, yet tended to maintain the general outline of the amœba. That is to say, the blunt rounded anterior end, consisting of the ectoplasm, was the same width as the remainder of the body. Movement was usually more or less direct, not as in some of the other species indeterminate, and the distance covered considerable.'

In brief, motile *E. histolytica* has a tendency to *travel* across the microscope field, whereas the other intestinal entamœbæ do not cover ground with anything like the same rapidity, tending far more to remain in or about the same spot. The advancing large rounded pseudopodium consists almost entirely of clear ectoplasm, the endoplasm flowing in from behind as the pseudopodium advances. A point which such actively motile amœbæ often exhibit is that the posterior end is often pulled out, as if trailing, with particles of debris adherent to it.

The endoplasm, which constitutes two-thirds of the amœba, is very finely granular. Its colour as seen in saline is not infrequently rather yellowish from digested hæmoglobin. In the endoplasm, in a large proportion of the individuals

encountered in an amœbic dysenteric stool, are ingested red blood corpuscles. These may number usually from 1 to 10, although as many as 48 have been encountered with a single individual. They may lie singly—more or less reduced in size by digestion—in the endoplasm, or may lie, either singly or in some numbers, in a more or less large food-vacuole. They stain black with iron-hæmatoxylin. Their size is more or less reduced, as they are in process of digestion; sometimes only a tiny remnant of a red corpuscle is seen. If the stool be a fluid but a non-dysenteric one, with no red corpuscles available, there will be none in the amœbæ.

This ingestion of red blood corpuscles affords a valuable means of identifying motile *E. histolytica* in a dysenteric stool. 'Any entamœba found in a dysenteric stool, showing active motility and containing ingested red blood corpuscles is *ipso facto E. histolytica*,' is the safest working rule for the student to go by.

In addition to feeding on red blood corpuscles, *E. histolytica* obtains an important part of its nutrition by osmosis from the rich dissolved tissue juice prepared for it by its powerful proteolytic ferment. It is this excreted ferment which explains its tissue-dissolving powers; the ulceration which it causes is not due to a mechanical forcing of its way by pseudopodial activity into the colon mucosa, but to its causing lysis of the tissue cells. In a section of infected colon mucosa it will be seen that the amœbæ lie in little pools of liquefied tissue.

Dobell states that rarely *E. histolytica* actually ingests tiny fragments of tissue cells of the host. During several years of study of *E. histolytica*, however, we have never observed this phenomenon, and it must be of considerable rarity. It will sometimes ingest starch grains, if these are present in the fæces.

The nucleus of *E. histolytica* is true to the nuclear pattern in the genus *Entamœba*, but of much finer and more delicate type than that of *E. coli*. It is vesicular and spherical, and measures some 4 μ to 7 μ in diameter. When stained by iron-hæmatoxylin, its structure is seen to be as follows:—There is a delicate, clear-cut achromatinic nuclear membrane delimiting the nucleus from the cytoplasm. On the inner aspect of this nuclear membrane is a thin uniform deposit of chromatin, apparently consisting of very fine granules in contact with one another. In optical section the nuclear membrane with its fine deposit of chromatin appears as a finely beaded ring. The karyosome is small, spherical, not more than 0·5 μ to 1 μ in diameter and lies in the exact centre of the nucleus. (In badly fixed specimens some distortion of the position of the karyosome may take place.) Between the fine, central karyosome and the peripheral chromatin on the nuclear membrane is a clear zone, containing no chromatin.

The result of the delicacy of structure of the nucleus of *E. histolytica* is that the nucleus is invisible in a saline preparation, in contra-distinction to the brightly visible refractile ring nucleus of *E. coli*.

Such is the picture presented by the vegetative phase of *E. histolytica* as seen in a perfectly fresh amœbic dysenteric stool, and it is quite unmistakable. The protoplasm of the amœba is perfectly sterile and it never ingests bacteria or yeasts.

In the passed stool, however, the vegetative amœba commences to die almost immediately, and (in the tropics) is often dead within about two hours after the stool has been passed. It is precisely this fact which has led to the tremendous confusion with regard to *E. histolytica* in the literature, since it is safe to say that quite the majority of workers have worked with stale stools and dying entamœbæ, and hence have given inaccurate descriptions of the parasite.

Dying vegetative *E. histolytica* presents a picture entirely different from that of the fresh, actively motile forms [Fig. 15 (11, 12, 13) and Fig. 14]. To quote Dobell: 'The animal soon ceases to progress and becomes more or less sessile. In this condition it usually continues to undergo pronounced changes of shape, accompanied by the emission of a few large, blunt and blade-like pseudopodia. These pseudopodia are perfectly hyaline and highly refringent, and are composed entirely of ectoplasm—a fairly sharp line of demarcation being visible between their clear protoplasm and the granular endoplasm. Movements of this type may continue for hours, before the animal finally rounds up, ceases to move, and dies. No similar movement is performed under the microscope by any of the other intestinal amœbæ of man.'

In brief, the amœba now ceases to travel and remains stationary. It continues to throw out large, voluminous, dome-shaped pseudopodia, consisting only of clear ectoplasm, from different points of its surface continuously. In the meantime the endoplasm becomes progressively more and more vacuolated; the vacuoles are characteristically spherical, and they tend to fuse together into ever larger vacuoles. Further, bacteria of all sorts now commence to invade and parasitise the dying amœba. As Dobell remarks: 'Bacteria are almost invariably absent from all *E. histolytica* in a perfectly fresh amœbic dysenteric stool, also in the entamœbæ of experimentally infected kittens. But, as the amœba dies, it becomes the prey of the bacteria in the stool and soon its protoplasm—both ectoplasm and endoplasm—is found to contain numerous bacteria of all sorts, cocci and bacilli alike. In stale stools, or liver abscess pus, the majority of the amœbæ often contain bacteria; and as a rule, the staler the material, and the more degenerate the amœbæ in it, the more plentiful are the bacteria contained in them.'

Further, as the amœba dies, its nucleus breaks up. The chromatin on the nuclear membrane breaks up into large irregular masses which may lie anywhere within the nucleus. The karyosome degenerates. The result is that, in place of the typical 'histolytica type' of nucleus, invisible in a saline preparation, we have now a breaking down nucleus, showing irregular masses of chromatin within the thin nuclear membrane. These chromatin masses may be visible in a saline

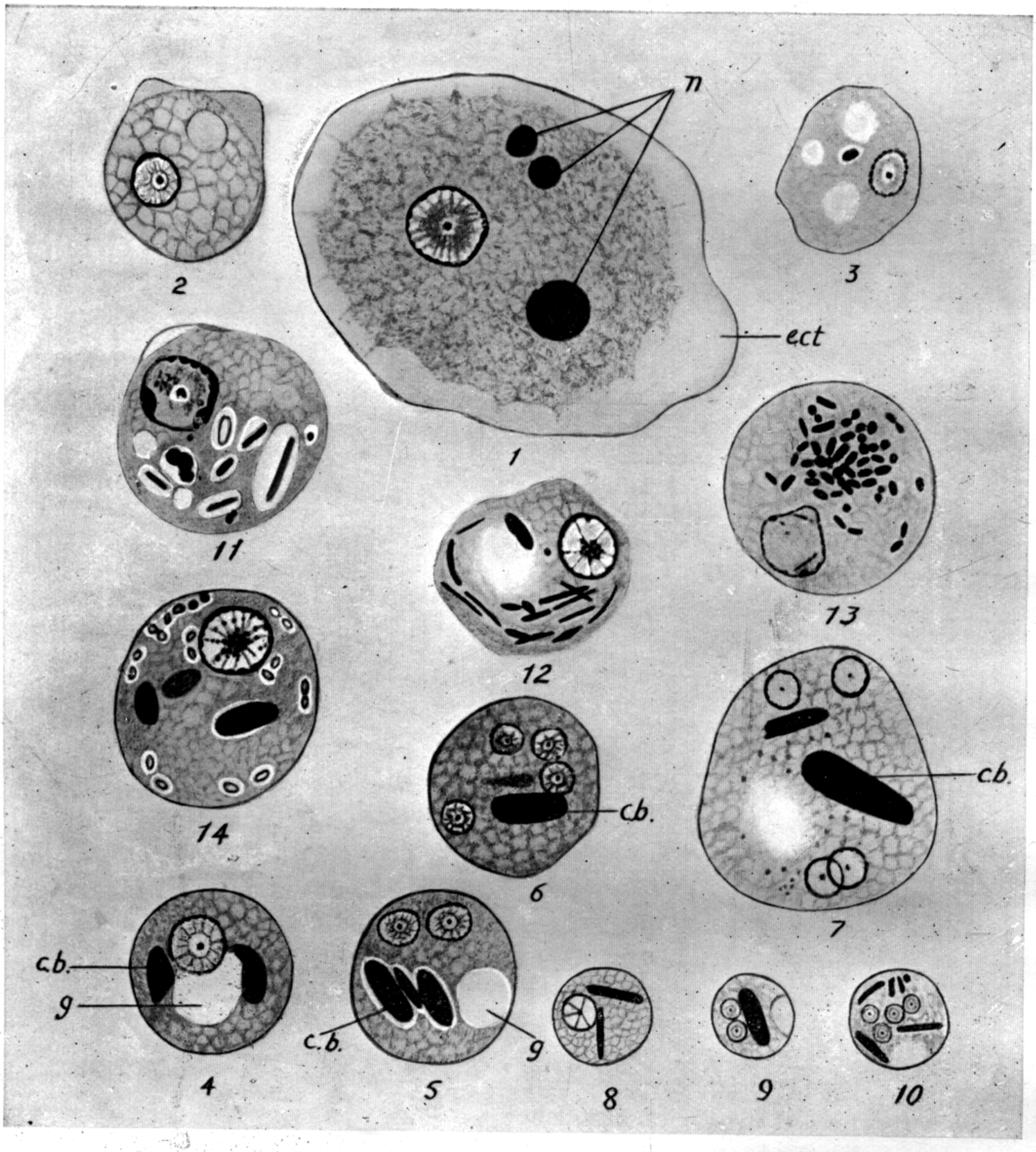


FIG. 15. *Entamœba histolytica.* (After Dobell, 1919, and Dobell and O'Connor, 1921.)

1. Vegetative phase. Note the nuclear structure, and absence of all ingested food particles except red blood corpuscles. *ect.*, ectoplasm—comprising one-third of the volume of the amœba ; *n.*, remains of ingested red corpuscles.

2, 3. Pre-cystic form ; the amœbæ rounding up and withdrawing their pseudopodia.

4. Cyst at the mono-nucleate phase ; *g.*, glycogen vacuole ; *c.b.*, chromatoid bars.

5. Cyst at the bi-nucleate phase ; *g.*, glycogen vacuole ; *c.b.*, chromatoid bars.

6, 7. Mature cysts at the tetra-nucleate phase ; *c.b.*, chromatoid bar.

8, 9, 10. Cysts of a small sized strain at 1-, 2-, and 4-nucleate phases. Note the massive chromatoid bars.

11, 12, 13. Dying vegetative *E. histolytica* in a stale stool. Nucleus degenerating ; endoplasm parasitised by bacteria.

14. Mono-nucleate cyst degenerating in a stale stool. Nucleus and chromatoid substance breaking up ; bacteria in endoplasm.

preparation as brightly refractile beads, and the nucleus may now become visible in saline as an irregular distorted ring showing contained refractile chromatin masses.

At this stage, with its endoplasm showing contained bacteria, and its breaking down nucleus having become visible, the student may mistake vegetative *E. histolytica* for vegetative *E. coli*. The fact, however, that two-thirds of the animal consists of clear ectoplasm, and that the large slowly emitted dome-shaped pseudopodia are wholly composed of ectoplasm only, serves, even at this stage, to distinguish *E. histolytica* from *E. coli*.

Finally, and usually within two hours after the stool has been passed (in the tropics) vegetative *E. histolytica* dies. The dead amœba is simply a rounded up and motionless mass of protoplasm, full of bacteria preying upon it, filled with semi-fused spherical vacuoles, and showing a few refractile chromatin residues. This form is quite unrecognisable as *E. histolytica*, or even as an amœba at all, to anyone who is not very familiar indeed with it. It is usually mistaken for a degenerated leucocyte ; in any case it is quite impossible to base a diagnosis of amœbic dysentery upon the finding of such forms. Hence again the imperative necessity for the laboratory worker to insist upon receiving only perfectly fresh stools for examination.

Even with a rather stale stool, however, there is still one further possible method of diagnosis. Many workers in the past have claimed that they have successfully cultivated *E. histolytica in vitro*, but it is now generally recognised that they merely cultivated free-living amœbæ from the stools. It is possible that Cutler (1918) succeeded ; though it is doubtful whether he succeeded in getting multiplication of the amœbæ rather than merely their survival *in vitro*. A repetition of his experiments by Dobell and Douglas was unsuccessful.

All such earlier attempts are now of historical interest only, since the pioneer work of Boeck and Drbohlav (1925). (In looking up the literature on this subject the student should consult the full detailed paper by these authors in 1925, rather than their earlier announcements. At the 20th annual meeting of the American Society of Tropical Medicine held at Chicago in the summer of 1924 Dr. Boeck read a preliminary note on the success of these workers in cultivating *E. histolytica in vitro*, and showed his preparations. A note on it was published in the minutes of the meeting. In November 1924, Dr. Drbohlav read a second paper on the subject at a meeting of the Royal Society of Tropical Medicine and Hygiene in London and this was published in the *Transactions* of that Society. He read a further paper on the same subject at the February 1925 meeting in Paris of the Société de Pathologie Exotique, and an abstract of this paper was published in the *Bulletin* of that Society. Hence the technique adopted by Boeck and Drbohlav was widely known long before their final paper with full details and illustrated by very fine microphotographs was published in the *American Journal of Hygiene*, 1925, Vol. V, No. 4, p. 371. It is this final paper, rather than the earlier scanty notices of the subject, to which the reader is referred for further details.)

In the meantime the work of Boeck and Drbohlav had been confirmed in many of the large laboratories in Europe and America, and in Calcutta as elsewhere. In Calcutta during 1925, *E. histolytica* was successfully cultivated *in vitro* by Boeck and Drbohlav's technique on many occasions, and once successfully carried through 18 subcultures before the strain was lost. Details of the technique are as follows :—

Since the first successful cultivation of *E. histolytica* by Boeck and Drbohlav in 1924, many modifications of their original technique have been introduced. Thomson and Robertson (1925) have

successfully cultivated *E. histolytica, E. coli, Endolimax nana* and *Dientamœba fragilis* on this medium. Das Gupta (1925) successfully cultivated *E. nuttalli* of the monkey on it. Dobell and Laidlaw (1926*a*) have cultivated the entamœbæ of monkeys on it, also *E. gingivalis* of man.

The essential principle of Boeck and Drbohlav's medium is that it consists of two parts, solid and liquid, and the amœbæ grow on the surface of the solid medium underneath the fluid. The latest modification given by Drbohlav (1925) is as follows :—

1. *Boeck and Drbohlav's medium : Drbohlav* (1925).

A buffered Ringer's solution is first prepared as follows :—

Sodium chloride	6 gms.
Potassium chloride	0·1 gm.
Calcium chloride	0·1 gm.
Sodium bicarbonate	0·1 gm.
Distilled water	1 litre.

To each litre add 5 gms. of mono-potassium phosphate, and adjust to a pH of 7·4 with NaOH or KOH solution.

(*a*) For the solid part of the medium one may use either

(1) Agar	14 gms.
Ringer's solution, pH = 7·4, buffered as above	1 litre.

or

(2) Rice starch	10 gms.
Agar	14 gms.
Ringer's solution, pH = 7·4, buffered as above	1 litre.

or

(3) Blood-agar slopes (N.N.N. medium) heated for 30 minutes at 100°C. and then cooled.

The solid medium should be in the form of the ordinary agar slant.

To prepare the liquid part of the medium take one litre of the buffered Ringer's solution in a sterile flask. Sterilize the surface of an egg with absolute alcohol and allow it to dry. Perforate the shell with the pointed end of sterile forceps, and then aspirate the white of the egg into a 5 c.c. syringe, with a stout needle of big bore, taking care that no yolk is taken in. (In India as hen's eggs are so small, it is better to use the white of two eggs.) Transfer the white of egg to the Ringer's fluid and thoroughly dissolve by shaking. With a sterile pipette transfer volumes of 5 c.c. or thereabouts of the fluid into the tubes containing the solid medium, so that the liquid reaches a height of 1 cm. above the solid slant.

Next keep the tubes in the 37°C. incubator. This is the most essential step in the whole procedure, as the media must be warm when inoculated. In order to inoculate the tubes (for growth of vegetative *E. histolytica*) pick up a portion of dysenteric mucus from the stool with a sterile capillary pipette and inoculate into the fluid part of the medium. Incubate with the tubes in the vertical position at 37°C.

From time to time material for examination can be removed from the bottom of the tube by means of a capillary pipette. It is advisable in doing so to scrape the surface of the solid slant with the end of the pipette in order to remove amœbæ which may be adherent to it. Multiplication takes place for two to three days, after which bacterial overgrowth usually kills off the amœbæ. Subcultures should, therefore, be taken every two days by sucking up some of the amœbæ with a capillary pipette and transferring them to a fresh tube of warmed medium.

To obtain really good cultures of *E. histolytica*, the best procedure is to inoculate a kitten per rectum with an amœbic dysenteric stool, and when it is suffering from amœbic dysentery to use the perfectly fresh stools full of actively motile *E. histolytica* for inoculation into the warmed medium. As a rule the second or third subculture gives a better growth than does the original one.

In all such cultures *Blastocystis hominis*, if present, is a veritable nuisance, since it multiplies in this medium with great rapidity and kills off the entamœbæ. Drbohlav advocates adding 1 per cent dextrin to the liquid part of the medium, as this suppresses the growth of *Blastocystis hominis*.

2. *Dobell and Laidlaw's* 'HSrc + S' *modification* of Boeck and Drbohlav's Medium. (Dobell and Laidlaw, 1926*a*.)

Of the eight different modifications of Boeck and Drbohlav's medium given by Dobell and Laidlaw (1926*a*) the writer has found that this, and the one subsequently given, are probably the best.

The Ringer's solution used has the following composition :—

Sodium chloride	.. ..	9 gms.
Potassium chloride	.. ..	0·2 gm.
Calcium chloride	.. ..	0·2 gm.
Distilled water	.. ..	1 litre.

The solid part of the medium consists of inspissated horse-serum, (HS in the formula). To prepare it whole horse-serum (sterilized by filtration if necessary) is tubed in suitable amounts with all aseptic precautions, and set in the form of ordinary slants by heating for from 60 to 70 minutes in an inspissator at 80°C. It is most important not to heat the serum longer, for over-heating ruins it as a culture-medium. When the slants have cooled, they are incubated to test their sterility.

The fluid part of the medium consists of the whites of four eggs dissolved in 1 litre of Ringer's fluid, and finally sterilized by filtration through a Seitz filter. One great advantage of this solution—which is stronger than that used by Drbohlav—is that it enables wet films of the amœbæ to be fixed very easily for cytological study.

The tubes are prepared as in Boeck and Drbohlav's method by distributing the egg solution into the tubes containing the solid slants in sufficient volume to cover the solid part of the medium with a depth of 1 cm. of fluid. The tubes of media are kept in the 37°C. incubator. Just before inseminating the tubes with material containing entamœbæ, a little sterile solid rice starch is added to the medium with a platinum loop or sterile spatula. The rice starch should be previously sterilized by heating it in small tubes containing about 2·5 gms. in each for one hour at 180°C. (dry heat).

On this medium Dobell and Laidlaw obtained abundant cultures of *E. histolytica* with a long life, similar cultures of *E. coli*, abundant cultures of *E. gingivalis*, but poor cultures of *E. nana*.

3. *Dobell and Laidlaw's* 'Ehs + S' *modification* of Boeck and Drbohlav's medium.

Four eggs are sterilized with alcohol and broken into a sterile flask containing glass beads. Fifty c.c. of Ringer's solution (of the formula given in No. 2 above) is added and solution effected by shaking. Test-tubes are then filled with a sufficient quantity to produce slants about 1 to 1½ inches in length upon coagulation by heat. The tubes are then slanted in an inspissator and heated at 70°C. until the egg mixture has solidified. They are then transferred to an autoclave and sterilized for 20 minutes at a pressure of 15 lbs. This constitutes the solid part of the medium.

The liquid part of the medium consists of inactivated horse-serum 1 part in 8 parts of Ringer's solution of the above formula. This is added to the tubes to give a depth of 1 cm. of fluid over the solid part of the medium. The tubes are then kept in the 37°C. incubator until wanted for inoculations. Just before insemination a little solid sterilized rice starch (*vide* No. 2) is added.

In this medium Dobell and Laidlaw note that *E. histolytica* and *E. coli* both gave abundant cultures which persisted for a considerable time; the growth with *E. gingivalis* was moderate, that with *E. nana* was good. The amœbæ may live for a week or even ten days, and subculture is only necessary about once a week.

Miscellanea.—Dobell and Laidlaw note that certain difficulties may attend attempts to cultivate the entamœbæ of warm-blooded hosts. Thus if starch-splitting bacteria get into the cultures, acids are produced and kill off the entamœbæ. They can be kept down, however, by subculturing into media containing 1 : 20,000 acriflavine. It is not necessary to adjust the reaction of the medium, for it is approximately neutral, and in the formula with inspissated serum the serum itself appears to act as a buffer.

Usually the material used for inoculation of the cultures should be fæcal emulsions containing vegetative forms of the entamœbæ concerned. Encystation occasionally occurs in the cultures, but as a rule the amœbæ multiply

E. gingivalis never encysts. In order to obtain cultures from material containing cysts the following technique should be adopted :—

Cysts just passed in the stools do not hatch or develop further if placed immediately in the culture-medium and incubated at 37°C. ; they merely die. They must first be exposed to cold and then kept for a certain time. The cyst-containing fæces are thoroughly emulsified in an excess of normal saline or of Ringer's fluid, and the larger fæcal particles removed by filtering through glass- or cotton-wool. The cysts are then concentrated either by sedimentation over several days, or by centrifuging on several days.

The washed and concentrated cysts are next treated with a large volume of 0·2 per cent HCl which is allowed to act on them for 2 hours. This kills off *Blastocystis* and the majority of bacteria and yeasts. After this the acid is carefully neutralized with a weak solution of sodium bicarbonate, using neutral red as an indicator ; and the cysts are then again collected by centrifuging, and washed two or three times, centrifuging after each washing. The final deposit, containing washed cysts and fæcal debris, is used to inoculate tubes of culture-medium which have been kept in the 37°C. incubator.

In a recent paper, Warrington Yorke and Adams (1926) claim that it is *not* necessary to cool the cysts before inoculating the medium with them. They find that in 'L. E. S.' medium immature cysts develop into mature ones, so that within a few hours the great majority of cysts have become tetranucleate. The degree of excystation resulting from sowing freshly passed fæces on the medium and incubating at 37°C. is very variable ; it may be nil, and it rarely exceeds 50 per cent. Freshly passed fæces contain some substance which inhibits excystation.

Dobell and Laidlaw find that certain bacteria react unfavourably upon cultures of entamœbæ, whereas others favour their growth. Thus they succeeded in isolating 'Bacillus No. 1' which is particularly favourable for cultivation of *E. histolytica* and *E. coli* ; a 'Bacillus III' which was unfavourable to all species of entamœbæ tested ; and a 'Bacillus IV' which was especially favourable to *E. nana*. In inoculating culture-media with washed cysts they previously inoculate the culture-medium with the bacillus which is most favourable for the species of entamœba concerned.

Mixed cultures are very common ; and it often happens that when microscopic examination has shown only one species of entamœba present, a second or even a third may appear in the cultures. *E. histolytica* can be separated from *E. coli* by inoculating the material per rectum into kittens ; the infection with *E. histolytica* takes in the kitten, but that with *E. coli* dies out. *E. coli* can be separated from *E. histolytica* by treating the mixture with 1 : 50,000 emetine ; this kills the *E. histolytica in vitro* but leaves the *E. coli* unharmed. If a mixed culture be removed from the incubator and kept at room temperature for a certain time, one species often survives longer than another, and by making sub-cultures at different intervals of time the more resistant species can finally be isolated in pure culture.

Dobell and Laidlaw note that prolonged cultivation of *E. histolytica* in starch-containing media leads to the production of a race of parasite which, although it will still ingest red blood corpuscles, becomes non-pathogenic for the kitten.

The rice starch used for Dobell and Laidlaw's modifications of Boeck and Drbohlav's must be chemically and microscopically pure. Merck's produce such a special rice starch preparation.

In Boeck and Drbohlav's medium *E. histolytica* multiplies with great rapidity and at 24 to 48 hours the culture will be found full of actively motile forms. It should be noted that the cultures are extremely sensitive to cold ; in Calcutta on two occasions at night when the gas supply to the incubator failed rich cultures of *E. histolytica* died out within 12 hours.

In culture vegetative *E. histolytica* presents the same structure and characteristics as do the amœbæ in a freshly passed amœbic dysenteric stool, with, however, one very important difference. In culture—though not in the human body—vegetative *E. histolytica* takes to feeding upon bacteria. There is here no question of dying amœbæ being parasitised by bacteria, for the amœbæ are actively motile and in full vigorous activity ; it is actual ingestion of bacteria by the amœbæ. It would seem as if *E. histolytica* is adaptable to changes in its environment. In the mucous membrane of the colon its essential diet is the nutritious tissue juice prepared for it by its proteolytic enzyme. In the dysenteric stool red blood corpuscles form its chief article of diet. But in culture—with neither of these

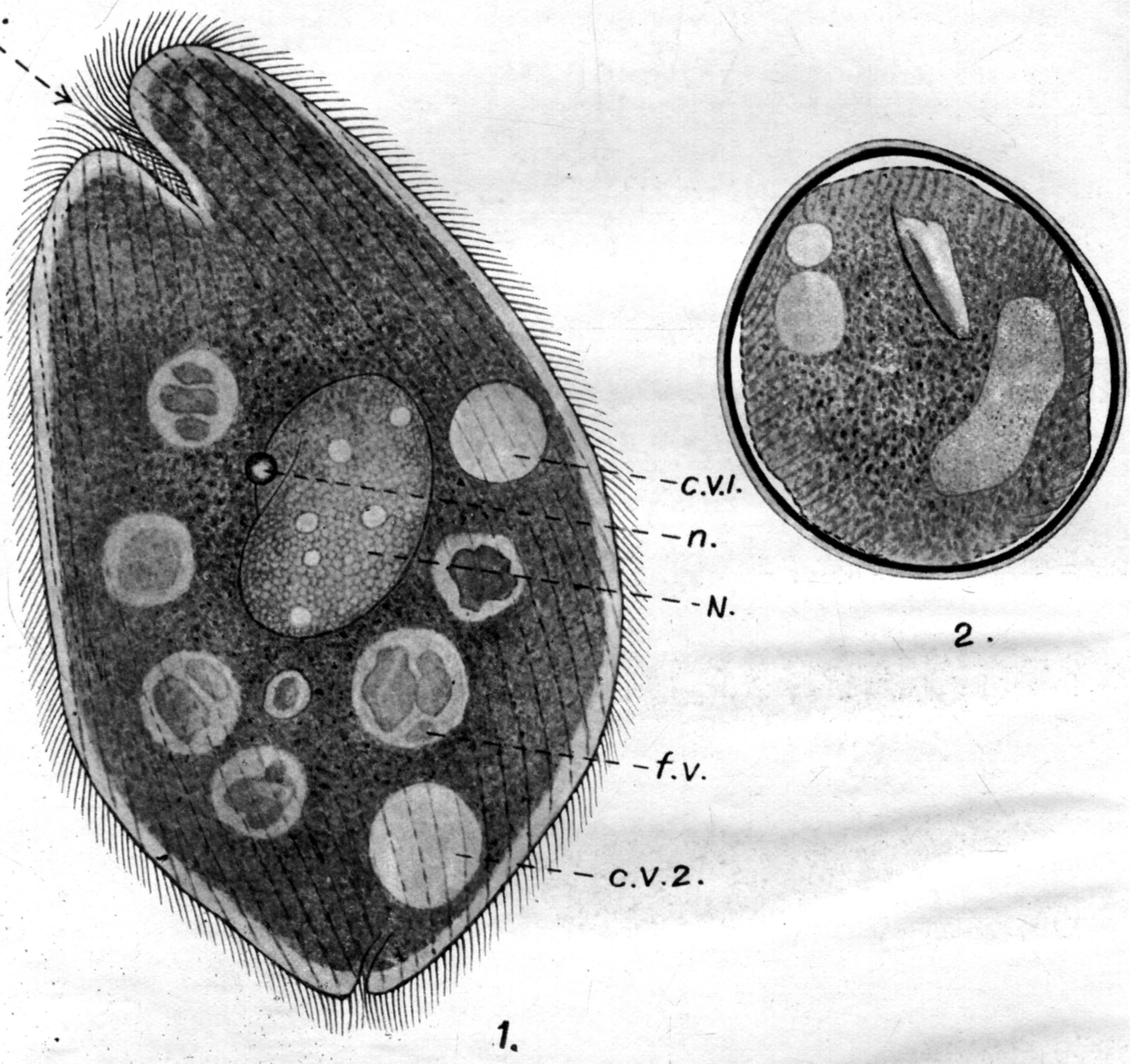


FIG. 16. *Balantidium coli.*

(1) Active ciliate, semi-diagrammatic.
Living specimen as seen from the left side.
N. = meganucleus.
n. = micronucleus.
c. v. 1 = anterior contractile vacuole.
c. v. 2 = posterior contractile vacuole.
f. v. = food vacuole.
mo. = mouth.

(2) Cyst. Living : from the fæces of a pig.
(After Dobell & O'Connor, 1921.)

sources of nourishment available—it takes to feeding upon bacteria, a kind of degradation of its tastes, as it were.

The genus *Balantidium* Claparède and Lachmann, 1858.

This genus was founded by Claparède and Lachmann for a ciliate protozoon which Ehrenberg (1838) had observed in the rectum of frogs, and which he had named *Bursaria entozoon*. The members of this genus, which include species in a considerable variety of hosts, both vertebrate and invertebrate, have pear-shaped bodies completely covered with longitudinal spirally arranged rows of cilia. At the anterior end of the ventral surface is the peristome, a depressed area, the anterior or broader end of which is at the anterior end of the body, whilst its narrow posterior end is on the ventral surface. The cytostome is an opening in the depression of the peristome and from it there extends an œsophagus which ends in the endoplasm. There are one or more contractile vacuoles and at the posterior end of the body a cell anus. The macronucleus may be sausage-shaped or spherical, while a small micronucleus is closely applied to it. A large number of species of *Balantidium* has been described, especially from batrachians. Two species occur in pigs, and one of them is found also in man.

Balantidium coli (Malmsten, 1857). (Fig. 16.)

Balantidium coli of man was first discovered in the stools of two patients suffering from dysentery by Malmsten in Stockholm in Sweden in 1857, who referred to it as *Paramæcium* (?) *coli*. It was placed in the genus *Balantidium* by Stein in 1863.

Balantidium coli is the largest protozoal parasite of the human intestine, and lives in the large intestine, chiefly—perhaps—in the cæcum. It is egg-shaped or pear-shaped, and about 50 μ to 80 μ in length by 40 μ to 60 μ in breadth. Different authors have given measurements for length varying from 35 μ as a minimum to 200 μ as a maximum. It is a well-known fact that many species of free-living ciliates, such as *Paramecium caudatum*, show several races of different mean sizes, and it is probable that different races of *Balantidium coli* exist, with different mean dimensions. McDonald (1922) gives its length as varying from 30 μ to 200 μ and its breadth from 25 μ to 120 μ. The body is clothed with a coat of fine cilia arising in parallel longitudinal rows from minute basal granules, the rows of cilia giving the animal the appearance of being striated. The main part of the body consists of granular endoplasm, in which the internal organs are situated. This is surrounded by a thin clear layer of ectoplasm, and the whole body is invested externally by a very thin and delicate cuticle through which the cilia emerge.

At the anterior pole is a funnel-shaped depression, the peristome, which is actually on the ventral surface of the ciliate. With the constant changes in position

of the anterior end of the body, the appearance of the peristome varies. Sometimes it shows up as a wide-open triangular depression, at other times as a longitudinal groove or slit. On its margins is the adoral zone of cilia, more prominently developed than are the cilia elsewhere on the body. The peristome leads down to a cytostome or cell mouth situated a short distance below the anterior pole of the ciliate, and from the cytostome a very short œsophagus leads into the endoplasm. The body of the animal is not quite symmetrical, the dorsal surface being more convex than the ventral surface. The cilia of the body are stated by McDonald to measure 4 μ to 6 μ in length, whilst those of the adoral zone measure from 8 μ to 12 μ. There are two contractile vacuoles in the endoplasm, one near the middle of the body and the other close to the posterior pole; in addition an anal aperture is present at the posterior end of the animal. The anterior contractile vacuole is often difficult to make out. The macronucleus is sausage-shaped and lies more or less transversely across the middle of the body, whilst close to it is the very small spherical micronucleus, often lying in a small depression on the surface of the macronucleus.

The condition of the endoplasm varies with the state of nutrition of the parasite; sometimes there are numerous vacuoles, each of which contains a highly refractile globule. At other times numerous food-vacuoles are present and circulate in the endoplasm of the ciliate. *B. coli* is a voracious feeder and ingests red blood corpuscles, leucocytes, all manner of fæcal debris, tissue fragments when available, starch grains, and oil globules. Glaessner (1908) has found that *B. coli* secretes a diastatic ferment, and was also able to extract a hæmolysin from it, but no proteolytic ferment.

Reproduction is by binary transverse fission. The micronucleus first divides by mitosis; then the macronucleus constricts into two by amitosis; finally the cytoplasm constricts transversely and two daughter individuals are thus formed. The posterior individual forms a new mouth at its anterior end and more or less extensive reorganisation of the ciliary coat and other parts occurs in both individuals.

Conjugating phases have been observed by Leuckart (1861) and by Brumpt (1909, 1913) but the exact details of conjugation have not so far been worked out. Brumpt states that during conjugation two ciliates become attached to one another by their peristomes and become enclosed in a cyst.

During encystment, the ciliate secretes a thick, transparent—almost cellulose-like—cyst wall which consists of two layers. Inside this the animal continues to revolve for some time, whilst its contractile vacuoles still contract. It then comes to rest, its ciliary coating is shed, and the vacuoles cease to contract and disappear. Food bodies are digested or eliminated before encystment and the most conspicuous structure in the cyst is the large macronucleus. Irregular refractile bodies—often of considerable size, and presumably of the nature of a food reserve substance—are

frequently seen inside the cysts. The cysts are round or slightly ovoid, and commonly measure from 50 μ to 60 μ in diameter. They are, therefore, the largest protozoal cysts encountered in human fæces. Cysts containing two individuals instead of one have been described by Brumpt, who considered that conjugation occurred within the cyst. The cyst appears to be a purely protective structure, for no multiplication has been seen to occur within it.

Barret and Yarbrough's Medium for Balantidium coli. Barret and Yarbrough (1921) have reported successful culture of *Balantidium coli* of man. The medium used consisted of 1 part of inactivated human serum plus 16 parts of 0·5 per cent saline. Tubes containing about 8 c.c. of this medium were inoculated at the bottom with one-tenth of a c.c. of undiluted fæces containing balantidia and incubated at 37°C. Division was observed and an increase in numbers took place. Maximum growth occurred in from 48 to 72 hours, and subcultures were made every 2nd day as a rule. Encysted forms were observed in some of the cultures and one instance of apparent conjugation was encountered.

CHAPTER IV.

The Bacteriology of Bacillary Dysentery.

THE term 'dysentery' is a very unfortunate one to use from the point of view of considering its causative organism, since it only describes a clinical syndrome. As we have already seen, amœbic dysentery is a complication in only some 10 per cent of persons infected with *E. histolytica*, and the bacillus of Flexner is the commonest cause of dysentery in India. On the other hand, there are many sufferers from chronic colitis whose lesions are due to organisms other than the dysentery group of bacilli. The bowel may be ulcerated at different levels, and by different organisms according to the age of the patient. Thus in children the lesion present is often an ileocolitis due to such organisms as the *Bacillus proteus* (Metchnikoff), *B. morgani*, *B. pyocyaneus*, etc. These conditions require study on lines totally different from those dealt with in this book. In adults most of the primary invaders of the bowel are organisms belonging to the so-called typhoid-coli group, i.e., Gram-negative coccal bacilli; most of those which produce ulcerative lesions of the large intestine are non-motile, and—so far as is known at present—none of them ferment lactose. They may, therefore, be defined as Gram-negative coccal bacilli, all of them non-lactose fermenters, and they can grow in the presence of bile-salts. They may be classified as follows:—

(*A*). *Non-motile: producing acid in glucose, but no gas.*

(*A* 1) Non-fermenters of mannite.

(*a*) The Shiga-Kruse group, which produce no indol.

(*b*) The *Bacillus paradysenteriæ* group, which produce indol.

(*A* 2) Fermenters of mannite, but producing indol in various degree.

The races of dysentery bacilli here concerned are:—

The bacillus of Flexner.

The bacillus of Strong.

The Y-bacillus of His.

(B). Motile : producing acid and gas in glucose.

In this group we have :—

The *Bacillus proteus* of Metchnikoff, which appears to be capable of producing enteritis in children, and which is occasionally found in adults.

Bacillus morgani, types *i* and *ii*, which are apparently capable of producing mucous diarrhœa in adults.

The Salmonella group, such as the *Bacillus aertrycke* and *Bacillus enteritidis* of Gärtner, which cause vomiting and diarrhœa (food poisoning).

In cases of chronic colitis, on plating out the stool one notices that, instead of the intestinal flora consisting mainly of lactose fermenters of the *B. coli* group, with colonies of more or less regular size, the plate shows :—

(*a*) Many colonies which are transparent non-lactose fermenters ; also opaque non-lactose fermenters ; or late lactose fermenters, i.e., colonies which become red after 48 hours.

(*b*) Instead of getting uniform sized colonies, one frequently sees large opaque moist colonies, yeasts, endomyces, etc., or tiny colonies of yeasts, streptococci, and staphylococci.

The question therefore arises, What rôle do these organisms play in the production of diarrhœa or dysentery, seeing that the whole of the intestinal flora is altered from the normal ? Are they

(*i*) The cause of the colitis, as Castellani believes such organisms as the metadysentery bacilli to be ?

(*ii*) Are they merely secondary invaders of the ulcerated surfaces, such secondary invasions being apparently especially common in the case of *Staphylococcus mollis* and the *Bacillus pyocyaneus ?*

(*iii*) Are the conditions present in the intestine merely more favourable for the growth of these organisms ? Or

(*iv*) Have these secondary invaders replaced the primary causative organism, such as the bacillus of Flexner, and are they keeping up the ulcerative process ? This applies especially to the *B. paradysenteriæ* and *B. metadysenteriæ.*

Much further work will have to be carried out on this subject before we are in a position to answer these questions properly. There are certain criteria which must be fulfilled before an organism can be accepted as the causal agent of a given condition. For example (*a*) the organism concerned should not be normally present in the intestine ; (*b*) it should be possible to produce the characteristic lesions concerned on injection or ingestion of cultures in the case of experimental animals or suitable human volunteers ; (*c*) the patient's serum should show specific antibodies such as agglutinins or precipitins to the organism concerned.

It is along such lines of work that this problem should be investigated. For the time being we may regard these organisms as secondary invaders of the ulcerated gut. They may be classified as follows :—

(*A*). *Non-lactose fermenters.*

(*A* 1) No change in glucose.

B. pyocyaneus.

B. fæcalis alkaligenes.

B. metadiffluens (an organism which usually gives a very copious growth).

(*A* 2) Produce acid, but no gas, in glucose.

B. fæcaloides.

B. pritnitzi.

B. lunavensis.

B. carolinus.

(*A* 3) Produce acid and gas in glucose.

B. asiaticus.

B. mobilis.

B. pseudo-asiaticus.

B. diffluens.

B. paradiffluens.

B. coagulans.

B. paracoagulans.

B. pseudo-morgani.

B. pseudo-carolinus.

(*B*). *Late lactose fermenters.*

B. metadysenteriæ.

B. giumai.

These have small colonies.

(*C*). *May or may not ferment lactose.*

Yeasts.

Streptococci.

Staphylococci.

The so-called *Monilia* or *Parasaccharomyces ashfordi*, which occurs in cases of sprue, will not grow well on McConkey's or Conradi-Drigalski's media. On Sabouraud's agar, however, on culturing the stools of such cases one gets two types of colonies :—

(*i*) Creamy coloured, greasy colonies.

(*ii*) Drier, yellower, and more spongy looking colonies.

The former are commoner in late cases of sprue.

A further point, to which our attention was first drawn by Dr. K. P. Banerji, M.B., D.T.M., Assistant Professor of Bacteriology, Calcutta School of Tropical Medicine, is that in these cases of chronic colitis, it is often possible to isolate these secondary invaders by culture of the urine, since they escape from the gut into the general circulation from time to time and are eliminated in the urine. This observation was first made when studying cases of epidemic dropsy. Up to date the following types of organisms have been recovered from the urine of such patients :—

Non-lactose fermenters.

No acid or gas in glucose.

B. fæcalis alkaligenes.

Acid and gas in glucose.

B. proteus.

B. asiaticus.

B. asiaticus mobilis.

Lactose fermenters. Coliform group.

B. coli communis.

B. coli tropicalis.

B. cloacæ.

B. entericus.

B. para-entericus.

B. acidi lactici.

B. lactis aërogenes.

B. metadiffluens.

B. vekanda.

Late lactose fermenters.

B. metadysentericus.

Staphylococcus mollis.

Streptococci of various kinds.

These organisms must have come from the intestinal tract and have invaded the blood-stream in embolic showers, though they are difficult to isolate in culture from the blood, since their passage through it is transient. The best method of isolating them is to take a 25 c.c. specimen of urine by catheter into a sterile flask, and to incubate this sample by itself at 37°C.

* * * * *

In dealing with the bacteriology of the dysentery bacilli and allied organisms, it is impossible within the limits of this book to cover the subject completely, and for details of methods of culture, sugar reactions, methods for agglutination, vaccine

preparation, etc., we must refer the reader to any standard text-book on bacteriology. Here we shall only attempt to deal with certain special features in such work. Taking this group of bacteria as a whole—and with special reference to the dysentery bacilli—we may deal with the subject under the following headings :—

(1) *Morphology.* In the fresh stools during the early phases of an attack of bacillary dysentery the microscopic picture presented consists of red blood corpuscles, innumerable leucocytes—chiefly of polymorphonuclear type, and not degenerated—and mucus. In the waterways between the clusters of cells—and often not visible until the focus is slightly raised—are small clusters of non-motile bacilli, the dysentery bacilli. After the first few days, however, the microscopical picture changes ; the red corpuscles disappear, numerous pus cells are seen, and much mucus. At the same time the environment now appears to become especially favourable for the growth of entozoic protozoa, so that vegetative forms of *Trichomonas hominis*, *Chilomastix mesnili*, *Entamœba coli* and *Endolimax nana* are frequently seen at this stage. The waterways in the fæcal emulsion are now crowded with motile bacilli of coliform type, and large diplococci (enterococci). Finally, the stool still shows mucus, and *Blastocystis hominis* is a common finding at this stage. In more chronic cases budding forms of yeasts are often seen. In the stool of early sprue one sees numerous fatty acid crystals, a large number of yeasts, many of them budding, with or without mycelial elements.

The dysentery bacilli are short, oval or more or less coccal bacilli, about 1 to 3 μ in length, rounded at the ends, and plumper in appearance than the *B. typhosus*. The length is slightly greater than the breadth. In fluid culture-media, after some days, involution forms are seen ; these are sometimes serpentine in shape, at other times spindle-shaped. The different races cannot be distinguished from one another morphologically.

(2) *Staining reactions.* All the organisms belonging to this group are Gram-negative ; bacilli from young cultures stain readily with any aniline dye.

(3) *Motility.* Examination for motility is best carried out by taking a drop of a young broth culture, about 6 hours old. This should be placed on the centre of a cover-slip and inverted on to a hanging drop slide. The edges of the cover-slip should now be well luted with vaseline. If this is not done evaporation from the edge of the hanging drop may lead to a lateral movement of the bacilli, which gives a false impression of motility ; this is especially the case when working under an electric fan. There are two types of pseudo-movement which must not be mistaken for true motility, viz. :—

(*a*) Brownian movement. This is a fine oscillatory movement which is inherent in any suspension of fine particles.

(*b*) A translation movement, when the organisms are observed to move from one place to another, either across the field or into the depths of the fluid. This is especially set up by evaporation from the edge of the hanging drop. In order

not to mistake such a movement for true motility, the hanging drop should be allowed to rest for some minutes on the stage of the microscope before it is examined, in order to give time for all sinking particles to settle to the bottom.

The dysentery bacilli are all non-motile, also the *B. paradysenteriæ* and the *B. asiaticus*. The organisms of the coliform group are nearly all motile.

The absolute test for motility is staining for flagella. The best method is Zettnow's. Details are as follows :—

Young agar cultures, about 20 hours old, are the best for use. Use a clean cover-slip, free from grease, so that a drop of water spreads uniformly over it and does not gather into a globule. The bacteria should lie as separately as possible and the film should contain as little of the nutrient medium as possible.

Procedure. Take some tap water in a watch-glass ; carefully take one platinum loopful of the water of condensation of the culture and gently touch the water in the watch-glass with it and allow the culture to diffuse. Add 2 drops of a 2 per cent osmic acid solution (this should be kept in the dark and away from air, and should not be more than a month old ; also it should not contain any black precipitate) to the water in the watch-glass, and give it a slight stir. Allow to stand for 5 minutes.

On each of two clean cover-slips place a drop of distilled water. Gently take a loopful of the emulsion from the watch-glass and make a film preparation on cover-glass No. 1 by giving it a circular movement, but not touching the cover-slip. This is to prevent breaking the flagella. Take one loopfu from cover-slip No. 1 and with this repeat the same procedure on cover-slip No. 2.

Allow to dry in air. When dry, hold the cover-slip by the fingers, and pass through the flame three times to fix. Too much heat should not be employed.

Mordant. Make a solution of 10 parts of pure tannic acid (which should be fresh and not oxidised) in 200 c.c. of distilled water, and warm it to 50 to 60°C. Add gradually to it 25 to 35 c.c. (the amount will vary with different brands of tannic acid) of a solution of antimony tartrate (2 grms. in 40 c.c. of water), and heat till the precipitate dissolves. If, on cooling, the mordant is very turbid, add some tannic acid solution, but if clear, add 1 c.c. of the antimony tartrate solution. The mordant should not form any precipitate, and it should be quite clear on heating to 100°C., without any flakes or scum.

Mordanting. Take a watch-glass, and place it on a water-bath. Place 5 c.c. of the mordant in the watch-glass, so as to fill it.

Bring the water in the water-bath to the boil, when the mordant should be quite clear. Gently put the cover-slip preparation (film surface downwards) into the boiling mordant, and allow it to remain in the mordant on the boiling water-bath for 7 minutes.

Next remove the watch-glass from the water-bath, and allow to cool down until the mordant begins to have a whitish appearance on the outside. Remove the cover-slip and wash well in cold water. There should be no white deposit on the cover-slip when dried after washing.

Stain. Ethylamine-silver solution ; 2 to 3 grms. of silver sulphate are thoroughly mixed with 200 c.c. of water to form a saturated solution. The desired quantity of this, together with an equal volume of water is put into a test-tube, and a 33 per cent solution of ethylamine is added drop by drop until the precipitate which forms is just dissolved. The solution should be clear, and should not smell of ammonia.

Staining. The cover-slip preparation, which has been mordanted, washed, and allowed to dry in air, is now held (film side upwards) in a pair of forceps and flooded with the ethylamine-silver stain, taking care that the solution does not overflow. It is then held in steam from the boiling water-bath until it fumes well, and the edges of the film (only) become blackened.

Wash in running water ; examine in water ; and if satisfactorily stained, mount in balsam.

If the flagella are not satisfactorily stained, the mordanting is defective. In such a case the mordant will require more antimony solution. Or perhaps the ethylamine-silver solution contains too much ethylamine, and more silver sulphate solution should be added to it.

The non-motile organisms have no flagella. The motile coliform organisms have numerous (12 to 18) flagella, situated peritrichously. The *B. pyocyaneus* has a single terminal flagellum.

(4) *Cultural Characters.* The majority of these organisms can grow either in the presence or absence of oxygen, as they are facultative anaërobes. They can grow under great variation of temperature conditions, but the pathogenic ones grow best at body temperature, 37·5°C. Their growth is not inhibited by the presence of bile-salts in concentrations of from 0·25 to 1 per cent, or by small quantities of antiseptics such as carbolic acid, 0·1 to 0·2 per cent. Their growth is also not inhibited by weak dilutions of certain aniline dyes, such as malachite green and crystal violet—a property which is taken advantage of in the preparation of such special media for them as the Conradi-Drigalski medium. The growth of certain of them, such as the bacillus of Shiga, is markedly inhibited by the presence of sugars; others, such as the bacillus of Flexner, grow well in sugar media.

On ordinary media, the following are their cultural characters :—

Broth. Growth is apparent in from 6 to 8 hours, and by the end of 24 hours the broth shows a uniform turbidity. A pellicle is not usually formed on the surface of the broth. On shaking the broth culture and examining it by transmitted light an appearance like watered silk is seen. On removing the cotton-wool plug and smelling the culture, the odour of indol may be present with certain races, such as the Flexner group; it is absent in the case of bacilli of the Shiga group.

Agar. Organisms of the coliform group usually give a profuse growth, whereas the dysentery bacilli give a very fine, delicate, moist, and semi-transparent growth. By transmitted light the growth may be transparent and honey-like (dysentery group) or opaque (coliform group).

Gelatine at 22°C. Certain of these organisms may liquefy gelatine. With the dysentery bacilli growth occurs as a thin opalescent film, and the gelatine is not liquefied.

Litmus milk. In this medium the reactions produced vary with the different species of organism concerned. The dysentery bacilli of both groups at first produce slight acidity, which changes later to alkalinity. The milk is not coagulated. The *B. fæcalis alkaligenes* produces progressive alkalinity with the liberation of a little ammonia. The *B. proteus* produces first acidity and clotting; after this the clot is peptonised. Lastly, some of these organisms may discharge the colour of the litmus milk, with the formation of colourless leuco bases.

Potato. In the case of the dysentery bacilli, at the end of 24 to 48 hours there is a thin and scarcely visible growth. It is at first white, but in the course of a few days becomes greyish or yellowish.

Special Media.

Numerous special media have been devised for the cultivation and isolation of the dysentery bacilli. Of these we will deal only with the three which are most universally in use, viz., McConkey's bile-salt neutral red agar, the Conradi-Drigalski medium, and Endo's medium.

(*I*) *McConkey's medium.* This consists of agar 30 grms., lactose 10 grms., sodium taurocholate 2·5 grms., aqueous neutral red solution (2 per cent) 20 c.c., and nutrient broth to 1 litre. (The 0·5 per cent strength of sodium taurocholate recommended in most text-books, whilst quite suitable for the bacillus of Flexner, rather tends to inhibit the growth of the bacillus of Shiga, and for general purposes we have found a strength of 0·25 per cent better.) The medium is sterilized by steaming at 100°C. for ten minutes on each of two successive days, and is poured into medium-sized Petri dishes, of 15 cms. diameter. In our experience this is by far and away the best and most reliable medium for isolation of the dysentery bacilli. On this medium the colonies of the *B. dysenteriæ* appear as minute, colourless, transparent, dew-drop-like growths.

(*II*) *Conradi-Drigalski medium.* In this medium crystal violet is used as the inhibitor, lactose as the sugar, and Teichmann's litmus solution as the indicator. To prepare it 100 c.c. of neutral agar base is first coloured a lilac colour with Teichmann's litmus solution. Then 5 c.c. of hot freshly prepared 20 per cent solution of lactose in distilled water is added. Finally add 1 c.c. of a 1 in 1,000 solution of crystal violet in distilled water. The medium is sterilized by steaming at 100°C. for ten minutes on two consecutive days, and poured into Petri dishes.

On this medium colonies of the *B. dysenteriæ* are minute, dew-drop-like, translucent, and of a delicate bluish-grey colour.

Before the War we used to use this medium extensively, but for some reason since the War it has given us far less satisfactory results than those with McConkey's medium. The Teichmann's litmus solution does not appear to be as satisfactory as formerly.

(*III*) *Endo's medium.* This is a favourite medium with many workers, and has been much used by the junior author at Shillong. When the right colour of the medium—a very delicate salmon pink—is obtained, Endo's is an excellent medium for the isolation of the dysentery bacilli. On the other hand, it is not always easy to get the plates the right colour; and if the colour is too deep or uneven, isolation of the dysentery bacilli on this medium may be difficult.

To prepare Endo's medium a 3 per cent nutrient agar is first prepared. This consists of Liebig's extract 5 grms., peptone 10 grms., salt 5 grms., agar 30 grms., and water to 1,000 c.c. It should be neutralized or brought to a reaction of +0·2. This is stored in 100 c.c. quantities in flasks till wanted.

When required for use 100 c.c. of this is melted in streaming steam. Then proceed as follows:—

(*i*) Dissolve 1 grm. of chemically pure lactose in 15 c.c. of distilled water with the aid of gentle heat.

(*ii*) Dissolve 0·25 grm. of anhydrous sodium sulphite in 10 c.c. of water.

(*iii*) To the sulphite solution add 0·5 c.c. of a saturated solution of basic fuchsin in 95 per cent alcohol.

(*iv*) Add the fuchsin-sulphite solution to the lactose solution, and then add the whole to the melted agar.

(*v*) Pour at once into Petri dishes, and allow to harden thoroughly in the incubator before use.

Everything depends on getting the correct pale, delicate salmon-pink colour in the plates. If this is obtained results are very clear-cut; coliform organisms give red colonies; the *B. typhosus* group fine, delicate slightly greyish colonies; and the *B. dysenteriæ*. fine, dew-drop-like colonies, which are to all intents and purposes colourless. If the colour of the medium be a little too deep, however, or if it be unevenly distributed in the plate, colonies of the *B. dysenteriæ* may assume a slightly pinkish tinge, which tends to be a source of confusion.

Method of Cultivation.

The stool should, if possible, be a freshly passed one, since it is practically impossible to isolate the dysentery bacillus from a stale stool. If the stool contains mucus, a shred of the mucus is taken for plating. In the case of a formed stool—as when examining for the carrier state—the best plan is probably to take a very minute fragment of the stool in a platinum loop and emulsify this in 10 c.c. of broth in a test-tube. This is then incubated for 6 to 8 hours, and a loopful of this emulsion is then used for spreading the plate.

The plates to be inoculated should be kept upside down for 24 hours before inoculation in the 37°C. incubator. This will ensure that they are sterile, that their surface is dry, and that they are warm when inoculated. If this precaution is neglected, water of condensation is very apt to form on the surface of the medium, and cause the colonies to run into one another.

The plate to be inoculated is divided into four equal sectors by marking it with two cross lines on the under surface of the lower half of the Petri dish with a grease pencil. The sectors are then numbered 1, 2, 3 and 4. The spreader is a glass rod bent to a right angle a short distance from its end by heating it in the flame; it must be sterile and cool, otherwise the bacilli will be killed by the heat of the rod.

If mucus is present in the stool a tiny shred of mucus is picked up on a sterile platinum loop and is first well washed in sterile saline to remove extraneous organisms. In the case of a formed stool, a loopful from the broth emulsion is used.

The shred of washed mucus or small loopful of emulsion is now placed on sector 1, and the spreader applied until the whole surface of the rod in contact with the medium is charged with material. This is now rubbed fairly heavily over sector 1, with 4 or 5 vigorous rubs ; less heavily over sector 2 ; and very lightly indeed, and only once or twice, over sectors 3 and 4. If this be properly done the colonies on sectors 3 and 4 will be easy to isolate and sufficiently far apart from one another for easy working.

The inoculated plates are now placed upside down in the 37°C. incubator, and examined at the end of 24 hours. The following types of colonies may now be encountered :—

(*i*) *Lactose fermenter colonies.* These are red in colour, and may be of large or medium size (the coliform group) ; or fine and dew-drop-like (streptococci and yeasts).

(*ii*) *Late lactose fermenters.* These are medium or large-sized colonies, opaquely white, and showing a red centre by transmitted light. Later on, usually at 48 hours' incubation, these colonies become pink or reddish.

(*iii*) *Non-lactose fermenters*, including the dysentery bacilli. The number of these present varies with the intestinal state of the patient, and the freshness or otherwise of the stool when it is plated. In a perfectly fresh stool from a case of acute bacillary dysentery in the early phase, an almost pure culture of colonies of dysentery bacilli may be obtained. If the attack has persisted for some days, however, one-fifth or less of the colonies present may be those of non-lactose fermenters. In the case of the carrier state, colourless colonies may be very difficult to find.

The non-lactose fermenters concerned are :—(*a*) The dysentery bacilli. These colonies are generally the smallest present on the plate, and tend to occur in irregular chains interposed between the larger and denser colonies. They are clear, colourless dew-drop-like colonies with a regular or very slightly wavy outline. (*b*) Colonies of the *B. typhosus* group may be present in the case of an enteric carrier. (*c*) The blue colonies of the *B. fæcalis alkaligenes* may be present ; or (*d*) opaque colonies of non-lactose fermenters, such as the *B. carolinus*.

The selection of the right type of colonies for further investigation requires a good deal of care and practical experience, otherwise a lot of unnecessary work is done in picking up by mistake colonies of organisms other than those of the dysentery group. The plate should be examined first by transmitted light with the aid of a watchmaker's glass or a hand magnifying lens. (For this work a ' corneal loupe ' with a headband that fits round the head and holds the loupe automatically in place is very useful.) When viewed by transmitted light the colonies of the dysentery bacilli appear as tiny, clear, colourless droplets with an even, regular,

or slightly wavy outline. As a rule Flexner bacillus colonies are less refractile and of a more irregular outline than those of Shiga's bacillus. The absolute transparency—or sometimes a very slight shade of pink—in the colony when viewed by reflected light against a white surface is helpful. Or the plate may be placed on a dark surface and examined by reflected light, when the translucency of the colonies shows up well.

As a rule from 4 to 6 suspicious colonies should be picked up from each plate. Each colony is now inoculated on to the surface of an agar slope, *only the upper half of the surface of the slope being inoculated.* These inoculated agar slopes are now incubated for 4 to 6 hours at 37°C. In working with a batch of plates this procedure will save a whole day of working time; the colonies are picked off the plates and inoculated on to the upper half of the agar slopes in the morning; by the afternoon there is then a sufficient growth on the agar slopes to allow of the inoculation of sugar media; after the sugar media have been inoculated the smear on the agar slope is then carried over its whole surface with a sterile platinum loop. On the next morning—2nd day—the sugar reactions will be ready to be read, whilst profuse growths will be available for serological tests, and—if necessary—for vaccine preparation.

In cases of suspected sprue, plates of Sabouraud's agar are inoculated in four sectors by the same technique as above. The composition of Sabouraud's medium is as follows :—

Maltose	.. 4·0 grms.
Peptone (Chassigny's is preferable to Witte's for the medium)	.. 1·0 grm.
Agar	.. 2·5 grms.
Water	.. 100 c.c.,

the reaction being adjusted to +2 (pH 6·0).

The plates are inoculated in the same way with a spreader; Monilia colonies are large, greasy, heaped up, and of an ivory colour.

The Identification of the Organism.

It will be seen from the preceding sections that a given race of *B. dysenteriæ* cannot be identified by merely examining it under the microscope. Having isolated a suspicious strain, we have still to investigate the following points with regard to it :—

(*i*) Morphology. Is the organism a Gram-negative coccal bacillus ?
(*ii*) Is it non-motile ?
(*iii*) Does it produce indol or not ?
(*iv*) What sugars does it ferment ?
(*v*) What are its agglutination reactions ?

Points (*i*) and (*ii*) have already been dealt with. With regard to (*iii*), the smell of indol can usually be recognized on smelling a 24 hours old broth culture. Or the nitroso-indol test may be applied. The technique of this is as follows :—

Nitroso-indol Test.—A 24 or 48 hours old culture in peptone water, or in sugar-free broth, is taken and 6 to 8 drops of concentrated sulphuric acid are added. Next add about 1 c.c. of a very dilute—e.g., 1 : 5,000 or 1 : 10,000—solution of sodium nitrite. Replace in the 37°C. incubator and examine an hour later. If the organism produces indol, a rose pink colour will be present.

The Para-dimethylamido-benzaldehyde test is even more delicate, and will detect traces only of indol. Two solutions are required, and should be stored in separate bottles :—

(A)	Para-dimethylamido-benzaldehyde	4 grms.
	Absolute alcohol (90 per cent)	380 c.c.
	Concentrated hydrochloric acid	80 c.c.
(B)	Saturated watery solution of potassium persulphate.	

The organism to be tested is cultivated for 48 to 72 hours in trypsin broth. To 5 c.c. of this culture add 1 c.c. of solution A, then 1 c.c. of solution B, and shake. Replace in the warm incubator for a few moments. If indol is present, a rose red colour will appear.

The indol test, however, is of minor importance in identifying the dysentery bacilli, and when the laboratory worker has isolated what he believes to be a strain of the *B. dysenteriæ*, the question immediately arises as to whether he shall apply first the sugar tests or the agglutination test.

In this connection it is important to note that worker after worker, both during the War and in recent years, has emphasized the fact that when freshly isolated from the stools strains of the *B. dysenteriæ* may not be agglutinable, though such strains frequently become agglutinable on subculture. For such strains Andrewes recommends repeated subculture in broth, and testing formalinised emulsions of the subcultures, when such strains usually become agglutinable. The bacillus of Shiga is much more reliable with regard to the agglutination test than the bacillus of Flexner, and usually agglutinates with the specific serum in dilutions of 1 : 100 or upwards. The bacillus of Schmitz, or para-Shiga bacillus of Dudgeon, is an organism which gives all the sugar reactions of Shiga's bacillus, but does not agglutinate with anti-Shiga serum, though it usually shows a marked agglutination with the patient's own serum. Also it may or may not produce indol. This organism first came into prominence in connection with an outbreak of dysentery in 1916 among Roumanian prisoners of war. It was also frequently encountered by laboratory workers in Macedonia, and was also met with by Fletcher when working at Southampton, and by Broughton-Alcock in Italy.

Non-agglutinating strains of the bacillus of Flexner are much more common. The original classification of the Flexner group of bacilli was made in accordance with their sugar reactions ; thus such types were recognised as the true bacillus of Flexner, the Y-bacillus of His and Russell, and Strong's bacillus. The studies of Andrewes and Inman (1919), however, have shown that there are four distinct

antigenic components in the group. In any one given strain any one of these four components may become so prominent that a definite serological type to that antigenic component becomes recognizable. These workers insist that in testing bacilli of the Flexner group serologically, an antiserum prepared against all four antigenic components should be used.

From these considerations it follows that the results of the agglutination test are of value only when they are positive; and especially in the case of Flexner bacillus infections failure of the organism to agglutinate with the specific antiserum by no means excludes an infection with this organism. In general, the laboratory worker will find it a safer working rule to rely on the results of the sugar tests than on the agglutination findings.

The Method of Rapid Preliminary Agglutination.

During the War this method came into prominence. It is obvious that it is very much 'hit or miss,' and results are only of value if positive. Yet it may occasionally enable the laboratory worker to identify the specific dysentery organism concerned within 24 hours. The procedure is as follows:—

(*i*) The stool is plated out on a McConkey plate, and incubated for 18 hours, e.g., overnight.

(*ii*) Next morning the plate is examined, and if any suspicious colonies are found, about 20 of them are picked off and emulsified together in a small quantity, about 0·25 c.c., of normal saline. A thick, opaque, milky emulsion should result.

(*iii*) This is now tested for agglutination against Lister Institute high titre anti-Shiga serum and anti-Flexner serum by Garrow's agglutinometer. The glass plate of the agglutinometer should be thoroughly cleaned with alcohol and ether and dried with a clean gauze cloth before use, otherwise the sera and emulsion will not intermingle properly. The glass slab of Garrow's agglutinometer contains 30 compartments, and as many as 10 McConkey plates from the same number of patients can be dealt with at the same time.

With the special pipette of the apparatus one places in three consecutive chambers (*a*) a drop of anti-Shiga serum diluted 1 : 50; (*b*) a drop of anti-Flexner serum diluted 1 : 50; (*c*) a drop of normal saline as control. To each drop an equal quantity of the thick bacillary emulsion is added, thus making the final dilution of the serum 1 : 100. The slab is then rotated for three minutes in a moist chamber (to prevent evaporation), and the result read against a dark background.

Coarse snowflake macroscopic agglutination, quite obvious to the naked eye, may take place in one or other compartment should the organism be either the bacillus of Shiga or the bacillus of Flexner. If a positive result is obtained the remainder of the bacillary emulsion is tested against the specific serum to determine the end point of agglutinability, at dilutions ranging from 1 : 200 to 1 : 750.

As a result of this preliminary test it is often possible for the laboratory worker to send to the physician within 24 hours of receiving the stool such a report as, 'Bacillary dysentery : Flexner's or Shiga's bacillus isolated'. Five typical colonies can then be picked off the plate and cultured on agar for the sugar tests, etc.

If the colonies on the plate are not numerous enough for this method, the more likely looking colonies should be picked off the plate, subcultured on agar for from 6 to 18 hours, when the agglutination test can be applied by Garrow's agglutinometer.

The Sugar Reactions.

In ordinary routine examination of the stools of cases of bacillary dysentery by the methods described above, using the method of inoculating only half the agar slope with each colony, by the afternoon of the 2nd day from receipt of the stool there will be a sufficient growth on the agar slopes to permit of inoculation of the sugar media that afternoon. (For the method of preparation of sugar media we must refer the reader to any standard text-book of bacteriology. The media may either be used fluid in test-tubes fitted with the small Durham's fermentation tubes, or in solid form. The latter method saves considerable expense, since the media can be put up in small test-tubes and inoculated by the stab method. Acidity will show itself along the line of the stab, whilst if gas is produced bubbles of it will appear entangled in the medium.) In using fluid sugar media the strength of sugar used should be 1 per cent in peptone broth of the particular sugar used, except in the case of dulcite, where the strength should be 2 per cent.

The most important sugar tests are those with mannite, glucose, lactose, dulcite and adenite. Tubes of saccharose and maltose media may also be inoculated, but with these sugars reactions are apt to be more variable than with the first five enumerated. A litmus milk tube should also be inoculated, and a broth tube for the indol test. The inoculated sugar tubes should be incubated at 37°C., and read at the end of 24 and of 48 hours. In the case of a McConkey plate which shows apparently negative results the plate should always be re-incubated for a second period of 24 hours, as the appearance of the colonies of the *B. dysenteriæ* is sometimes delayed.

The dysentery bacilli are divisible into two main groups : (*a*) the Shiga-Kruse group, and (*b*) the Flexner-Strong group. The former do not ferment mannite ; the latter do. The type reactions of the two classical strains are as follows :

	Lactose.	*Glucose.*	*Mannite.*	*Dulcite.*	*Litmus milk.*	*Indol.*
The Shiga bacillus ..	0	Acid	0	0	First acid, later alkaline.	0
The Flexner bacillus ..	0	Acid	Acid	0	First acid, later alkaline.	+ or 0

Table V, which is modified from the one in Castellani and Chalmers' *Manual of Tropical Medicine*, gives the main characters of the non-lactose-fermenting organisms found in the intestine and fæces. The table, we fear, is nothing like complete or accurate, but, as far as it goes, it may serve as a rough guide to the identification of these organisms.

Confirmation by the Agglutination Test.

We have seen that the tests hitherto employed in our routine examination for the *B. dysenteriæ* have consisted of testing its morphology and staining reactions, examining it for motility, and testing its biochemical reactions. Having proceeded so far, the next and final step is to confirm the finding by the agglutination reactions.

It is impossible within the limits of this book to describe the various methods of applying the agglutination test, and for details of the capillary pipette method, and of Dreyer's method, we must refer the reader to standard text-books of bacteriology. On one point all workers on the dysentery bacilli are agreed : that for these organisms the macroscopic method is far and away preferable to the microscopic one. The velocity of the agglutination reaction with the dysentery bacilli is much less than that with the *B. typhosus* group. Where an immediate report is wanted the tubes can be incubated at 55°C. for at least four and a half hours. Ordinarily the tubes should be left in the warm incubator overnight, or allowed to stand on the laboratory bench for 24 hours. An occasional Flexner strain may even require a period of 24 hours on a water-bath at 55°C. before agglutination occurs.

The senior writer usually uses the capillary pipette method, first putting up the culture with Lister Institute polyvalent high titre serum to determine that the organism belongs to the *B. dysenteriæ* group, then testing it with the specific high titre serum at high dilutions to obtain the end point. The following method is given by Manson-Bahr, Perry and Manson (1922).

Emulsions are made of the living organisms in sterile normal saline. The resultant fluid should be distinctly opalescent. It should be dropped by means of a drop pipette into narrow glass agglutination tubes (preferably with a conical end) containing an equal quantity of the specific immune rabbit serum as issued by the Lister Institute. Two rows of tubes should be used, one for Shiga sera, the other for Flexner sera (preferably made from the several recognized agglutination strains). The dilutions should commence at 1 : 100 and should be taken as high as 1 : 1,000 ; or, better still, dilutions can be made by Dreyer's method, which, however, requires more mathematical reckoning, but utilizes less serum and fewer tubes. After addition of the serum the tubes should be well shaken and placed in the incubator for two hours at 37°C. Sedimentation does not occur so readily as it does with enteric organisms ; therefore on removal from the incubator the

	Organisms.	Motility.	Indol.	Voges's reaction.	Saccharose.	Dulcite.	Mannite.	Maltose.	Salicin.	Litmus milk.	Glucose (A).
1	*B. albofaciens*	0	0	—	0	0	0	0	0	AC	
2	*B. ceylonensis* A	0	0	0	0	0	0	0	0	AC	
3	*B. Shiga-Kruse*	0	0	—	0	0	0	0	0	A Alk	
4	*B. gintotensis*	0	0	0	0	0	0	0	0	D AC	
5	*B. negombensis*	0	0	0	0	0	0	0	0	0 Alk	
6	*B. paradysentericus*	0	±	—	0	0	0	0	0	A	Glucose (0 or A
7	*B, tardus*	0	0	—	0	0	0	0	0	DP	
8	*B. carolinus*	+	+	0	0	0	A or AG	A or AG	—	A Alk	Glucose (Alk)
9	*B. dysenteriæ*, His and Russell ..	0	+ or ±	—	0	0	A	0	0	A Alk	
10	*B. dysenteriæ*, Flexner	0	+	—	0	0	A	A	0	A Alk	
11	*B. fæcaloides*	+	0	0	0	0	A	A	0	Alk	
12	*B. typhosus*	+	0	0	0	0	A	A	0	A	
13	*B. pritnitzi*	+	0	—	0	0	0	A	A	A	
14	*B. douglasi*	0	+	—	0	A	A	A	—	Alk	
15	*B. werahensis*	+	+S	—	0	AG	A	AG	A	A	
16	*B. kandiensis*	+	0	0	As	0	A	0	0	As D Alk	
17	*B. lunavensis*	0	+	0	A	0	0	A	0	As Alk	
18	*B. talavensis*	+	+	0	A	0	0	0	A	Alk D	
19	*B. tangallensis*	0	+	0	A	A	A	A	A	As Alk	
20	*B. dysenteriæ*, Strong	0	+	—	A	A	A	0	0	AC	

TABLE V.

FÆCES.

(*McConkey's bile-salt-lactose-neutral-red-agar.*)

Intestinal non-sporing aërobes.

Non-lactose fermenters (Lactose = 0).

Glucose (0).

	Organisms.	Motility.	Indol.	Voges's reaction.	Saccharose.	Dulcite.	Mannite.	Maltose.	Salicin.	Litmus milk	
1	*B. fæcalis alkaligenes*	+	0	0	0	0	0	0	0	Alk	
2	*B. metadiffluens*	+	—	—	0	0	0	0	0	Alk	
3	*B. pyocyaneus*	+	..	..	0	0	0	0	0	As	Glucose (Green
4	*B. zeylanicus*	+	0	0	Alk	Alk	Alk	Alk	0 or Alk	Alk	Glucose (Alk)

Abbreviations

A = acid.
G = gas.
C = clot.
O = negative result.
D = colour discharged.
Alk = alkaline.
A or Alk = acid, then alkaline 2—3 days after.
As = acid slightly.
Avs = acid very slightly.
— = negative result.
+ = positive result.
± = sometimes positive. / sometimes negative.

	Organisms.	Motility.	Indol.	Voges's reaction.	Glucose (AG).	Saccharose.	Dulcite.	Mannite.	Maltose.	Salicin.	Litmus milk.	
1	*B. diffluens*	+	0	—	0	0	0 or A	0	0	Alk D		
2	*B. morgani*	0	±	—	0	0	0	0 or A	0	0 or As Alk		
3	*B. paracoagulans*	0	+	0	0	0	AG	AG	—	AC		
4	*B. pseudo-carolinus*	0	+	0	0	0	AG	AG	—	0		
5	*B. pseudo-morgani*	+	+	0	0	0	0	0	0	0 Alk		
6	*B. aertrycke*	+	0 or +S	0	0	AG	AG	AG	0	A Alk		
7	*B. archibaldi*	+	+	+	0	AG	AG	AG	—	A Alk		
8	*B. columbensis*	+	+	0	0	AG	AG	AG	AG	Avs Alk	Lactose (O or Gvs.)	
9	*B. enteritidis*, Gärtner	+	0	—	0	AG	AG	AG	0	D or A. A Alk		
10	*B. icteroides*	+	±	0	0	A or AG	AG	AG	—	A Alk		
11	*B. para-aertrycke*	+	0	0	0	AG	AG	AG	0	A Alk		
12	*B. para-asiaticus*	0	+S	0	0	AG	AG	AG	0	0		
13	*B. paratyphosus* A	+	0	0	0	AG	AG	AG	0	A		
14	*B. paratyphosus* B	+	0	0	0	AG	AG	AG	0	A Alk		
15	*B. pseudo-columbensis*	0	+	0	0	AG	AG	AG	AG	0		
16	*B. psittacosis*	+	0	0	0	AG	AG	AG	0	A Alk		
17	*B. suipestifer*	+	+S	0	0	AG	AG	AG	0	A Alk		
18	*B. typhi murium*	+	0	0	0	AG	AG	AG	0	As Alk		
19	*B. veboda*	+	0	—	0	AG	A	AG	0	A Alk		
20	*B. watareka*	+	+	—	0	AG	AG	AG	0	A		
21	*B. coagulans*	0	±	—	0	—	0	AG	—	AC		
22	*B. paracolon*	+	+	0	0	A	AG	AG	—	A Alk		
23	*B. willegodai*	+	+S	—	0	A	A	AG	AG	A Alk		
24	*B. asiaticus*	0	+S	0	AG	0	AG	AG	0	A Alk		
25	*B. asiaticus mobilis*	+	+S	0	AG	0	AG	AG	0	A Alk		
26	*B. paradiffluens*	+	0	—	AG	0	0 or A	0	0	Alk D or P		
27	*B. proteus vulgaris*	+	+	—	AG	0	0	AG	0	C or P		
28	*B. pseudo-wesenbergi*	0	+	—	AG	0	0	—	—	0		
29	*B. wesenbergoides*	+	+	—	AG	0	0	AG	—	0		
30	*B. wolinicæ*	+	0	—	A Alk	0	AG	AG	0	A A or Alk		
31	*B. pseudo-asiaticus*	0	+	0	AG	AGS	AG	AG	AG	A Alk		
32	*B. pseudo-asiaticus mobilis*	+	+	0	AG	AG	AG	AG	AG	A 0. Alk		
33	*B. diphtheroid*	..	..	..	AG	AG	A	AG	..	0 As		

tubes should be placed in a rack at room temperature for twelve hours in order that full sedimentation may take place. If an incubator at 55°C. is available this test can be performed in a shorter time. There is no difficulty in reading the result.

'Where true macroscopic agglutination has taken place, the bacillary mass will be precipitated at the bottom of the tube with a supernatant layer of clear fluid. In the case of Shiga's bacillus a reading as high as 1 : 1,000 will frequently be observed, but there is greater variation in the mannite fermenting strains ; even with fresh batches of agglutination serum a dilution of 1 : 600 must be regarded as diagnostic.'

In using agglutinating sera for diagnosis, the full titre of the serum by the technique employed should be known. The Bacteriological Committee of the War Office on Dysentery advise that the unknown bacillus should be put up against the serum in three dilutions of the latter, corresponding to one-quarter, one-half, and full titre. With regard to the non-agglutinating Flexner bacillus strains, the senior writer has found that these organisms are very resistant to the bacteriophage of d'Herelle.

* * * * * *

The factors upon which success or otherwise in the isolation of dysentery bacilli from the stools of bacillary dysentery cases depends are many and are of considerable importance. Thus Manson-Bahr, Perry and Manson (1922) summarize these as follows :—

(1) Period of the disease. The longer the duration of the disease, the more difficult it becomes to isolate the dysentery bacilli. They are hardly ever recovered after the sixth day. Martin and Williams, on plating 1,050 stools, obtained 68 per cent of positive results in the first five days, 17·4 per cent in the second five days, and only 6·3 per cent in the third five days.

(2) Even apparently suitable stools, early in the attack, sometimes fail to yield positive cultures. This is especially true of the stools containing much dark, altered blood passed in the early phases of a fulminant attack. A negative finding does not exclude the presence of bacillary dysentery.

(3) 'Failure to isolate the bacillus from the stools does not necessarily indicate that it is non-existent in the patient's intestinal canal. This is really a comparatively common event. The bacillus has been recovered frequently from the bases of chronic ulcers in the intestine post-mortem in autopsies on cases in which several attempts to recover it from diarrhœic stools during life had failed.'

(4) 'The character of the cells in the exudate is an index of the probability of successful culture. The most favourable stools for culture are those which contain a large proportion of undamaged pus cells.'

(5) 'Under tropical conditions the specific bacillus can be isolated only with difficulty after the stools have stood for four hours.' Shiga's bacillus

especially is rapidly killed off in the passed stools by the growth of saprophytic organisms.

(6) 'Successful isolation depends upon the nature of the contaminating organism or organisms.' Thus certain organisms, and especially the *B. pyocyaneus* when present, inhibit the growth of the dysentery bacilli. Admixture of urine with the stool also inhibits their growth.

These authors record the following findings from the records of 250 cultures of bacillary dysentery stools in Palestine :—

Character of specimen.	*Percentage of successful isolations.*
(*a*) Fresh gelatinous blood-stained mucus. Cellular exudate, fresh pus cells and few visible bacilli	73·3
(*b*) Glairy mucus. No blood. Cellular exudate, pus cells and macrophages ..	62·5
(*c*) Blood and mucus. Disintegrating pus cells and numerous motile bacilli ..	44·8
(*d*) Blood and mucus flakes intermingled with fæces	36·7
(*e*) Bile-stained blood and mucus. Disintegrating bile-stained pus cells and red cells	33·0

In the case of examination for bacillary carriers these authors advise that a minute portion of the fæces should be thoroughly emulsified in 10 c.c. of sterile distilled water or saline, and a drop of the emulsion be spread with a platinum loop on the plate in a spiral manner, using progressively smaller quantities of emulsion for each successive plate. This gives a satisfactory distribution of the colonies. For isolation of the dysentery bacilli at post-mortem examination, the best material to take is either from the bases of the ulcers or from the mucus retention cysts; the latter often yield almost pure cultures of *B. dysenteriæ*.

In the case of secondary invading organisms in the stool, in addition to cultures in sugar media, it may be necessary to apply the methyl red test and the Voges-Proskauer reaction to differentiate organisms of the *B. coli* group from those of the *B. cloacæ* group. Details of these tests are as follows :—

Methyl Red Test.—This is positive with organisms of the *B. coli* group, and negative with those of the *B. cloacæ* group. A special peptone medium has to be employed, which is made up as follows :—

(1) To 800 c.c. of distilled water add 5 grms. of proteose-peptone (Difco or Witte's peptone), 5 grms. of dextrose, and 5 grms. of dipotassium hydrogen phosphate (K_2HPO_4). (A dilute solution of K_2HPO_4 should give a distinct pink with phenol-phthalein.)

(2) Heat over steam, with occasional stirring, for 20 minutes.

(3) Filter through folded filter-paper; cool to 20°C. and dilute to 1,000 c.c. with distilled water.

(4) Distribute in 5 c.c. portions in sterilized tubes.

(5) Sterilize by steaming for 20 minutes on each of three consecutive days.

The indicator solution is made by dissolving 0·1 grm. of methyl red in 300 c.c. of absolute alcohol, and diluting to 500 c.c. with distilled water.

TABLE

FÆC

(*McConkey's bile-salt-l*

Intestinal non-s

All are Gram-negat
Staphylococci,
Streptococci,
Pneumococci, et

Lactose fermenters = red
(Lactose = AG).

	Organisms.	Motility.	Indol.	Voges's reaction.	Saccharose.	Dulcite.	Mannite.	Maltose.	Salicin.	Litmus milk.	
1	*B. capsulatus*	0	±	+	AG	0	AG	AG	–	AC	
2	*B. cloacæ*	+	+	+	AG	0	AG	AG	0	AC	
3	*B. coscoroba*	0	0	–	AG	0	AG	AG	–	AC	
4	*B. lactis aërogenes*	0	0	+	AG	0	AG	AG	AG	AC	
5	*B. metacoli*	+	+	0	AG	AG	AG	AG	AG	AC	
6	*B. neapolitanus*	0	+	0	AG	AG	AG	AG	AGs	AC	Glucose (AG)
7	*B. oxytocus perniciosus*	0	+	+	AG	AG	AG	–	AG	AC	
8	*B. para-entericus*	+	+	0	AG	AG	AG	AG	–	A	
9	*B. pseudo-coli*	+	+	0	AG	AG	AG	AG	AG	AC	
10	*B. pseudo-coliformis*	+	+	0	O, AG	AG	AG	AG	AG	AC	
11	*B. gasoformans non-liquefaciens* ..	0	0	+	AG	0	–	–	–	AC	Glucose (–)
12	*B. acidi lactici*	0	+	0	0	0	AG	AG	0	AC	
13	*B. colo-tropicalis*	0	+	–	0	0	AG	AG	AG	AC	
14	*B. grünthali*	+	+	0	0	0	AG	–	–	AC	
15	*B. levans*	+	0	+	0	0	AG	–	AG	AC	
16	Moniliâ	..	..	..	0	0	0	AG	0	A or 0	
17	*B. para-grünthali*	+	±	–	0	0	AG	AG	AG	AC	
18	*B. cavicida*	+	+	0	0	AG	AG	0	A	AC	Glucose (AG)
19	*B. coli*	+	+	0	0	AG	AG	AG	AG	AC	
20	*B. coloides* A	0	–	–	0	AG	–	AG	AG	AC	
21	*B. coloides* B	0	–	–	0	AG	–	AG	AG	AC	
22	*B. entericus*	0	+	0	0	AG	AG	AG	–	0	
23	*B. khartoumensis*	0	+	0	0	AG	AG	AG	AG	A	
24	*B. metacoloides*	+	+	–	0	G	AG	AG	0	AC	
25	*B. vekanda*	+	0	–	0	AG	AG	AG	0	A	
26	*B. schafferi*	0	+	0	0	AG	–	–	–	AC	Glucose (–)
27	*B. vesiculosis*	0	+	0	0	0	–	–	–	AC	
28	*B. coli mutabilis*	0	0	–	0	0	–	–	–	AC	

Abbreviations { A = acid ; C = clot. G = gas ; Alk = alkaline.

A or Alk = acid, then alkaline, 2—3 days after.
O = negative result.
D = colour discharged.

ES.

ıctose-neutral-red-agar.)

poring aërobes.

	Organisms.	Motility.	Indol.	Voges's reaction.	Saccharose.	Dulcite.	Mannite.	Maltose.	Salicin.	Litmus milk.	
	ive except										
	Partial or late lactose fermenters Lactose = A or G.										
1	*B. giumai*	0	+	0	0	0	0	AG	AG	A, Alks	Glucose (AG)
2	*B. wesenbergi*	+	+	—	AG	A	A	—	—	A	
3	*B. pneumoniæ*, Friedlander	0	0	0	AG	AG	AG	AG	AG	AC	
4	*B. bentotensis*	+	+	0	A	As	0	A	As	A	Glucose (A)
5	*B. ceylonensis* B	0	+	0	A	A	A	A	0	AC	
6	*B. meta-dysentericus* D	0	±	—	A	A	A	A	—	A, Alk	
7	*B. pyogenes fœtidus*	+	+	0	A	A	A	A	—	AC	
8	Diplococcus	..	..	..	A	0	0	A	..	0	
9	*B. madampensis*	0	+	0	A	0	A	A	0	AC	
10	*B. meta-dysentericus* A	0	±	—	A	0 or As	A	A	—	A or Alk	
11	*B. meta-dysentericus* B	0	+	—	0 or Avs	0 or Avs	0 or Avs	A	—	A, Alk	
12	*B. meta-dysentericus* C	0	0	—	do	do	do	As	—	A, Alk, D	
13	Pneumococcus	..	..	..	A	0	0	A	0	AC or As	
14	Staphylococcus	..	..	..	A	0	0	A	A	0	
15	Streptococcus	..	..	..	A	0	0	A	A	As	
16	Yeasts	..	..	..	A	0	0	A	—	AC	
17	Chromogenic B	..	..	..	A	0	0	As	A	0	

As = acid slightly.
Avs = acid very slightly.

— = negative result.
\+ = positive result.

± = { sometimes positive. sometimes negative.

Procedure. Inoculate the special peptone medium, and incubate at 37°C. for 48 hours. Then add 5 drops of the methyl red indicator solution. A distinctly red colour is to be regarded as a positive result ; a distinct yellow colour as a definitely negative result ; intermediate colours as an indeterminate result.

Voges-Proskauer Reaction. This is positive with organisms of the *B. cloacæ* type, and negative with those of the *B. coli* type. It depends on the formation of acetyl-methyl-carbinol in the presence of glucose.

The procedure is as follows :—Inoculate a 2 per cent glucose peptone tube with the organism to be tested, and incubate for 3 days. Add 2 to 3 c.c. of strong caustic potash solution and allow the tube to stand for 24 hours at room temperature. If positive a fluorescent orange colour, resembling weak eosin, results.

The Lactose and Late-Lactose Fermenters.

The importance of these organisms has already been discussed. Table VI gives the chief points in the identification of the various strains.

The Toxins and Immunity Reactions of the Dysentery Bacilli.

That the *Bacillus dysenteriæ* is the cause of bacillary dysentery was first proved by Strong and Musgrave (1900). These workers administered a 48 hours old culture of *B. dysenteriæ* by the mouth to a condemned criminal. A typical attack of bacillary dysentery followed, and dysentery bacilli were recovered from the stools. The patient then recovered from the attack. Since then there have been several instances of accidental infection of man from cultures in the laboratory.

The animals most susceptible to inoculation with the *B. dysenteriæ* are rabbits, dogs and young guinea-pigs. Intraperitoneal inoculation is followed by suppurative peritonitis, which proves fatal. The intestine may show acute hyperæmia, but death usually ensues before there has been time for symptoms of dysentery to develop. Intravenous inoculation is followed by a septicæmia with symptoms of paralysis, and death occurs very rapidly. After subcutaneous inoculation of a 24 hours old culture, there is intense local inflammation at the site of injection, and fever. A day or so later acute diarrhœa sets in, the stools containing much mucus and sometimes blood. Paralysis of the hind extremities next sets in and may become generalized. The temperature falls steadily and the animal dies about the fourth or fifth day after inoculation.

The bacillus of Shiga is, as a rule, a very toxic organism, producing very powerful toxins, which give rise to the severest types of dysentery with fever. The toxins produced by this organism are threefold in nature. They are :—

(1) An exotoxin, which is dialysable and free from the bodies of the bacilli. It can be separated from the bacilli by filtration and is a protein in nature. Against this exotoxin an antitoxic serum can be prepared which will neutralize the toxin *in vitro* as well as in the patient's system.

(2) An endotoxin, which is contained within the bodies of the bacteria, is non-filtrable and non-dialysable. An anti-bacterial serum can be prepared by

injecting killed cultures of the bacteria intravenously into rabbits. A first injection of 0·5 c.c. is given, followed five days later by a dose of 1·0 c.c. The rabbit is bled about the twelfth day after the second injection, when its serum is usually found to possess very powerful agglutinins and gives a very high end point.

(3) Pressor bases, which are extremely toxic, are dialysable and diffusible, and not easily destroyed by heat. Acton, Chopra and Boyd (1923) have shown that these pressor bases are formed from the amino-acids of the protein molecules in the gut and can be isolated in the argenin fraction. They are therefore not identical with histamine, which is found in the histidine fraction. When injected into animals these bases cause all the symptoms of acute dysentery, with collapse, and the passage of blood and mucus. On administration the toxin causes increased peristalsis, dilatation of the vessels in the portal area, and hæmorrhages into the submucosa of the large intestine. It also has a marked action on the uterus, and this accounts for the frequency of miscarriage in the case of pregnant women suffering from dysentery due to the bacillus of Shiga.

From these findings it follows, as detailed in Chapter V, that the essential principles in the treatment of an acute attack of dysentery due to Shiga's bacillus should be: (1) to inject the specific antiserum in order to neutralize the exotoxin; (2) to remove the source of supply of the pressor bases by giving a preliminary purge such as castor oil, and to cut animal proteins out of the diet in order to minimize the supply of such proteins; and (3) to inhibit the multiplication of the Shiga bacilli in the intestine by giving a purely carbohydrate diet, with plenty of glucose by the mouth.

The bacillus of Flexner and the mannite fermenting group are, as a rule, much less toxic than the bacillus of Shiga, and give rise to a much less severe dysentery. The toxins produced by these organisms are twofold in nature, viz. :—

(1) An endotoxin which is not filtrable and not diffusible. A bactericidal serum can be prepared against this toxin by injecting dead emulsions of the bacilli into an animal, such as the rabbit. This bactericidal serum is of no use during the acute attack of dysentery, but it has a high agglutinating power.

(2) During its growth the organism converts the amino-acid tryptophane into indol, but no pressor bases that are active pharmacologically are formed.

(3) Many of the sugars are fermented, with the production of irritating acids.

The rational line of treatment of bacillary dysentery due to the mannite-fermenting group of organisms, therefore, should consist of (1) the elimination of the carbohydrates from the bowel by a preliminary purge; (2) the administration of a purely protein diet, since no poisonous pressor bases are formed. These patients show a marked intolerance to carbohydrates.

The Serological Diagnosis of Bacillary Dysentery.

There has been considerable difference of opinion as to the value of serological methods in the diagnosis of bacillary dysentery, i.e., the method of testing the agglutinating powers of the patient's serum against known strains of the *B. dysenteriæ*. A freshly prepared emulsion of *B. dysenteriæ* is extremely sensitive to agglutination, and fallacious results may be due to this. The macroscopic method of carrying out the test alone is suitable. Manson-Bahr, Perry and Manson emphasize the special value of Dreyer's technique for this test, and claim that the use of the standard formalinised emulsions eliminates any ultra-sensitive strains. Using this method, they claim that a positive agglutination at a dilution of 1 : 25 is diagnostic of an infection with the bacillus of Shiga, and one at 1 : 50 is diagnostic of infection with the bacillus of Flexner. The agglutination reaction with the patient's serum is far more constant and reliable in the case of infections with Shiga's bacillus than in the case of infections with the mannite-fermenting group.

The agglutinins generally first appear in the serum about the seventh day of the disease, reach their maximum about the twenty-first day, and thereafter rapidly decline. The agglutination test is, therefore, not of much value before about the eleventh day of the disease. On the other hand, by this time it is nearly hopeless to attempt to isolate the dysentery bacilli from the stools by plating ; so that the agglutination test has a definite value in cases seen at a late phase in the disease. Previous inoculation of the patient with a protective vaccine may cause agglutinins to be present in his serum for some months, and in such cases the agglutination test should be repeated at four-day intervals in order to test for a rise in the titre of the agglutinins. Here again Dreyer's technique is of special value in demonstrating the end point of the reaction.

After the subsidence of the disease the agglutinins may continue in the blood for some time. Manson-Bahr, Perry and Manson record positive agglutination as long as $3\frac{1}{2}$ years after convalescence. A previous attack of bacillary dysentery, therefore, may interfere with diagnosis by serological methods.

The limitations of serological diagnosis are therefore obvious, and, in any case, the test is of no value prior to the seventh day of the disease.

Vaccine Therapy in Bacillary Dysentery.

This subject will be referred to again in Chapter VI, but we may here discuss its rationale and its application. Vaccine therapy is useless for acute cases, and should be reserved for chronic infections.

(1) In chronic Shiga bacillus infections and in infections with para-Shiga bacilli in a civilian community, vaccine therapy is extremely useful in bringing about a cure. These infections are only rarely seen in a chronic stage, however.

(2) In chronic infections with the mannite-fermenting group, especially in chronic infections with Flexner's bacillus, and less commonly in chronic infections

with the bacillus of Strong, vaccine therapy usually brings about a cure. In many such cases, however, it is extremely difficult to isolate the primary dysenteric organism and it has often disappeared, and has been replaced by secondary invaders, such as the *B. pyocyaneus*, the *B. meta-dysenteriæ*, etc. In such cases the patient's serum should be tested by the agglutination reaction against whatever secondary invaders are isolated. Should the reaction be sufficiently indicative that the secondary invader is playing a pathogenic rôle, this organism may be added to the vaccine of the primary dysentery bacilli.

Thus, after repeated examinations of the stool, we may fail to find the bacillus of Flexner, whereas the patient's serum gives a positive agglutination to this organism, indicating a previous infection with it. The cultures of the stool, however, yield the *B. meta-dysenteriæ*. In such cases one would use a stock vaccine of Flexner's bacillus to which the autogenous strain of *B. meta-dysenteriæ* is added. In other instances, for example, we may isolate the bacillus of Strong, and in spite of treatment with an autogenous vaccine of this strain diarrhœa may continue; on further plating the *B. pyocyaneus* may be isolated. In this case we add the autogenous strain of *B. pyocyaneus* to the vaccine. In many of these cases of chronic bacillary infection, vaccine therapy with a vaccine of *B. dysenteriæ* causes improvement up to a certain point, and then the condition remains stationary. In such cases every attempt should be made to isolate secondary invading organisms, and to test their pathogenicity by the agglutination reaction against the patient's serum. If these tests fail, it may be advisable to have the entire intestinal tract *x*-rayed after a barium meal in order to see whether some mechanical defect which causes stasis may not be responsible for the condition.

(3) Still more rarely we may have to deal with non-lactose fermenters which produce acid and gas in glucose, such as *B. morgani*, types *i* and *ii*. Again, autogenous vaccine therapy may be indicated.

(4) *The vaccine treatment of sprue.* If the view put forward in Chapter VIII be accepted, that sprue is usually a sequel of a chronic infection with the bacillus of Flexner, or sometimes Strong's bacillus, followed by a secondary invasion of the gut epithelium by a streptococcus of *viridans* type, then treatment by vaccines must depend on the phase of the disease present.

In the early phase, if Flexner's bacillus or Strong's bacillus be isolated, an autogenous vaccine should be prepared from this source. If streptococci, and especially streptococci of hæmolytic type be isolated, either from the stools or from the lesions on the tongue, the vaccine should be prepared from this source. Finally, in the late stage, where Endomyces or Parasaccharomyces infection has set in in the gut, an autolysed vaccine of these fungi may occasionally give brilliant results. In the final phases of the disease, however, where there is extensive atrophy of the intestinal epithelium, vaccine therapy is useless.

Preparation of Vaccine and Dosage.

For details of the method of vaccine preparation we must refer the reader to the standard text-books on bacteriology. Here we can deal only with certain points in connection with this matter.

Most workers consider that vaccines of Shiga's bacillus are too toxic for use in man. In consequence of this there have been many attempts to produce modified Shiga bacillus vaccines; thus Shiga himself originally proposed simultaneous injection with a vaccine and with anti-dysentery serum. Graeme Gibson (1917) produced a sero-vaccine during the War. Besredka used a fully sensitized vaccine, whilst Olitsky and others have employed lipovaccines. Fortunately the cases in which a vaccine of Shiga's bacillus is called for are relatively rare, being confined to the few chronic carriers of this organism or the few cases of chronic infection with it. In our experience simple carbolised vaccines of Shiga's bacillus, prepared from agar cultures, are safe to use *provided the dosage given is not too high*. The initial dose should not exceed 5 million organisms, and the dosage should be gradually raised to 10 or 15 million.

Having obtained a pure culture of the *B. dysenteriæ*, an agar slope is inoculated and incubated at 37°C. for 24 hours. 10 c.c. of 0·5 per cent carbolised saline is now added to it, and with a sterile platinum loop the surface growth is gently rubbed off the agar and thoroughly emulsified in the carbolised saline. The emulsion is then pipetted off into a fresh sterile test-tube, which is plugged with flamed cotton-wool.

We have next to standardise this emulsion. There are several different methods for doing this, of which we may mention the following:—

(1) *Standardisation by area of surface* of the medium. With a steel rule carefully measure the length and breadth of the growth on the surface of the agar before preparing the emulsion. This gives the square surface area of the growth. Suppose, for example, that it is 6 cms. by 1·5 cms. This gives 9 square cms. of growth. Add to this 9 c.c. of 0·5 per cent carbolised saline and emulsify. With rapidly growing organisms, such as the typhoid and dysentery bacilli, then 1 c.c. of this emulsion has a strength of approximately 4,000 million organisms. For more slowly growing organisms, such as streptococci, the strength of the emulsion is approximately 1 c.c. = 2,000 million organisms. The emulsion should then be diluted to a strength of 1 c.c. = 100 million organisms.

(2) *Brown's opacity method.* [Brown and Kirwan (1915), Brown (1919).] In this method a 1 per cent emulsion of well washed and roasted barium sulphate is prepared in 1 per cent aqueous sodium citrate solution. This is diluted into a series of dilutions from 1 : 8, 1 : 9, etc., to 1 : 16 of the original emulsion. Each dilution is then put up in a small miniature test-tube, and the end sealed off. The tubes are then placed in a rack; the tubes and standard table can be obtained in India from the Director of the Central Research Institute, Kasauli. They are

also stocked by Baird and Tatlock (*Biological Apparatus Catalogue*, 1927, item No. B. 3637) at £1-1-0 the set.

The bacterial emulsion having been prepared, it is diluted, placed in a miniature test-tube similar to those containing the barium sulphate emulsion and matched with one or other of the standard tubes. In doing this the tube containing the bacterial emulsion and the different barium solution tubes are placed side by side on a page of printed matter in a good light. Matching occurs when the print is equally dimmed in both tubes. The strength of this emulsion is then read off in the table provided, and the bacterial emulsion diluted down to the required strength.

Brown's opacity method is perhaps the quickest reliable method of standardisation of bacterial vaccines, and the laboratory worker who has much vaccine preparation to do would do well to equip himself with the apparatus.

(3) *Standardisation by the hæmocytometer.* This method is the most accurate of all. The bacterial emulsion is diluted to a known dilution in 0·5 per cent carbolised saline, and a trace of carbol fuchsin added to a portion of it in a watch-glass. The emulsion is then well mixed in the watch-glass and the chamber of a hæmocytometer with a shallow cell 0·02 mm. in depth is filled, and the special cover-glass applied. Ten minutes or so is allowed for the bacteria to sediment to the bottom of the chamber. The number of bacteria in 100 small squares is then counted, using the $\frac{1}{6}$th inch objective and a high eyepiece. From the count so obtained the actual strength of the emulsion is determined, and the necessary dilutions made. If great accuracy is required two or three drops may be counted and an average struck.

(4) *Standardisation against a red blood corpuscle count.* This method is not as accurate as the direct count in the hæmocytometer. The laboratory worker first carries out a count of his red blood corpuscles in the Thoma-Zeiss hæmocytometer in the usual way. Taking a sterile capillary pipette, equal volumes of the bacterial emulsion and the laboratory worker's blood from the pricked finger are mixed in it, and the mixture spread in thin films on slides. These are allowed to dry, and are then fixed with alcohol, and stained—preferably by carbol fuchsin. Using a square Ehrlich's ocular eyepiece the number of red corpuscles and of bacteria in 100 fields is counted. As the red cell count is known by the preliminary count, it is then possible to ascertain the strength of the bacillary emulsion.

This method is a laborious one, but involves no special apparatus. The square Ehrlich ocular is advisable, but not essential.

With regard to streptococcal vaccines, Harvey (1921) states that vaccines prepared from agar cultures have much less antigenic value than those prepared from broth cultures. He advocates culturing the streptococcus in trypsin broth free from glucose, and killing by adding 1 per cent carbolic acid, using no heat at all. Such a vaccine will have to be standardised by method (3) or (4) above, since Brown's

opacity method is only applicable to emulsions from growths on agar slopes. On the other hand, we have always employed vaccines prepared from agar slopes.

The carbolised bacillary emulsion having been standardised, it is next diluted with 0·5 per cent carbolised saline to a strength of 1 c.c. = 100 million, and incubated at 37°C. for 24 hours. The next day three tests should always be applied to each brew of vaccine made, viz. :—

(*a*) An aërobic culture is taken on agar to ensure that the organisms in the vaccine have been killed.

(*b*) An anaërobic culture should be taken on agar to ensure that the emulsion has not become contaminated with anaërobic organisms, such as the *B. tetani*.

(*c*) A full dose of 1 c.c. should be inoculated hypodermically into a guinea-pig or other susceptible animal. This animal is then kept under observation for three or four days. If no toxic symptoms manifest themselves the vaccine will presumably not cause too toxic symptoms in man.

In the meantime the vaccine is filled into an amber-coloured vaccine bottle and sealed with a sterilized rubber cap. When the cap has been applied, the whole is sealed by tying the cap in place with sterilized thread, inverting it into a bath of molten paraffin wax, and stored in a dark and cool place until wanted for use.

Dosage. It is impossible to lay down any hard and fast rule for dosage with regard to vaccines of the dysentery bacilli. The only safe working rule is to 'go slow'. Reactions may be of two types : either fever and malaise, with headache, or a sharp attack of diarrhœa. If either of these occurs, the next dose given should be the same or a little less than the dose with which reaction occurred. It is to be noted that light-haired persons usually react more severely to vaccines in general than do dark-haired persons.

With regard to vaccines of Shiga's bacillus, the first dose should not exceed 5 million organisms. If there is no marked reaction the second dose may be 10 millions, and the dosage may be increased to 15 millions as a maximum. With vaccines of Flexner's bacillus the initial dose may be 10 million, followed in turn—if no marked reaction takes place—by 20 million, 40, 50, 50, 75, and finally 100 million, the maximal dose for this vaccine. Streptococcal vaccines may be given in the same dosage as for vaccines of Flexner's bacillus.

The following instructions for the use of autogenous vaccines are taken from the senior author's laboratory :—

The dose should be modified according to the nature of the reaction obtained. Doses must be small in cases of children and aged persons. The maximum dose for an old person is 0·5 c.c.

Injections are to be given twice a week intracutaneously (not subcutaneously), and once a week when the maximum dose is reached.

About eight injections will probably be needed. It is needless to say that local and general treatment should be carried out along with the injections.

The cap of the vaccine bottle should be sterilized with tincture of iodine before puncturing with the hypodermic needle, and the puncture point should be sealed with a heated rod after each use.

The vaccine must be kept in a dark and cool place, and should be thoroughly shaken before use. Sediments in the vaccine should not be mistaken for contamination.

The prophylactic use of vaccines against bacillary dysentery is discussed in Chapter IX.

CHAPTER V.

The Treatment of Acute Dysentery.

THE treatment of an acute or subacute attack of dysentery consists of two main principles :—

(*a*) knowing what to do for your patient, and

(*b*) knowing when to do it.

The very first essential is an accurate diagnosis. As has been shown previously, it is usually possible by clinical examination of the patient and by microscopical examination of the stools—supplemented, if necessary, by the use of the sigmoidoscope—to give an immediate diagnosis of either amœbic dysentery, balantidial dysentery or 'probably bacillary dysentery'. This is sufficient to go on with.

Acute Bacillary Dysentery.

Here we have to recognise that there are two main types of the disease :

(*a*) Bacillary dysentery due to non-mannite-fermenting bacilli of the Shiga-Kruse type. In these cases collapse may be present, and pyrexia is usually marked. The stools are very frequent, 16 or more a day, but may vary from none at all in the acute gangrenous type with paralysis of the gut to the incessant passage of stools resembling rice water, but containing flakes of blood-stained mucus. The Shiga bacillus produces both an intracellular and an extracellular toxin, and also produces poisonous pressor bases from animal proteins.

(*b*) Bacillary dysentery due to mannite-fermenting bacilli of the Flexner-Strong type. In these cases collapse does not occur as a rule, pyrexia is less marked, and the stools are usually less than 16 a day. The blood and mucus in the stool may not be visible to the naked eye, and many cases present the symptoms of a mucous diarrhœa, the stools being fæcal coloured or pale. The so-called 'hill diarrhœa' is usually due to infection with the bacillus of Flexner. The Flexner bacillus produces an intracellular, but no extracellular toxin. It produces indol and similar compounds from animal proteins and ferments carbohydrates, with the exception of lactose.

Both groups are facultative anaërobes, and hence come to infect the large intestine, in contrast to the cholera vibrio, which is a strict aërobe and hence comes to infect the small intestine. Both groups can exist at a wide pH range of

from 5·4 to 9·1, so the administration of alkalies is of little use in bacillary dysentery. The production of toxin by the bacillus of Shiga takes place best at a pH of 7·5. The growth of Shiga's bacillus is inhibited by sugars, such as glucose.

Secondly, it is essential for the medical practitioner to visualise the pathological lesions present in the gut. In infections with Flexner-Strong bacilli the lesions are as a rule superficial only in character, consisting chiefly of exfoliations and erosions of the mucous membrane with the bacilli situated chiefly in the follicles of Lieberkühn. In infections with the Shiga-Kruse group there is much more extensive infection of the solitary follicles, with deeper ulceration, and here the importance of rest is very great. In both groups the ulceration may be kept up by invasion with secondary organisms, such as streptococci or Vincent's infection with the fusiform bacillus and Vincent's spirochæte, even after the dysentery bacilli have disappeared from the gut. Further, as some 15 per cent of humanity in the tropics is parasitised with *Entamœba histolytica*, a proportion of some 15 per cent or more of all cases will be mixed infections.

Armed with this knowledge we shall know what treatment to adopt and when to adopt it.

General Lines of Treatment. The first and most important principle in treatment is to place the patient at absolute rest in bed. The ulcers in the gut will take ten days or so to heal, and no medical practitioner would allow a patient with a severe ulcer of the foot to walk about. Because the patient cannot feel pain in his intestinal ulcers is no reason for allowing him to walk about. He must be put to bed and kept there, no matter what are his wishes or protests. Further, he must not be allowed to get up to go to the latrine, but be made to use the bed-pan. If the patient is not kept in bed the bacillary dysentery frequently becomes chronic in type, and this is especially the case with mild infections due to the bacillus of Flexner, where the patient only has a mucoid diarrhœa for a few days and neglects proper treatment of the condition.

Warmth is of importance in the treatment of bacillary dysentery, especially so where there is a tendency to collapse, and a hot-water bottle applied to the abdomen is often very helpful. The stools must be inspected daily, as their character and number and the state of the tongue are the best guides to prognosis.

With regard to *diet*, all solids must be withheld. In infections with Shiga's bacillus--which will have to be diagnosed tentatively, pending the isolation of the bacillus in the laboratory—all animal proteins should be eliminated from the diet, as this measure will materially help in reducing the toxæmia. The diet should consist solely of carbohydrates, such as arrowroot, barley-water, glucose feeds, tea or coffee—with very little or no milk. These cases do not tolerate milk well as a rule, but when the temperature has come down to normal and the stools are improving, milk and finally proteins may be gradually added to the diet. In Flexner bacillus

infections, on the other hand, carbohydrates should be eliminated from the diet, and such articles as meat-extracts, chicken broth, citrated milk, jellies, weak beef tea, and later eggs, should be given. During convalescence fish and meat may be gradually added to the diet, but carbohydrates should be added last of all. Many of these patients show intolerance to carbohydrates for a long time. In both groups of cases the food should be given slightly warmed, as cold drinks are apt to increase intestinal peristalsis, and in small quantities at a time. Dysentery patients should not be rushed through convalescence, for the ulcers take time to heal, and any indiscretion in diet is very apt to be followed by a relapse.

In very severe and fulminant cases, the incessant use of the bed-pan exhausts the patient's strength, and a better plan is to put a waterproof sheet which can be changed every few hours under the patient, and to pack the buttocks with tow or cotton-wool. It must always be remembered by the attendant that the stools are highly infectious, and it is as well if the nurse wears rubber gloves when washing the patient or changing his bedding.

Specific Treatment.

Antiserum. 'Polyvalent' antisera against strains of Shiga-Kruse type are manufactured by the Lister Institute, Burroughs, Wellcome and Co., Parke, Davis and Co., Mulford and Co. (Philadelphia), the Berne Institute, and by Professor Shiga in Japan. Opinion is nearly unanimous that their administration is of very great value in dysentery due to Shiga's bacillus. (They are of no value in Flexner infections, as the toxin of the Flexner bacillus is an intracellular one.) It has long been a matter of surprise to us that no standardised antidysentery serum is manufactured in India. Shiga bacillus infections are so common in India that the need for a supply of fresh standardised serum seems very great.

The serum should be administered within the first 48 hours of the disease, if it is to be of any use, and its use is valueless after 48 hours from the onset of symptoms. It should be given intravenously and in large doses, e.g., 60 to 80 c.c. for an adult. If there is any reason to suspect that the patient has previously received an injection of serum,—e.g., against tetanus or diphtheria,—a de-sensitizing dose of $\frac{1}{2}$ to 2 c.c. of the serum may be given subcutaneously 12 hours before the larger intravenous dose; or one may start the intravenous injection with 5 c.c. of the serum well diluted with saline, and if no reaction occurs, continue to inject the full dose.

Fletcher and Jepps (1924) record very disappointing results with antidysentery serum, but they seem to have used it indiscriminately on cases due to both types of bacilli. They record that serum was given to 246 consecutive cases (*B. dysenteriæ*, Flexner, 226; *B. dysenteriæ*, Shiga, 20), with 74 deaths—case mortality 30·1 per cent. In the control group of 329 patients (*B. dysenteriæ*, Flexner, 318; *B. dysenteriæ*, Shiga, 11), where no serum was given, 100 died—case mortality 30·4 per cent. 'Even when the serum was administered at the beginning of an

attack it was almost always useless, and it effected no real reduction in the mortality,' they write. They then proceed to discuss the reasons for this disappointing result. The doses given were large—as a rule about 60 c.c.—and the serum was sent out from the Lister Institute in cold storage. It showed a full agglutination titre against Flexner's bacillus but rapidly lost its agglutinating properties against Shiga's bacillus. They conclude that the reason for the failure of the serum lay not in the serum itself, but in the fact that malaria and other concurrent diseases had reduced the condition of their patients to such a state of weakness and exhaustion that they were beyond the possibility of recovery. The serum used in one year cost £305, and 'if it had been possible to apply this sum of £305 to the prevention of the destitution, which is so often the precursor of fatal dysentery, many of those who died might have been alive to-day.'

On the other hand, it is obvious from Fletcher and Jepps' figures that the greater majority of the patients in whom the serum was used were cases of infection with the bacillus of Flexner, and in such cases the serum cannot have much value. A serum prepared by immunising horses with the bacillus of Flexner has a bactericidal action on the bacillus but no antitoxic action, as the bacillus does not produce extracellular toxins. On storage the serum rapidly loses its normal complement, and when injected into the human subject there will be but little combining reaction between the bactericidal substance in the horse-serum and human complement. It is especially in severe cases of Shiga bacillus infection, seen within the first 48 hours of the disease, that the serum is of value, and general opinion is that its value in such cases is very great. But—in view of Fletcher and Jepps' findings that even serum sent out to the tropics in cold storage rapidly loses its potency in transit and storage—it seems very advisable that the specific serum should be manufactured in India.

Bacteriophage.

What appears to be a very promising line of treatment in bacillary dysentery is the use of bacteriophage. Everything here, however, appears to depend on the selection of the right strain of bacteriophage. Through the kindness of Professor d'Herelle we have been able to try the bacteriophage treatment on 15 cases of Flexner bacillus infection. The dose usually given is 1 to 2 c.c. of the bacteriophage daily by the mouth. Some of the cases appeared to do very well on this line of treatment; in others administration of bacteriophage did not appear to assist in the patient's recovery. Fletcher (1927) records disappointing results after the use of bacteriophage in Flexner infections. He tried the treatment on 22 patients, making daily bacteriological observations on the stools. Dysentery bacilli persisted in the stools of 6 patients for more than 10 days after the commencement of treatment; in 11 cases bacilli were found up to the 6th day, but not on the 8th day. In 5 cases dysentery bacilli were not found after the 4th day. Three of

the patients died, and dysentery bacilli were isolated from the colon of all three at post-mortem examination. He records that experimentally it was found that the bacteriophage used was more active against Shiga's bacillus than against Flexner's bacillus. It was tried in one case of dysentery due to Shiga's bacillus, and here no dysentery bacilli could be isolated from the stools after the 2nd day of treatment.

Fletcher's results seem to indicate the necessity for a most careful selection of the strain of bacteriophage used ; when tested *in vitro* it should show strong potency against the specific strain of dysentery bacillus concerned. Malone and Bird (1927) record the use of bacteriophage in three cases of Flexner infection of rather severe subacute type at Kasauli. In two of these, dysentery bacilli disappeared from the stools on the 3rd day ; in the third case the stool was not examined on the 3rd day, but gave negative results on the 4th day.

Further observations on the use of bacteriophage in bacillary dysentery are badly wanted, for this line of treatment, if successful, would be an ideal one ; it would enable one to deal with the chronic bacillary carrier, also perhaps even to disinfect infected water-supplies by inoculating them with bacteriophage.

Medicinal Treatment.

If the patient is seen during the earlier phases of the disease it is advisable to administer castor oil to which a little tincture of opium has been added. This has the effect of clearing out the contents of the small intestine, which may be loaded with proteins and carbohydrates—the result of pancreatic digestion. This dose is best given the last thing at night, in order that the saline aperient treatment may be begun the next morning. Or it may be administered at once, if the patient is seen in the early stages of the disease.

As soon as the castor oil has acted, and preferably from the early morning, treatment with saline purgatives is commenced. There is no other line of medicinal treatment of bacillary dysentery so satisfactory and so simple as the use of magnesium sulphate or sodium sulphate in 1 drachm doses every four hours. The aperient sulphates act mechanically, flushing the toxins out of the gut, altering the pH of its contents to a more alkaline condition, and hence checking the production and absorption of toxins. The sodium salt is probably less irritant than the magnesium salt, and the following prescription for its administration is given by Manson-Bahr : –

℞	Sodii sulphatis	1 drm.
	Acid sulphurici dil.	m xv.
	Tinctura zingiberis	m v.
	Aquam Menth. Pip.	½ oz.

this dose to be administered every four hours until the stools become fæculent. After this the same dose may be given at six hour intervals, and later three times in the day.

The routine use of opium in the treatment of dysentery is to be most strongly condemned. In many cases, however, where the patient is worn out with the constant tenesmus and pain and cannot obtain sleep, $\frac{1}{4}$ grain of morphia may be given hypodermically at night. The resulting rest and sleep will materially help in his fight against the disease. A good working rule is that if the patient has had no sleep for two nights, and the temperature is falling, to give $\frac{1}{4}$ gr. of morphia with $\frac{1}{100}$ gr. of atropine sulphate.

A few patients tolerate saline aperients badly, and in such cases it may be necessary to resort to small divided and repeated doses of calomel, such as $\frac{1}{4}$ gr. of calomel with 5 grs. of sodium bicarbonate every 2 or 4 hours.

Of other drugs, the use of bismuth is often very valuable in severe cases. The carbonate is probably a better preparation to use than the subnitrate, as the latter is apt to contain impurities; a dose of 1 or 2 drachms may be given suspended in half a tumblerful of water or soda-water every 4 to 6 hours until the stools become black and the prognosis is a reassuring one; the dosage should then be reduced. Kaolin is often very useful in bacillary dysentery, and a preparation which we have found to be particularly useful is Morson's 'Osmo-kaolin.'* This is an electrically precipitated kaolin of very great purity and so fine that it is practically impalpable to the touch. It is perfectly harmless and may be given in large doses in the same way as the bismuth carbonate. It probably provides a protective coating to the inflamed mucosa, and certainly often gives the patient considerable comfort, lessening the frequency of the stools and reducing the abdominal pain and griping. Bolus alba and animal charcoal also have their advocates.

Of other drugs, the so-called intestinal antiseptics do not appear to be of much use in the treatment of the acute phase, though they may perhaps have their place in after-treatment; the mechanical removal of the dysentery bacilli from the surface of the mucosa seems to be a more practicable measure than the almost impossible attempt to kill them *in situ*. Salol in doses of 5 to 15 gr. may be given in cachets or suspension, but we have not found it of much value. Manson-Bahr speaks well of the use of cyllin in cachets, each containing 2 minims; of these 20 or more cachets may be given a day. Yatren is a drug which has some supporters; it is stated to consist of iodo-oxy-quinolin-sulphnic acid, according to the manufacturers, and is stated to contain 36·2 per cent of iodine. The manufacturers advocate very big doses of this compound, but any dose of more than 15 grains a day appears to be distinctly irritant to the gut.

Irrigation of the colon is of distinct value in very severe cases, and in one very severe case seen, where the patient had been drenched with emetine and his condition became critical, with the incessant passage of large sloughs and much blood in very offensive stools, it appeared as if repeated large warm irrigations with very dilute

---

* Crookes' 'Collosol' Kaolin is also a very useful preparation.

permanganate solution was the measure which saved life. The simpler the irrigating fluid the better, as its effect is mechanical rather than antiseptic; warm saline or boracic solution, 1 drachm to the pint, is perhaps best. The douche should be given slowly with a stout rubber tube, at a temperature of 104°F. Anal irritation is apt to prove very distressing in children, and in such patients the parts should be thoroughly cleaned and lanoline or vaseline applied.

Treatment of Special Symptoms and Cases.

Collapse is easier to guard against than to overcome when it is once established. Stimulants should be given, such as half an ounce of brandy by the mouth or by rectal enema. Intravenous saline should be administered in generous quantities, 2 to 3 pints or more, and antidysenteric serum, 20 c.c. or more, brandy 1 drachm, and atropine sulphate gr. $\frac{1}{100}$th may be added to the injection. In the choleraic cases Rogers' hypertonic saline method should be adopted. The solution consists of sodium chloride 120 gr., calcium chloride 4 gr., potassium chloride 6 gr., and sterilized water to the pint. Glucose 35 gr. may be added to this solution. The solution should be given very slowly at a temperature of 104°F., about 4 oz. being run in intravenously per minute. Vomiting and hiccough are serious symptoms; and if they set in hot stupes should be applied to the abdomen and the patient be given ice to suck. Arrowroot and brandy, 2 drachms, may be given by the mouth. A small dose of adrenalin—such as 3 minims—may be tried by the mouth and sometimes allays severe hiccough.

Children require special consideration, as the disease in them is often associated with fairly high pyrexia. A small preliminary dose of castor oil should be given, followed by the aperient salines. For a child under 5 years of age sodium sulphate may be given in doses of 15 grains t.d.s. The dosage of antiserum given should also be less, 20 c.c. or so, and it may have to be administered intraperitoneally or intramuscularly if a suitable vein cannot be found. Bacillary dysentery occurring in pregnant women is especially liable to lead to abortion, and in such patients the dose of aperient sulphates should be reduced.

After-Treatment.

The majority of cases of bacillary dysentery do very well as a rule with rest in bed, judicious dieting, and the use of aperient salines for three or four days. As soon as the stools become fæcal the administration of salines should be stopped, and one may now give bismuth salicylate gr. 10 with pulv. ipecac. co. gr. 5 at 4 or 6 hourly intervals. The chief trouble with the patient who is convalescent after bacillary dysentery, as a rule, is constipation. The best aperient for such patients is probably liquid paraffin, as it is entirely non-irritant, and a dose of it may be required every evening. The patient should be told to guard most carefully against

constipation for at least three weeks after his recovery in order that the ulcerated gut may heal firmly.

Bael sherbet is a useful addition to the dietary at this stage, and acts as a demulcent. A single large bael fruit (*Ægle marmelos*) will make two good glasses of bael sherbet. The pulp of the fruit is scraped out of its shell and emulsified in water. This should then be strained through muslin to remove seeds and mucilage, and then sweetened and flavoured to the taste. Or the pulp may be mixed with sugar and cream, or with *dahi* (Indian curdled milk), and eaten raw in small quantities at a time. Another good demulcent during convalescence is ispaghul. This is the gelatinous exudate from the seeds of *Plantago ovata*. About half to one drachm of the seeds are either chewed, when a gelatinous exudate comes out which acts as a demulcent, or the pericarp is made into a paste.

A week to ten days after the injection of the antidysenteric serum, serum sickness may set in, with pain and inflammation at the site of injection if this has been given intramuscularly, rigor, headache, diarrhœa, a blotchy urticaria which may be localized or generalized, hyperæsthesia of the muscles, joint pains and even joint effusions. The fever will have to be treated on symptomatic lines, and an alkaline lotion given to allay the urticaria.

Complications.

But little need be said of the complications of acute bacillary dysentery. The commonest probably is arthritis, with effusion—usually of a serous character—into the joints. This is due to the action of the toxins on the synovial membrane of the joint, and the commonest site is usually the knee, though in one patient seen almost all the interphalangeal joints of both hands were affected. As a rule the serous exudate is bacteriologically sterile, although Elworthy records an instance in which Shiga's bacillus was isolated from the fluid. At first the affected limb may have to be splinted and a Scott's dressing applied. Later, hot air treatment and massage may be required. The fluid is usually not sufficient in amount to call for aspiration. Iridocyclitis is a second complication, and both this and arthritis have been experimentally produced in rabbits by intravenous injection of toxins filtered from a culture of the bacillus of Shiga. Iridocyclitis is best treated by the instillation of atropine and the use of an eye-shade. Parotitis is an occasional complication, due to absorption of septic matter from the mouth, and may require treatment with fomentations and cleansing of the mouth. A very rare complication, but one which the medical practitioner should always bear in mind, is invasion of the blood-stream either by streptococci or the *Bacillus coli communis* through the ulcerated gut; but this is a far commoner complication of amœbic than of bacillary dysentery. These complications in bacillary dysentery are usually confined to cases of Shiga bacillus infection and are uncommon, though Manson-Bahr (1925) records

a series of cases in which arthritis occurred as a complication in 27 per cent of the cases.

Acute and Subacute Amœbic Dysentery. Treatment.

The medical practitioner who is called upon to treat a case of acute or subacute amœbic dysentery to-day is in a most unfortunate position, for the number of supposed 'cures' is legion, and is being added to daily. By every mail there descends upon his office table a flood of literature on such drugs as yatren, dimol, stovarsol and a host of others. If the claims made for some of these 'specifics' could be substantiated, we wonder why amœbic dysentery should continue to afflict mankind. We have tried all—or nearly all—of these specifics during the past few years and will discuss their value later. In the meantime we may here state that we have found nothing as yet that will replace emetine in the treatment of amœbic dysentery, and it still remains our sheet-anchor in the treatment of this condition.

The mode of action of emetine on *Entamœba histolytica* still remains somewhat of a mystery. Vedder in 1912 was the first person to show that the action of ipecacuanha in amœbic dysentery depended on its alkaloid, emetine. It is rather amusing to both authors of this book to reflect that when we first came out to India (1908) the then latest mode of treatment of amœbic dysentery was by the oral administration of 'ipecac. sine emetine.' Sir Leonard Rogers (1913) was the first person to take up Vedder's suggestion, and to introduce the alkaloid for the routine treatment of amœbic dysentery. Both these workers considered that emetine had a direct parasiticidal effect on the amœbæ. Wenyon (1926, p. 255), however, points out that active *E. histolytica* either in fæces or in liver abscess pus, can be mixed with relatively strong solutions of emetine, and that the amœbæ will remain as perfectly active as those in control preparations. 'Unless it is assumed that the medium in which the amœbæ happen to be—namely, the fæcal matter or the pus—absorbs or fixes the emetine, so that it never actually comes in contact with the amœbæ, it must be concluded that the alkaloid has no immediate toxic action on the amœbæ. That such an explanation of the failure of emetine to kill amœbæ in these experiments may have something in its favour is borne out by certain tests made by Pyman and Wenyon (1917) on cultures of free-living amœbæ on agar plates. The agar was made up with varying strengths of emetine, and it was found that the amœbæ did not grow on the medium which contained the salts which are known to be specifics for amœbic dysentery, though the bacterial growth upon which the amœbæ feed was little altered in character. Furthermore, it has been shown by Brown (1922) that if the emetine solution which is to be introduced into the agar is first mixed with pus for a few minutes, the liquid portion separated by centrifugation has lost its power of arresting growth of amœbæ on the plate. It would seem that in this experiment the dead cells and debris in the pus had

adsorbed the emetine from the solution, so that there may be some reason for suspecting that when material such as fæces or pus containing *E. histolytica* is mixed with solutions of emetine, the failure of the drug to kill the amœbæ may be due, in part at least, to its absorption by the dead material. It has also to be remembered that even if emetine has no direct action on *E. histolytica* exposed to it for a comparatively short time, it may still have such an action over a longer period in preventing growth and multiplication. It should be possible to test this point on cultures of *E. histolytica*.'

Dale and Dobell (1917) investigated the action of emetine on experimentally infected cats, and—at that period—came to the conclusion that its action on the amœbæ was an indirect and not a direct one. Its primary action was apparently on the host, in some way rendering his tissues unsuitable for the amœbæ. Mayer (1919) came to a similar conclusion, but Sellards and de Leiva (1923) have shown that amœbic dysentery is so very severe a disease in kittens that results in the kitten can hardly be compared with those in man. By administering solutions *per rectum* they showed that infected kittens could be saved at a dosage of 10 milligrammes per kilogram weight. They conclude that emetine has a weak amœbicidal action, and that this, plus the powers of resistance of the patient, afford the explanation of the success of emetine therapy in acute amœbic dysentery.

Allen (1922) found that the blood and serum of man and cats withdrawn after the administration of therapeutic doses of emetine, or when admixed *in vitro* with emetine, failed to arrest the activity of *E. histolytica*. Knowles (1925, p. 69) has shown that an occasional kitten, even when suffering from very severe amœbic dysentery, can be saved by the administration of emetine intramuscularly at a dosage of 5 mgms. per kilo. of body weight, together with large doses of bismuth carbonate by the mouth.

The latest study of the whole problem is the admirable memoir by Dobell and Laidlaw (1926). These workers tested the action of emetine and of other alkaloids on *Entamœba histolytica* and other entamœbæ in culture. Their conclusions are as follows :—

'1. Emetine and cephaëline have been found to be specific poisons for *Entamœba histolytica* under cultural conditions.

(*a*) For this amœba (in culture) these alkaloids are at least 50 times as poisonous as iso-emetine, psychotrine, methylpsychotrine, demethoxyemetine or noremetine.

(*b*) For this species also emetine has been found to be about 10 times as poisonous as stovarsol, and about 50 times as poisonous as quinine under identical conditions of experiment.

2. *Entamœba coli*, *Entamœba gingivalis*, and *Endolimax nana* have been found comparatively insensitive to the presence of emetine in cultures—*E. coli* being able to withstand a concentration of the alkaloid at least 100 times that which is lethal to *E. histolytica*.

3. The effects of solutions of emetine on *E. histolytica* are peculiar. Very strong concentrations (1 per cent or more) are needed to kill this parasite instantaneously ; but only very weak solutions (1 in 50,000 or less) are necessary to kill it *if allowed to act for a sufficient time.*

4. In view of these findings it is concluded that the curative effects of emetine in human amœbic dysentery are best explained as a result of the direct lethal action of the alkaloid on *E. histolytica.*'

In brief we may conclude that emetine has a weak amœbicidal action on *E. histolytica* and cures amœbic dysentery by direct destruction of the amœbæ. One important point which obviously follows the work of Dobell and Laidlaw is that, in order to eradicate the amœbic infection by treatment, we must aim at maintaining continuously over as long a period as is safe a sufficiently strong concentration to kill the amœbæ.

In all protozoal infections, when we attempt to exterminate the parasites in the tissues of the host, what appears to take place is that the drug overcomes the majority of the parasites ; then the bodily resistance rises and the patient's own natural powers of resistance finally exterminate the residual infection. This is almost certainly the case in kala-azar, where not infrequently a patient at the conclusion of a course of treatment may still show a few leishmania in the film on spleen puncture, and yet remain in perfect health thereafter. The same appears to hold good for malaria and trypanosomiasis and probably holds good for amœbiasis also.

Whilst emetine is a most valuable drug in the treatment of amœbic dysentery, yet its administration must be most carefully controlled. As shown by Chopra and Ghosh (1922), and others, its effects are cumulative ; it increases peristalsis, it is a cardiac and central nervous system depressant, and the maximal course which is permissible for administration to an adult male in relatively fair health should not exceed 12—or at the most 15—grains. It is true that one often comes across patients who have had courses of 18 or 20 grains or even more. In one case seen in Calcutta the unfortunate patient was a clerk who could only afford Rs. 10 a week for treatment ; he had received 23 grains of emetine during the course of 11 weeks, the drug having been administered twice a week. Dysentery was still present, and the stool showed actively motile *E. histolytica.* On the other hand courses such as 20 or more grains have a cumulative effect and have been known to prove fatal, whilst, even if they do not prove fatal, emetine diarrhœa may ensue, the practitioner may consider that this is due to insufficient dosage, and push the emetine administration to dangerous extremes. We know of one instance during the war where a military medical officer was accustomed to give as much as 5 grains of emetine daily hypodermically to all his dysentery cases. If the dysentery cleared up, it was presumed to have been of amœbic origin. If it did not, or if the patient died, a diagnosis of bacillary dysentery was made. How many patients he killed, we do not know ; but one of the saddest of the numerous war cases which

we know of personally is that of a military medical officer whose cardiac mechanism has been permanently damaged by over-dosage with emetine, but who still suffers to-day from periodic relapses of amœbic dysentery, cannot take emetine at all, and has tried a large variety of the new treatments without success.

A Standard Treatment for Acute Amœbic Dysentery.

When given orally, the action of emetine is uncertain, whilst its nauseating properties are most marked. Sellards and de Leiva (1923) strongly advocate the administration of emetine *per rectum*, and record the actual cure of experimentally infected kittens by this method; yet such a method is unsuitable for large scale practice in dispensaries, and it is doubtful whether such injections in man under ordinary circumstances would reach much further than the splenic flexure. What is desirable in actual large scale practice in India is some ready, reliable and efficient mode of administration by the mouth or hypodermically.

During the last few years we have adopted the following as our routine treatment for cases of amœbic dysentery:—

1. The patient is kept strictly in bed for ten days and made to use the bedpan. This is to give the ulcerated surfaces as complete rest as possible.

2. In the early morning a full dose of saline aperient is given to flush out the colon.

3. After this aperient has acted, Deeks' bismuth treatment is instituted (Deeks, 1914). As far as we can make out, when large doses of bismuth salts are administered by the mouth, but little is absorbed into the system. On the other hand such administration tends to convert the acidity of the colon contents in amœbic dysentery to alkalinity, and we have found in experimental cats that the administration of large doses of bismuth salts slightly increases the alkalinity of the portal blood-stream. Accordingly two drachms of bismuth carbonate are given every 4 hours during the day. It is best administered suspended in half a glassful of water or soda-water.

4. Two and a half hours after the first dose of bismuth carbonate for the day, one grain of emetine hydrochloride in solution is given intramuscularly. It is a little difficult to know whether to give these injections subcutaneously, intramuscularly or intravenously. We have tried all three methods, but have found intravenous administration to have no better results than by the other two methods, whilst after intravenous injection of emetine the heart may be subjected to undue strain. De Castro and Deuskar (1927) also record that the results after intravenous administration are not better than after subcutaneous. Subcutaneous injections of emetine are rather apt to be followed by local ecchymoses; these may alarm the patient. Intramuscular injection is painful, but the patient at least cannot see the local capillary hæmorrhage which follows, and the drug is well absorbed by this method. Cawston (1922) recommends dissolving the tablet of emetine in one per

cent carbolic acid, which he states, renders the injection quite painless, yet does not interfere with its efficacy.

5. The timing of this injection is important. The senior author (Acton, 1921) has found that with emetine, as with quinine, the alkaloid exerts its maximal activity when the environment in which it acts is on the alkaline side. Two and a half hours after the administration of large doses of bismuth salts to experimental cats there is a slight rise in the alkalinity of the portal blood-stream. What we wish to attack are not the *E. histolytica* which have come out into the lumen of the colon, and which have ceased to have opportunities for tissue-destruction, but the tissue-invading forms which are causing the ulceration. Hence we desire to throw the emetine into the portal circulation and the colon submucosa, if possible, at the moment when the blood-stream is at its most alkaline tide.

The above treatment is carried out daily for nine consecutive days. The patient is next given a three day interval during which the emetine and bismuth administration is suspended, and only the light early morning saline aperient given. The complete treatment—saline aperient, gr. 1 of emetine intramuscularly daily, and bismuth administration—is then repeated for a further three (or sometimes six) days.

We have now reached the 15th day of treatment, and it is precisely at this stage that the medical practitioner's chief trouble begins. It is next necessary to ascertain by repeated examination of the stools whether the infection with *E. histolytica* has or has not been eradicated. Not less than six—and preferably eight—subsequent examinations of the stool for the cysts of *E. histolytica* should be made. (The technique for this will be dealt with in the section dealing with the *E. histolytica* carrier.) The patient, however, is convinced that he is cured and demands to leave hospital. Even with the most intelligent European patients it is often impossible to secure the necessary stools for examination. It is useless to examine the stools for *E. histolytica* whilst the patient is under emetine treatment, for the parasite is only found very exceptionally under such circumstances. It is for this reason that we have found it almost impossible to follow up patients, and test out the real value of *any* line of treatment in eradicating the infection—apart from the (apparent) clinical cure which this line of treatment invariably brings about.

With regard to the subsidiary points in treatment, *dicting* is not a matter of very great importance. The amœbæ live in the tissues and hence can scarcely be affected by a change of diet. A light mild diet should be given; milk may be given freely, and chicken and fish gradually added to the diet. Such patients are very liable to suffer from abdominal chills, and a warm light blanket should be worn over the abdomen. During the treatment the frequency of the stools gradually passes off: indeed there is hardly any line of treatment in medicine attended with more immediately gratifying results. On the day of admission the patient may

be in a state of real misery ; yet 24 hours later he may be in relative comfort. On the 6th day or so of treatment there may be a slight diarrhœa, due to the emetine administration. With the completion of treatment action of the bowels tends to become irregular, owing to fibrosis of the ulcers and irregular peristalsis. Constipation must be most carefully avoided for at least three weeks after the cessation of treatment, and a dose of liquid paraffin every night may be useful. Abdominal massage may be necessary, especially if there is cæcal stasis.

Stimulants are not necessary, as a rule, in cases of amœbic dysentery, whilst alcohol in any form is very apt to prove irritant to an intestine ulcerated by *E. histolytica.*

Under the above treatment the patient is usually in a condition of clinical cure by the 15th day. But only too often the cure is a clinical cure only and the infection has not been eradicated. In these cases cysts of *E. histolytica* and Charcot-Leyden crystals will be found in the formed stools of the convalescent patient, and hæmolytic streptococci may be isolated on plating the stool on Conradi-Drigalski medium. In this case, one will have to wait for a few days for all emetine to be excreted from the body, and then treat the patient with bismuth-emetine-iodide and possibly an autogenous streptococcal vaccine, as described in the section dealing with the *E. histolytica* carrier.

Drugs other than Emetine.

We have tried a considerable number of drugs other than emetine in subacute amœbic dysentery, but not one of them has given us as satisfactory results as the combined emetine and bismuth treatment outlined above. Here, however, we may briefly deal with such drugs.

Osmo-kaolin is as useful in amœbic dysentery as it is in bacillary dysentery, and it may be substituted for the bismuth carbonate in the above line of treatment. It may be given freely in large doses : 1 or 2 drachms suspended in water every four hours or more often.

Yatren we have found to give rather disappointing results. Any dose of more than 15 grains a day seems to bring on diarrhœa. German and Dutch writers speak very highly of the value of this preparation, but we cannot regard it as a substitute for emetine. Manson-Bahr (1925) speaks well of its use, but more in connection with the cases of chronic amœbiasis than in acute and subacute amœbic dysentery. He advocates a combined oral and rectal treatment. The patient is given 15 grains a day, either in cachets or in tablet form. Each morning the patient's colon is first irrigated with an alkaline enema containing sodium bicarbonate ; after this an enema consisting of 200 c.c. of a 2·5 per cent solution of yatren is run into the colon, and the patient should retain this as long as possible. The drug is taken for ten days continuously by the mouth, and an enema given

each day, beginning at the same time, for fourteen days. If necessary, a second similar course of treatment may have to be given two or three weeks later.

We have known two European patients suffering from relapsing amœbic dysentery to be apparently cured by this line of treatment, as judged by repeated examination of their stools after treatment. On the other hand yatren is expensive—Rs. 2-8-0 for a bottle of 25 of the $7\frac{1}{2}$ grain pills; the combined treatment alone is apparently successful and the drug cannot, in our opinion, replace emetine.

Stovarsol, which is manufactured by May and Baker, London, has a distinct place in the treatment of amœbiasis. It is stated to be acetyl-oxy-amino-phenyl-arsenic acid, and to contain 27·2 per cent of organic arsenic. On the other hand, again, it is expensive—Rs. 3-13-0 for a bottle containing 28 of the 4 grain tablets. We have not found stovarsol to be a substitute for emetine in the treatment of acute and subacute amœbic dysentery, but it is of special value as an *after-treatment.* Indeed in the case of European patients or others who can afford it, it is the junior writer's custom to prescribe a course of stovarsol a few days after the completion of the course of emetine and bismuth, whilst the drug has a definite value in the treatment of chronic amœbiasis. Its real action appears to be a tonic one on the body system, leading to a rapid improvement in the patient's general health—probably due to its high arsenic content. On the other hand, although it is not usual to find cysts of *E. histolytica* in the stools of a patient who is taking stovarsol, once the course of stovarsol is discontinued the cysts only too frequently re-appear. If one can get the patient to carry out one's orders the best plan in convalescence after the emetine and bismuth treatment is to examine six or eight stools after the cessation of the emetine and bismuth treatment; then to prescribe a course of stovarsol for ten days; then to re-commence the examination of the stools. The dose usually prescribed is one of the four grain tablets broken up in half a tumblerful of water taken once a day systematically for ten days. In five instances of relapsing and chronic amœbic dysentery, three of which had proved resistant to previous courses of emetine therapy, this ten day course of stovarsol appeared to eradicate the infection, as judged from repeated examination of the stools after the cessation of all treatment.

To sum up with regard to stovarsol, we are of opinion that the drug has a definite place in the treatment of intestinal amœbiasis, probably owing to its general hæmatinic value; though we regard it as a supplement to, rather than a substitute for emetine.

Kurchi is a drug with a possible future in front of it in the treatment of intestinal amœbiasis, whilst it has long been a favourite prescription in dysentery in the indigenous systems of medicine in India. It is prepared from *Holarrhena antidysenterica,* a small deciduous tree which grows in the Himalayas and throughout the dry forest regions of India. The bazar liquid extract, prepared from the

powdered bark, is quite unstandardised, and hardly suitable for use, though it is well tolerated, and can be given in doses up to 2 or 3 drachms t.d.s.

The active principles of *kurchi* bark are the alkaloids conessine and holarrhenine. The former was found by H. C. Brown (1922) to have as strong an inhibitory action on the growth of free-living amœbæ as that of emetine, whilst it was 50 times less toxic to mice. Chopra, Gupta, David and Ghosh (1927) find that conessine has a specific action on *E. histolytica* obtained from the stools of infected kittens. It kills the amœbæ in mucus flakes in a dilution of 1 : 280,000 in 8 minutes in the presence of an alkali, and in 18 minutes in the absence of alkali, and was more potent than emetine under similar circumstances. Contrary to the observations of Brown, these workers found that conessine salts can be administered subcutaneously without any ill-effects. On the other hand, the drug is not suitable for intravenous injection owing to its markedly depressant action on the auriculo-ventricular bundle, but it has no marked effect on the central nervous system of animals, and when given orally does not inhibit the action of the intestinal ferments. They accordingly suggest the trial of conessine in place of emetine in the treatment of amœbic dysentery. During 1927, Lieut.-Col. Chopra, I.M.S. very kindly placed a purified sample of conessine tartrate at the disposal of the junior author of this volume, who treated six cases of subacute amœbic dysentery with it, using it in 1 grain doses daily hypodermically in place of the emetine in the above standard emetine and bismuth treatment. Clinically it appeared that the conessine took longer than does emetine to get the symptoms under control. All six patients were very fit at the end of the treatment clinically, but unfortunately it has not been possible to follow up their after-history and to obtain stools for after-treatment examination. The drug was very well tolerated on hypodermic injection,—far better indeed than emetine,—the injections being much less painful, while the patients did not show any of the mental depression which one often meets with emetine.

In 1924, Messrs. Burroughs, Wellcome and Co. kindly placed a small sample of their ' Tabloid ' Extract Kurchi Corticis, gr. v, at the disposal of the junior author. There was sufficient to treat two acute cases of amœbic dysentery, whose stools showed numerous actively motile *E. histolytica*. The drug was administered with no other subsidiary line of treatment in large doses by the mouth. It was found that both patients readily tolerated a dose of 60 grains a day with no unpleasant symptoms ; the symptoms rapidly cleared up,—although not as quickly as under emetine therapy,—and on subsequent examination of the stools for a few days after the completion of treatment, no *E. histolytica* or its cysts could be found. Since then the junior author has used *kurchi* a good deal in the treatment of acute amœbic infections. The bazar liquid extract unfortunately is not standardised at all, whilst the ' Tabloid ' product is expensive, but the drug is certainly well worth further investigation.

The position with regard to *kurchi*, in fact, is so interesting that further investigations are urgently called for. Unlike ipecacuanha, *kurchi* can be administered in large doses by the mouth without unpleasant symptoms; in experimental practice it appears to be an active amœbicide. There are large supplies of *kurchi* available in India, and both it and conessine could be manufactured at a price well below that of emetine. We would like to draw the attention of the big chemical manufacturers in India to this drug. As a beginning they might at least place a supply of compressed tablets of fresh *kurchi* bark on the market, for if any cheap *and efficient* method of treating amœbic dysentery by oral administration can be worked out, it might well come to replace emetine. Colonel Chopra has now a large supply of purified conessine in hand, also a supply of the total alkaloids of *kurchi* bark, and it is hoped to undertake further investigations with this.

With regard to the proof of radical cure of an *E. histolytica* infection we cannot do better than quote the following passage from Dobell and Low (1922, p. 1377) :—

'It is the general rule that patients undergoing treatment with emetine become "negative"—i.e., no amœbæ or cysts are discoverable in the stools—whether they are ultimately found to be rid of their infections or not. Negative examinations made during treatment are therefore of no value as a criterion of cure. This "negative phase" may continue for some time after the administration of the drug has ceased, though the effects of the emetine usually disappear within two or three weeks of the cessation of treatment. It is, moreover, frequently impossible to discover either free amœbæ or cysts of *E. histolytica* in the stools of infected persons —even when they have not been subjected to specific treatment; in other words, the stools of untreated cases, infected with the parasite, are frequently negative. For such reasons, therefore, it is necessary to make a considerable number of examinations of the stools of any patient, and to make them at suitable times, if negative findings are to have any decisive value as an index of non-infection.

'In dealing with a few cases only, the stools may be examined microscopically every day after treatment; and if they remain consistently negative for three weeks, the chances are that the patient has been permanently freed of his infection. The parasites rarely reappear in the stools after such a period—if the examinations have been made daily, and by a competent and careful protozoologist. In practice, examination of the stools every few days for a period of about a month after treatment is usually sufficient to establish with considerable probability—if all examinations have been negative—that the patient has been cured..... Six negative examinations made in three weeks should be regarded as the irreducible minimum required before one even ventures to speak of a "cure" having been effected.'

The *complications* of acute and subacute amœbic dysentery hardly come within the scope of this book. A mild grade of amœbic hepatitis associated with fever, but without the formation of pus, is commoner than actual amœbic abscess of the liver. The latter condition may call for aspiration in addition to the emetine

therapy which the patient is undergoing. Local peritonitis without perforation is not uncommon; its site is usually in the neighbourhood of the cæcum and ascending colon, and such cases may be mistaken for appendicitis. Sometimes, but fortunately very rarely, the whole thickness of the colon may pass into a condition of severe gangrene, in which case no treatment is of any avail. Perforation is definitely more common in amœbic than in bacillary dysentery, since the ulceration is deeper and not limited by the muscularis mucosa in the same way. It may occur under two entirely different conditions: first during acute amœbic dysentery, where the whole thickness of the bowel wall has been destroyed. In these cases perforation frequently takes place at several sites simultaneously, and nothing can be done for the patient. The second type of perforation is seen in chronic and relapsing dysentery; here the perforation is single, the gut not gangrenous, and immediate laparotomy may save life. Plastic peritonitis may even set in and cure such a condition spontaneously. Sudden and severe intestinal hæmorrhage may occur if a large vessel in the submucous coat has been opened up by the ulceration, and Rogers (1921) mentions such a case as having been at first mistaken for one of duodenal ulcer.

Relapsing and Chronic Amœbic Dysentery.

Chronic and relapsing amœbic dysentery is one of the commonest diseases of the tropics, and one of the most difficult to treat, since the extensive fibrosis of the gut wall walls in the entamœbæ and renders the possibility of any such drug as emetine getting at them unlikely.

The condition may follow an acute attack of amœbic dysentery, and the patient, who has recovered from the acute attack, either spontaneously or under treatment, has a relapse, again recovers, again has a relapse—this state of affairs continuing for even years on end. On the other hand the condition much more often sets in insidiously, beginning as an amœbic diarrhœa, and passing by gradual phases into established and relapsing amœbic dysentery. The mucosa of the colon in such cases is greatly thickened and inflamed, and studded with the orifices of numerous small ulcers, many of which communicate with one another in the submucous tissue. The gut wall is very greatly thickened and fibrosed, and the cæcum and ascending colon are usually readily palpable. Fletcher and Jepps (1924) write: 'We found the walls of the cæcum and ascending colon thinned and dilated in all the nineteen post-mortems except two. In several instances portions of the gut between the ulcers had stretched more than the surrounding parts and had formed bulging balloons on its external surface. In two cases of long continued dysentery the whole of the large intestine was much thickened and the appendices epiploicæ were greatly enlarged. In one, the wall of the gut was as stiff as though it had been pickled in formalin; but even in these two specimens there were certain areas where hypertrophy had failed and where there was dilatation instead.'

Such patients often show constipation alternating with periods of looseness of the bowels and occasional passage of blood. Mucus is invariably present in the stool. There is no sharp line of demarcation between the patient with chronic amœbic dysentery and the carrier with mild symptoms. Even when the stools are formed, however, careful examination of them will show streaks of blood-stained mucus on their surface. At other times the chief symptom is diarrhœa, the stool resembling pea-soup, but with little islands of mucus-like grains of sago floating in it.

By degrees such patients become sallow ; they steadily lose weight and become neurasthenic. Also they tend to become very introspective, taking an interest in nothing but their own abdominal condition.

The treatment of chronic and relapsing amœbic dysentery is often very difficult, and it has to be even more thorough than that of acute and subacute amœbic dysentery. The patient should be put to bed and kept there. The full treatment, as for acute amœbic dysentery, with emetine and bismuth should first be tried. After this if examination of the stools shows that the infection has not been eradicated, it may be necessary to give a course of bismuth-emetine-iodide, as described in the section dealing with the treatment of the amœbic carrier. Stovarsol is often of definite value in such cases.

Balantidial Dysentery. Treatment.

Balantidial dysentery is so rare in India that very little need be said with regard to its treatment. No end of different drugs have been tried in this condition without success, and the condition is one which appears to be most difficult to treat. Walker (1913) especially advocates irrigation of the colon with organic compounds of silver, and in general, local medication by medicated enemata appears to be more successful than oral administration of drugs. A bland non-irritating diet must be given, and rest in bed is essential for the ulceration is apt to be very severe and extensive. Thymol by the mouth has been advocated. Hermitte, Sen Gupta and Biswas (1926) write of stovarsol as practically a specific cure for balantidial infections. They found injections of emetine to be without effect upon the parasite, but the infection very rapidly cleared on giving the patients 1 four grain tablet of stovarsol daily, crushed in water, for 6 to 12 days.

The Treatment of Mixed Infections.

In the treatment of mixed infections the medical attendant must first of all make up his mind which is the more important element in the case and deal with that first. In our experience the commonest type of mixed infection—owing to the predominance of Flexner bacillus infections—is for acute bacillary dysentery to supervene on more or less chronic amœbic infection. In such cases the cellular characters of the stool will be those of a bacillary dysentery, but the red corpuscles

may show a tendency towards clumping, and Charcot-Leyden crystals and cysts—but only rarely vegetative forms—of *Entamœba histolytica* may be found. Usually, however, the condition is not recognised until the physician finds that treatment of the bacillary dysentery fails to cure the dysentery present, and is driven to re-examine the stools repeatedly.

In such cases it may be possible to combine a daily injection of emetine with the treatment of the bacillary dysentery by saline aperients, to first cure the bacillary infection, which is the more important, and then deal later with the amœbic one. Fletcher and Jepps point out that it is not at all uncommon for patients admitted for the treatment of chronic amœbic dysentery to contract bacillary dysentery whilst in hospital.

The opposite condition—of acute amœbic infection supervening on chronic bacillary dysentery—is very much rarer, though it must be remembered that some 15 per cent of patients with bacillary dysentery, like the rest of humanity in the tropics, are carriers of *E. histolytica* infection. Here the amœbic infection may require to be treated first, and the best line of treatment would probably be to give large doses of osmo-kaolin by the mouth and emetine hypodermically.

CHAPTER VI.

Chronic Bacillary Dysentery and the Bacillary Carrier.

WERE every case of acute or subacute bacillary dysentery kept in bed and properly treated, we should probably see but little of chronic bacillary dysentery and the carrier state. As matters actually stand, however, the condition is very common indeed—though perhaps less common than chronic amœbic infection.

The bacillary carrier is almost invariably a person with a definite history of previous dysentery or definite diarrhœa some time previously—it may be two or three years before. Unlike what happens in the chronic amœbic carrier, the intestinal history is usually well marked.

It is a little difficult to get figures as to the incidence of this condition, and the most reliable are probably those gathered during the Great War. Martin and Williams (1918), working in Rouen, found that on convalescence from acute or subacute bacillary dysentery the excretion of dysentery bacilli in the stools dropped very rapidly. In material embracing more than 1,000 cultural examinations 68 per cent were positive during the first 5 days, 17 per cent during the second 5 days, 6 per cent during the third 5 days. By the 50th day only 3 per cent were positive, and after this only one case was positive—at the 80th day. Andrewes (1923) records that in hospitals in the United Kingdom 3·56 per cent of some 5,000 returned dysentery cases became carriers, but that in the majority of cases the condition soon cleared up. Glynn, Berridge, Foley, Price and Robinson (1918) found 1·8 per cent of carriers among 265 patients who had suffered from bacillary dysentery and were supposed to be cured. Dudgeon (1919) states that in Macedonia Lepper found that three months or more after the attack of bacillary dysentery 1·5 per cent of the patients concerned were carriers.

Perhaps the most exhaustive study of the carrier problem is that given by Fletcher (1920), who worked at Southampton. Of 1,782 convalescent patients at this hospital, 935 had been diagnosed as cases of dysentery, and of these 13 were found to be carriers of the bacillus of Shiga and 61 carriers of Flexner's bacillus. As regards the former the condition was an inveterate one in 11 out of the 13 Shiga bacillus carriers, and special note was made of the physical and mental depression which these men presented; all passed mucus and sometimes blood in their stools, and there was marked liability to relapse. The stools of these 13 men were examined 469 times, and Shiga's bacillus was isolated on 207 occasions. It is this incessant

excretion of dysentery bacilli by Shiga bacillus carriers that probably renders them so important a source of small and violent epidemics of this form of bacillary dysentery. With regard to carriers of Flexner's bacillus conditions were found to be quite different ; the men were in relatively good health, the stools formed, but containing mucus, and the excretion of the bacilli markedly intermittent. Treatment of both conditions was found to be extremely unsatisfactory. The Shiga bacillus carrier was useless for military purposes at the end of three months, and a danger to his companions, and had to be invalided ; the Flexner bacillus carrier, on the other hand, could be sent back to the front.

The figures given above for incidence of the carrier condition are probably well below the actuals, owing to the difficulty in isolating the bacilli.

Pathology.

The degree of ulceration of the colon in chronic bacillary dysentery and in the carrier state varies very widely. The smallest lesions are lenticular in shape and involve the mucous membrane only. The ulcers commence on the free edge of the transverse folds and run at right angles to the longitudinal axis of the gut. The more advanced lesions amount to ulceration of limited tracts of the mucous membrane, rarely, if ever, penetrating below the muscularis mucosæ. In chronic relapsing cases the mucosa may be so extensively destroyed that recovery is impossible ; in such cases the gut may resemble a piece of chamois leather with interlaced fibrotic strands on the surface. Many cases show but little ulceration, but rather a granular condition of the mucosa, usually confined to the lower portion of the colon and rectum, but sometimes distributed in an irregular manner. Considerable infiltration of the walls of the gut is associated with this condition.

A special feature of the colon mucosa in chronic bacillary infection is the presence of ' mucous retention cysts '—to which attention was first drawn by Manson-Bahr (1919). These rather resemble grains of tapioca and vary in size from that of a hemp seed to that of a cherry. They are distributed throughout the large gut and stand out from the mucous membrane into the lumen of the gut as knob-like excrescences. On incision clear jelly-like mucus can be expressed from them. These cysts form beneath the base of a contracting bacillary ulcer and their existence probably does much to explain the intractable mucous colitis which is so liable to persist after an attack of bacillary dysentery and which it is so difficult to treat successfully. They may contain almost pure cultures of the *B. dysenteriæ* or may become secondarily infected with the *B. coli communis* and thereby converted into small abscesses in the wall of the colon. Sometimes a pin-hole orifice leads down into the cyst from the lumen of the gut. Actual pus pits may exist, the mucous membrane being full of little pits full of pus, the walls of the intestine much thinned out, and in places the pus may burrow down to the serous coat.

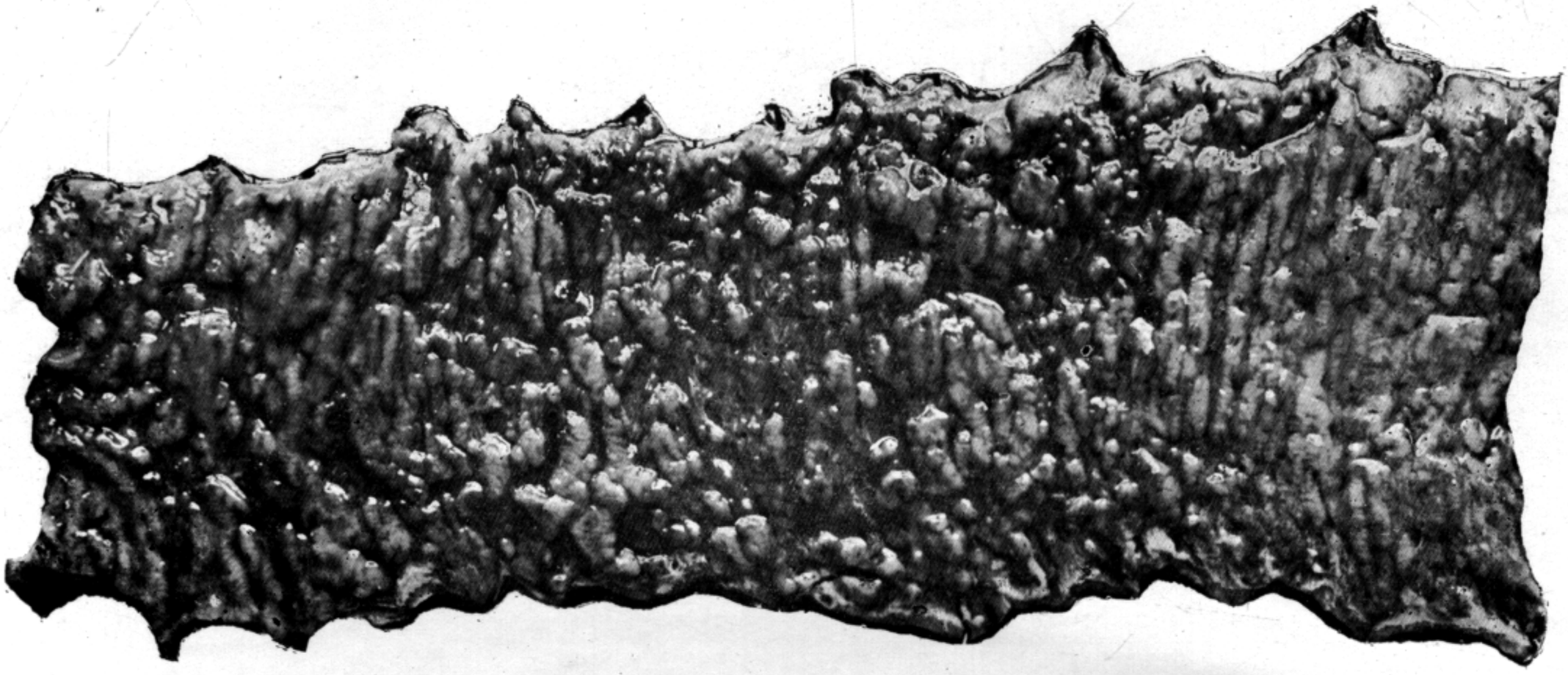


FIG. 17. Chronic bacillary dysentery. Infection with Flexner's bacillus. Patches of black, semi-healed ulceration from which *B. dysenteriæ* was cultivated. Died from cirrhosis of the liver and anasarca.
(After Fletcher and Jepps, 1924.)

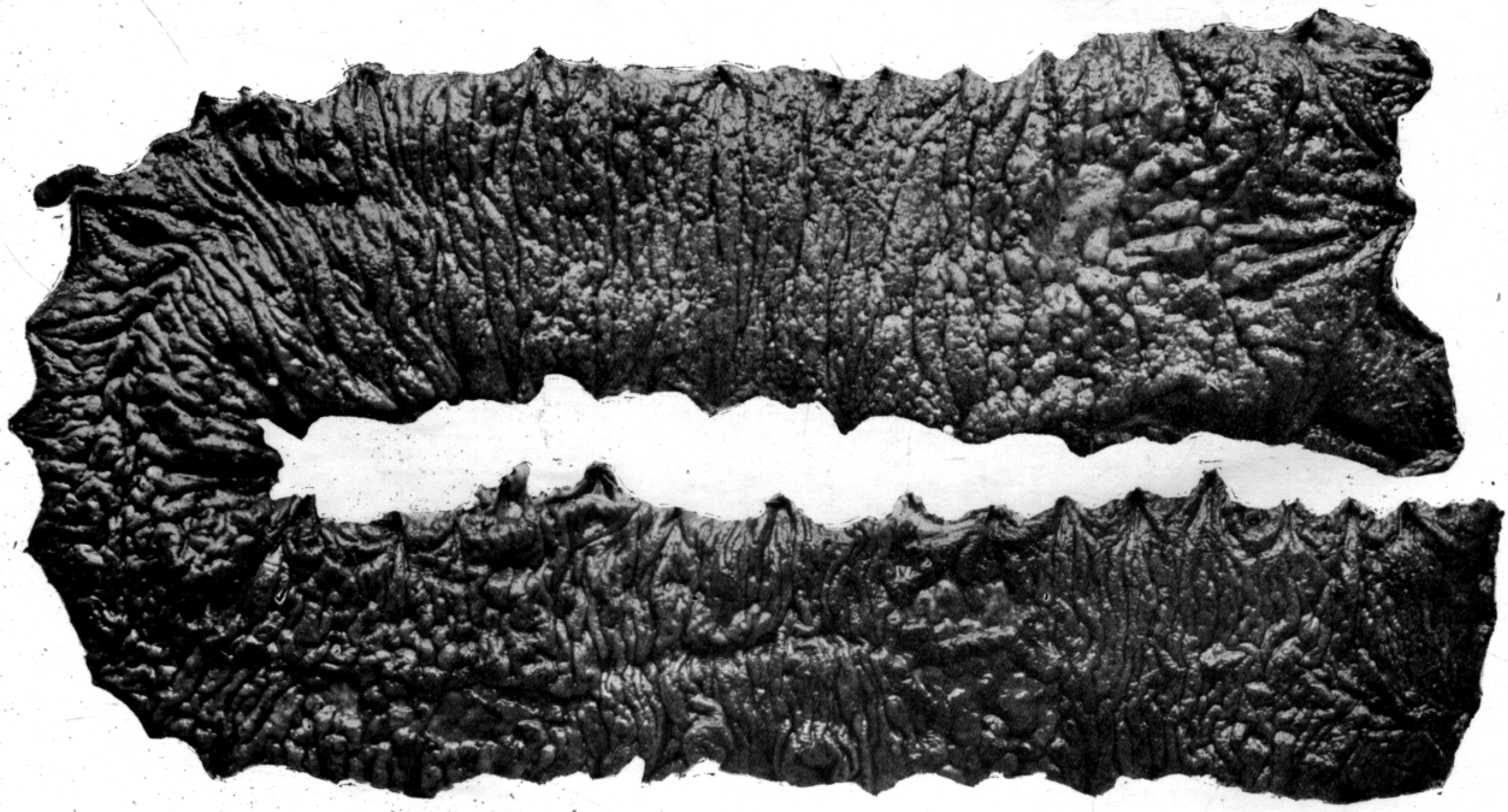


FIG. 18. Subacute bacillary dysentery. Infection with Flexner's bacillus. Granular, toad-skin ulceration.
(After Fletcher and Jepps, 1924.)

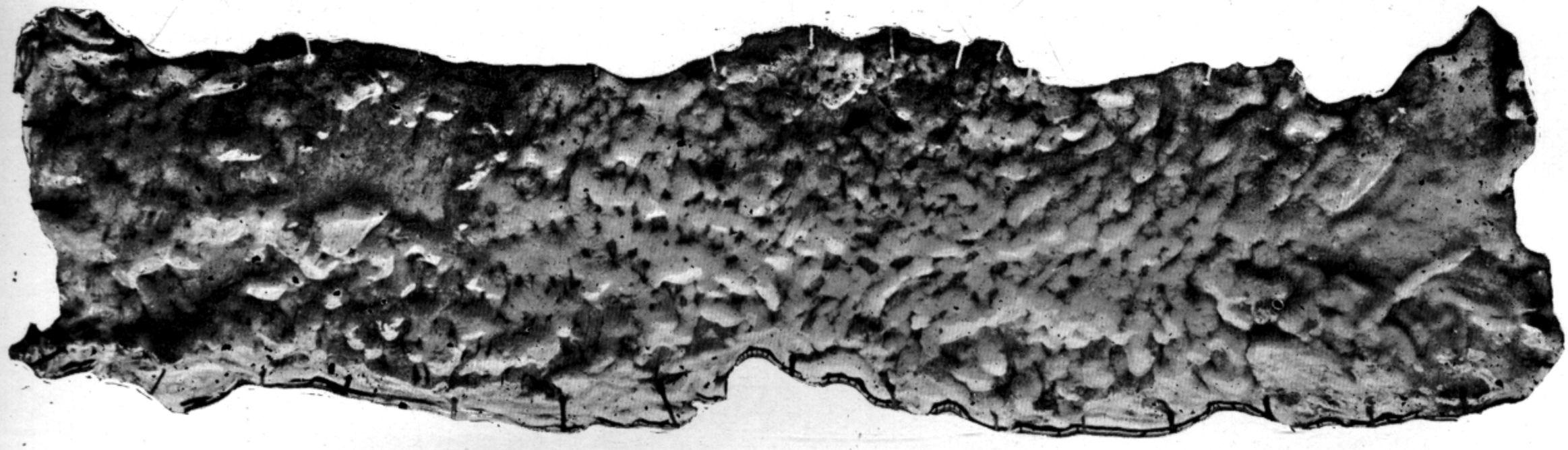


FIG. 19. Subacute bacillary dysentery. Infection with Flexner's bacillus. Fenestration of mucous membrane, which is destroyed to left and right. In the central part of the photograph it is undermined and full of holes. (After Fletcher and Jepps, 1924.)

FIG. 20. Chronic bacillary dysentery. Infection with Flexner's bacillus. Pus pits. History of dysentery for 4 months. Mucous membrane full of small openings, leading into little pits full of pus from which Flexner's bacillus was isolated. The walls of the intestine were very thin and, in places, the pus had burrowed down to the serous coat. (After Fletcher and Jepps, 1924.)

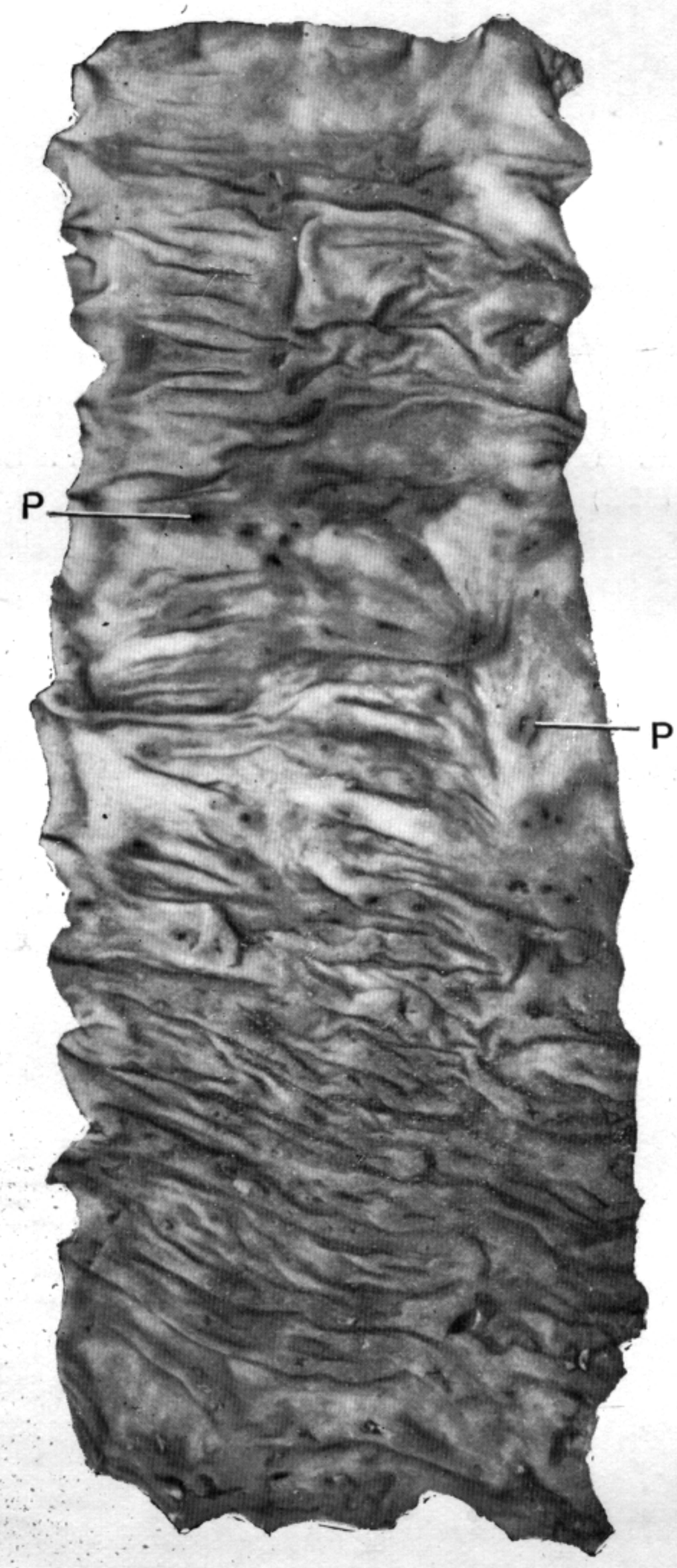


FIG. 21. Bacillary carrier. *B. dysenteriæ* in retention cysts. Ascending colon with isolated pigmented pits, marked P, containing pus. *B. dysenteriæ*, Flexner, was cultivated from pus squeezed out of these little pits.

(After Fletcher and Jepps, 1924.)

The base of the bacillary dysenteric ulcer consists of red or pigmented granulation tissue, and its margins are not raised. Where healing has occurred pigmentation is characteristic of the chronic bacillary ulcer. In rather severe but chronic cases the ulceration may extend beneath the mucous membrane, undermining it in all directions, and linking up neighbouring ulcers by submucous tunnels. The mucosa may finally become converted into a fenestrated membrane, loosely attached here and there to tissue underneath, partly concealing large areas of ulceration and necrosis.

In other cases the ulcers become covered with thin, pigmented scar tissue under which slow suppuration takes place until the scar breaks down and pus is discharged. After this the ulcer may heal again, only to break down once more. Chronic ulcers in all stages of ulceration or healing may be found at post-mortem.

Another feature of the gut in chronic bacillary dysentery is the formation of actual polypoid growths, which may attain a length of from three-quarters to one inch. They are generally found scattered throughout the lower part of the rectum and may be the seat of hæmorrhage. They are often associated with retention cysts, and if they should become detached considerable hæmorrhage may occur.

On section of the chronic bacillary ulcer, remains of epithelium may be found at the base of the ulcer, nipped in by fibrous tissue, whilst a downward growth of columnar epithelium takes place into the submucosa. The mucosa in the immediate vicinity of the ulcer is hypertrophied, but otherwise fairly normal. In the submucosa much fibrous tissue can be seen. The downward growth of the epithelium may continue until pseudo-adenomata are formed filled with mucoid secretion. These mucus retention cysts may occupy the whole thickness of the mucous membrane. At first they are lined by perfectly regular columnar epithelium, but when they attain a certain size the cavity is lined merely by basement membrane, the columnar epithelial cells having become atrophied from pressure. The centre of the cavity is occupied by structureless material in which only scanty and degenerated polymorphonuclear leucocytes can be made out.

Symptomatology.

There is one fact which is invariably associated with chronic bacillary—as well as chronic amœbic—infection of the colon, and that is that *the stool invariably contains a visible amount of mucus*. This is of very great importance from the point of view of prophylaxis. As shown by Cunningham (1923), macroscopic examination of the stools of all inmates daily is a most important method of controlling dysentery in jails or similar institutions, a point to which we will recur later, when considering the subject of prophylaxis.

The commonest type of chronic bacillary dysentery or of the carrier condition is due to infection with Flexner's bacillus. Next in order of frequency comes chronic dysentery due to Strong's bacillus ; then infections with Shiga's bacillus ; whilst some of the chronic diarrhœas of the tropics are due to infections with the bacillus of Morgan, or to bacilli of the para-dysentery group. The toxins which are absorbed from such an ulcerated gut act in various ways, chiefly causing diminution in the tone of involuntary muscle. This leads to intestinal stasis, visceroptosis, and later tropical neurasthenia. Chronic diarrhœa with painful peristalsis may persist for long periods, or may alternate with periods of constipation. There may be marked and palpable thickening of the gut. Apparently normal stools coated with mucus may be passed for a shorter or longer period, but any error in diet, chill, fatigue, or indulgence in alcohol may be followed by sudden and violent attacks of diarrhœa or dysentery. From time to time blood and mucus are present in the stools in the form of gelatinous sago-like grains floating on the fluid fæces. The condition is particularly intractable and may persist for years. The patient—not infrequently a middle aged European female—may gradually pass into an utterably miserable condition, the ' chronic abdominal type ' so amusingly described by Hutchison (1923), presenting at last a confirmed neurasthenic picture, a misery to herself and a nuisance to all around her, the subject of the attentions of the quack, the homœopath, the gynæcologist, and even the Christian scientist. Finally the surgeon may be called in and add surgical trauma to the other factors which assist in the development of neurasthenia.

There is considerable difference in the symptomatology of chronic bacillary dysentery when seen in children, as compared with the symptoms in adults. In young children chronic infections with Flexner's bacillus are not uncommon, and the diagnosis usually made is one of ' mucous disease or Still's disease.' These patients become very intolerant to carbohydrates, and are liable to develop acidosis with cyclic vomiting. Irregular fever is usually present, and the patient tends to become pot-bellied, with a capricious appetite. The stools are usually large, pale coloured and offensive.

In adults chronic infections with Flexner's bacillus are apt to lead to diarrhœa of ' hill-diarrhœa ' type rather than to dysentery. Secondary infection with the *B. albofaciens* is not infrequently present, leading to the production of leuco bases, and hence the light coloured stools, as the stercobilin in the fæces is altered to a colourless base. The patient tends to pass three or four copious fluid stools in the early morning, and to feel tired out for the rest of the day ; whilst the condition tends to be aggravated by any hot or solid food.

* * * * *

We may consider the symptomatology of chronic bacillary dysentery under several different headings, for it is almost protean in its characters.

Severe Cases.

These have been so admirably described by Fletcher and Jepps (1924) that in the main we may follow their description. The course in such patients is usually progressively downhill; until they reach the final stage of extreme asthenia described by Norman Chevers as *morbus bengalensis*. The patient continues to pass blood and mucus for months or even years on end, until eventually the stool comes to consist of little else than blood-stained mucus and necrotic epithelium. Emaciation sets in and becomes extreme. The anæmia deepens until cardiac insufficiency comes on, accompanied by the onset of œdema. There may be periods of temporary improvement followed by relapses. The abdomen is markedly shrunken, but in the terminal stages there may be ascites. The stools are usually very foul, and it is usually impossible to isolate the *B. dysenteriæ* from them, although this is usually possible at post-mortem. Death may occur from exhaustion, or from intercurrent disease, whilst, according to Sir Leonard Rogers, there may be sudden severe hæmorrhages from the gut. Perforation of the gut with septic peritonitis undoubtedly does occur, but is very rare.

Many such cases occur as the 'terminal dysentery' of kala-azar, pulmonary or intestinal tuberculosis, or malarial cachexia. These cases require the most vigorous measures if they are to be cured, and the prognosis is usually very bad.

Mild Cases and the Carrier State (a) in Indians.

From what we have seen in Calcutta during the past six years it would seem that chronic mild bacillary dysentery and the carrier state are associated with a different symptomatology in Indians and in Europeans respectively. In Indians these mild infections appear to be especially associated with an asthenic diarrhœa, whereas in Europeans the condition appears to be one of the most important causes of tropical neurasthenia.

In Indians this asthenic diarrhœa is associated with marked wasting. The pulse is of low tension, and the patient becomes more and more deeply pigmented, on account of adrenal deficiency. These cases are often mistaken for cases of intestinal tuberculosis. On passing the finger along the skin the white line of adrenal deficiency is seen. The skin becomes dry and harsh. The tongue may be red and glazed and rather like that of a sprue patient, but there is no ulceration of it.

The stools tend to be numerous, from 4 to 8 a day, to be large, pale in colour, and containing much mucus. These patients show a marked intolerance as a rule to carbohydrates.

Although this condition is one which may vary widely in its degree of severity, it is one which requires prompt and vigorous treatment.

Mild Cases and the Carrier State (b) in Europeans.

In mild infections in Europeans—and to some extent in well-to-do Indians living in European style—the symptomatology appears to be quite different. Here the first and most important symptom is irregularity of the bowels. This may be associated with constipation, or with constipation alternating with diarrhœa. The second and a very important sign is the invariable presence of visible mucus in the stool.

The toxins which are absorbed from the ulcerated gut at first in small doses slightly stimulate, then fatigue, and finally profoundly depress the various systems of the body, as the toxæmia deepens.

The first effect of the toxæmia falls on the involuntary musculature of the body, and especially on the gut wall. The gut tends to become atonic, so that the cæcum loses its tone and becomes distended and thin walled. Gurgling in the right iliac fossa is, in consequence, a common symptom. If the bowels are not kept systematically open, e.g. by liquid paraffin, this leads to constipation, alternating with periods of diarrhœa during which the overloaded cæcum is emptied. The appendicular valve becomes patent and fæces may enter the appendix and give rise to the symptoms of appendicular colic. With irregular peristalsis setting in, abdominal colic is a frequent symptom. Irregular spasmodic contractions at the hepatic or splenic flexure may give rise to sudden sharp attacks of pain in these regions, which may simulate the symptoms of gall-stone colic or an acute duodenal lesion.

The second effect of the toxins is to depress the tone of the involuntary muscular bands which support the intestine. The cæcum sags down into the pelvis and visceroptosis sets in, affecting in turn the transverse colon, the liver, spleen, and kidneys. The tone of the muscles in the genital organs is affected; in the male with the loss of tone in the prostate and seminal vesicles this may lead to loss of seminal control and nocturnal emissions.

Lastly there is loss of control of the peripheral vascular circulation. These patients tend to get chilblains in the cold weather, and dermatographia and urticaria are common.

It is at this point that the surgeon and gynæcologist are frequently seen at their best in such patients. A large proportion of such patients lose their appendix. They are subjected to laparotomy for investigation, to operations on bands and kinks, anchorage of floating kidneys, gall-bladder operations, and many and sundry gynæcological procedures from pessaries to shortening of the round ligaments. Such operations are wont to be unsuccessful in their results, as they represent an attempt to bind up toneless ligaments and do not recognize the underlying toxæmia which is responsible for the loss of tone.

Together with the loss of tone in the gut and visceroptosis goes diminution in the secretions of the alimentary canal. Gastric secretion is diminished, with

hypochlorhydria or achlorhydria, followed by atony and dilatation of the stomach. Much rarer is a condition of hyperchlorhydria with ulceration. The secretion of amylopsin, erepsin and invertase is lessened with indigestion to starch, which causes flatulence and increases the abdominal colic. With a diminished flow of bile and the loss of its antiseptic action on the intestinal contents the stools become very offensive. The tongue is furred, with an offensive taste in the mouth in the mornings.

Finally, the brunt of the infection falls upon the endocrine system, whose activities are lowered by two causes: (*a*) the lack of the normal substances absorbed from the gut, which are the precursors from which the endocrine glands manufacture their secretions; and (*b*) by direct toxic action of the toxins on the glands themselves.

The thyroid appears to be the gland which is most depressed, and hypothyroidism is the rule among these patients. They feel cold, even in the hottest weather; they sweat and flush with nervousness on the slightest stimulus. The skin becomes slightly harsh, the hair dull and lifeless. There is usually loss of the outer third of the eyebrows. In the case of women they tend to become mentally vivacious when in society, but dull and irritable in their own homes; men tend to become morose and to shun society.

Depression of the adrenals leads to a low tension pulse, and the characteristic white adrenal line can be provoked on the skin. The complexion becomes muddy, sometimes with chloasmic patches. These patients easily get excited, and then the adrenal glands suddenly work at high tension for a short time, with a greater depression than ever afterwards. In women the cortex may sometimes be stimulated, with resulting hypertrichosis.

The function of the gonads is also depressed, leading in the case of women to scanty menses and painful menstruation, with loss of or disinclination for sexual intercourse. In men there is loss of sexual appetite.

As the result of these various factors the patient now passes into a condition of confirmed tropical neurasthenia. He is full of morbid anxiety about himself. And here we see:—

(*a*) First, introspectiveness. The patient is really ill, but without obvious or apparent cause. He seeks to find within himself the reason. He becomes bowel conscious and in consequence his intestinal symptoms become more prominent than before; the indigestion and flatulence increase. He worries about his heart, suffers from palpitation, and fears that he has heart disease. He consults the physician about his blood-pressure and the likelihood of his developing cerebral hæmorrhage. The flatulence and abdominal colic suggest to him that he has abdominal cancer. The disinclination for sexual intercourse leads him to believe that he is impotent, and to worry about that.

(*b*) Anxiety neurosis. By degrees the patient passes into a state of constant anxious and morbid dread. In men the dread is often of the onset of some fatal disease, though such patients want to regain their health, and to live and not die. In women, with the development of sexual anæsthesia, the sex tendency is subliminated into other paths. They become extremely jealous. If they have children, they develop maternal anxiety and dread lest anything shall befall the child. If there is no child they develop narcissism or self-adoration, and the wish to gratify this self-adoration may lead to illicit or clandestine intercourse.

(*c*) Phobias. Finally, as the result of excessive response to external stimuli the actual phobias may develop, such as claustrophobia, morbid fear of disease, etc.

(We do not mean to suggest for one moment that tropical neurasthenia is always caused by chronic bacillary dysenteric infection. The latter is not the only cause, but in our opinion is an important cause of tropical neurasthenia. The toxins which lead to this condition may be absorbed from the teeth, mouth, stomach, gut, prostate, etc., whilst severe, debilitating, or chronic diseases of many different types may lead to a similar depression of tone of the endocrine glands.)

By this time, if her means will permit it, the patient is probably on her way to Plombières or Harrogate. If not, she comes to constitute one of that terrible army of women of whom Crabbe wrote :—

'Who with sad prayers the weary doctor tease,
To name the ever nameless new disease.'

'My *bête noire*, Miss X., is coming to see you soon,' once wrote Dr. A. to Dr. B. of this class of patient.

The Diagnosis of Chronic Bacillary Dysentery.

The diagnosis of chronic bacillary dysentery is not easy. It is far more difficult than that of acute bacillary dysentery, and it calls for the utmost diligence and skill of the physician and the laboratory worker, also not infrequently for the help of the radiologist.

The first essential is a careful and thorough clinical examination of the patient, and a detailed enquiry into his previous history. If the patient is in the condition of chronic neurasthenia described, he will often come to the physician with a small portfolio of notes, temperature charts, and the like. It is unwise to disregard this portfolio totally, for, on delving into its contents, one may come across information of value. Careful examination of the abdomen may be required to distinguish these cases from cases of intestinal tuberculosis or abdominal carcinoma.

The *sigmoidoscope* is especially advocated by several authors in the diagnosis of this condition. It is essential to give morphia beforehand, for instrumentation is painful—a point which is very characteristic of chronic bacillary dysentery. The sphincter tone is poor, the gut walls thickened and firm, the folds narrow and scanty. The surface of the mucosa is in places normal or anæmic, in others hyperæmic

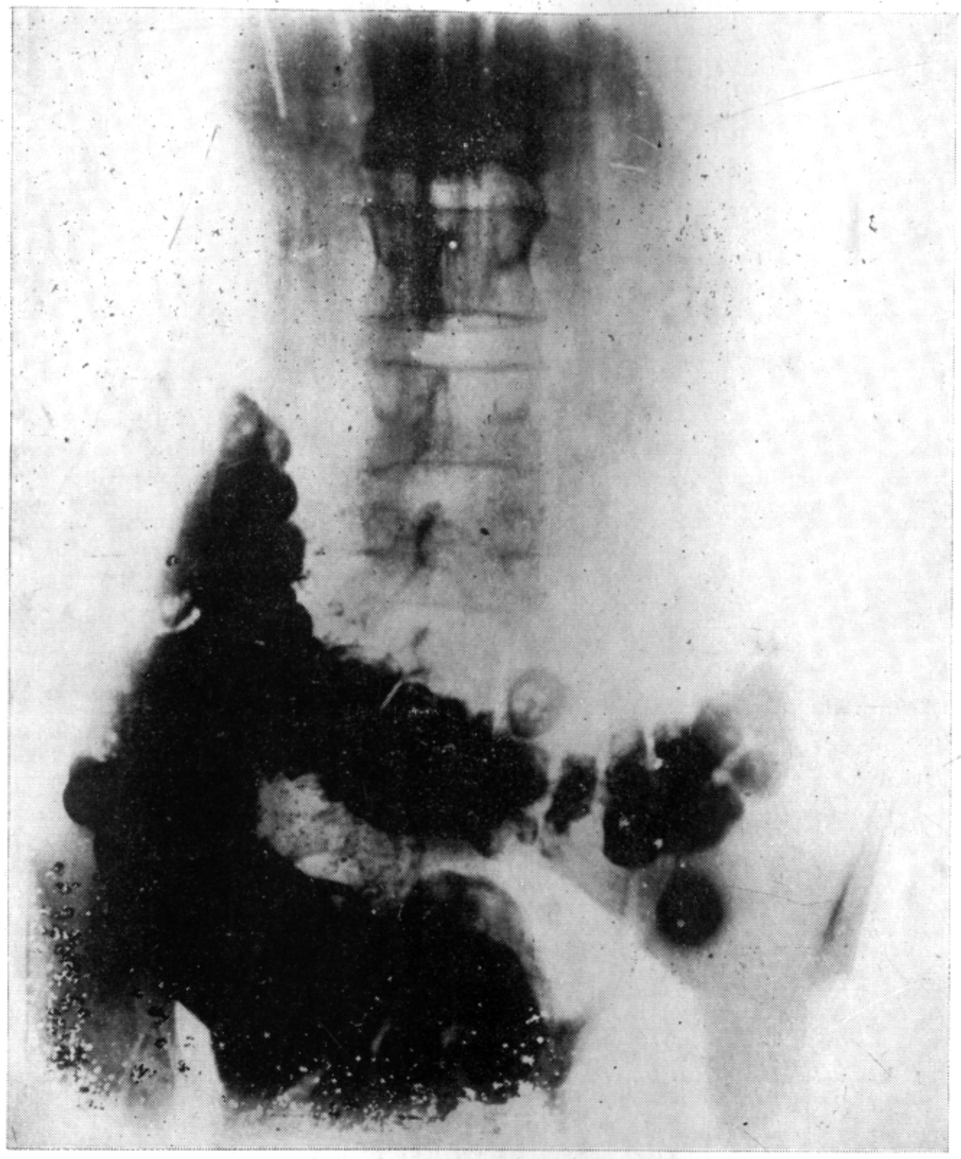


FIG. 22. European male, 35 years. History of chronic diarrhœa and dyspepsia of several years' standing, but not of actual dysentery. Stools pale coloured, large, sometimes watery, sometimes semi-solid, 1 to 4 a day. Flexner's bacillus isolated from them.
Skiagram 4 hours after a barium meal. Marked visceroptosis present. The cæcum has dropped into the true pelvis, dragging the ascending colon down with it.

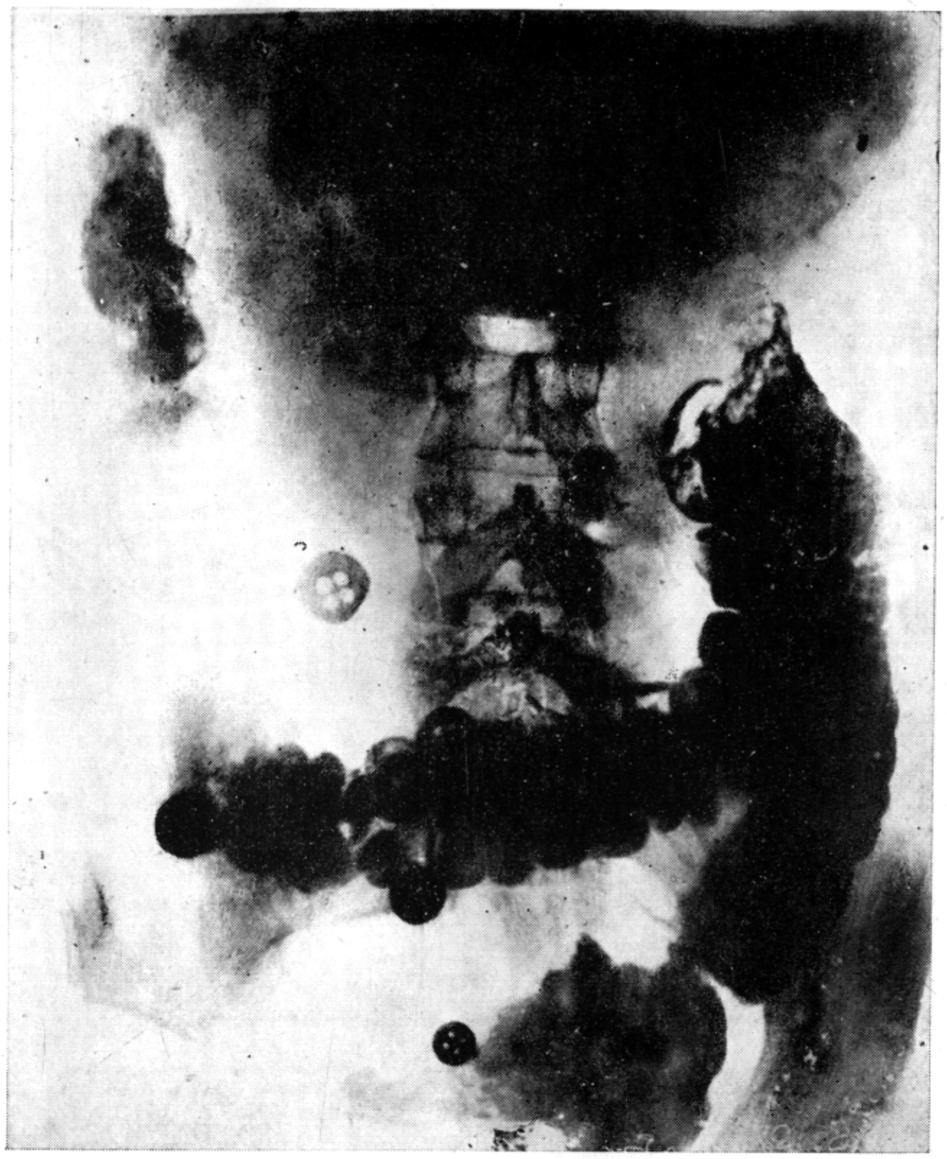


FIG. 23. From the same patient as in Fig. 22. Skiagram 6 hours after barium meal. Visceroptosis of cæcum and transverse colon, causing a marked kink at the splenic flexure.

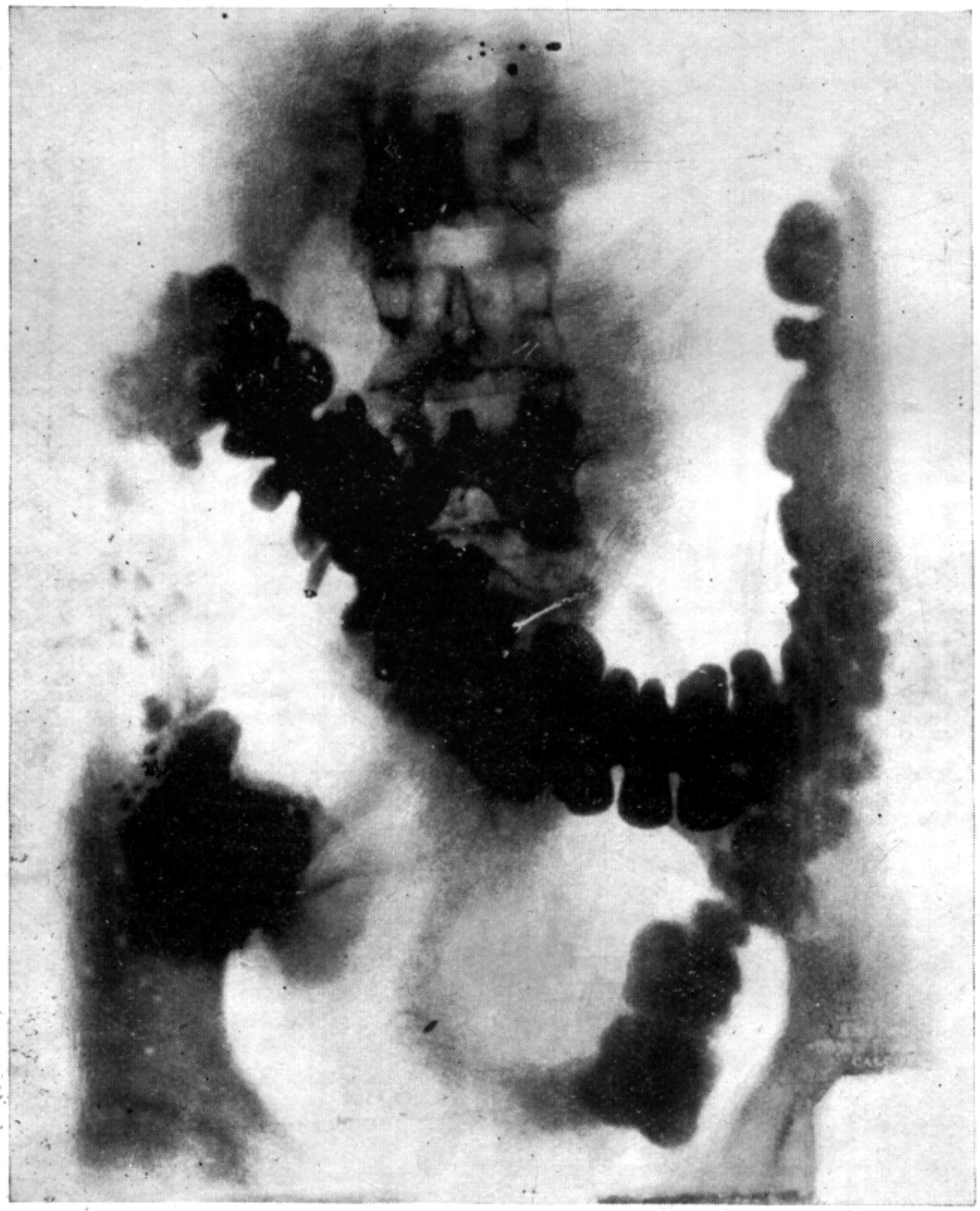


FIG. 24. From the same patient as in Fig. 22. Skiagram 24 hours after barium meal. Patchy ulceration in the ascending colon where the barium meal has passed, but has left traces of barium attached to the ulcers. Delayed evacuation of intestinal contents.

and glazed or granular in appearance—the latter appearance resembling that of the surface of the cortex of a granular kidney after the capsule has been stripped from it. There may be small ridges or polypi of spongy, granular consistency. Freedom of movement of the bowel in the pelvis is diminished.

The value of *radioscopic examination after a barium meal* is very great in such cases, both from the point of view of diagnosis and prognosis, for it will give one much information as to the state of affairs in the patient's intestinal tract. After the barium meal is given photographs are taken 4, 6, 8, 10 and 24 hours later, and the series is then ready for study. The first clear evidence of the disease will usually be seen in the condition of stasis and dilatation of the colon. The opening into the appendix is frequently patent, and the barium will show up inside the lumen of the appendix. Visceroptosis is present; the cæcum may have dropped into the pelvis or even into the true pelvis, or be lying partly within and partly without the pelvis. The transverse colon may be sagged down into the pelvis. The stomach may be atonied, dilated, and below its normal position. The site and extent of the ulcerated portions of the gut can be gathered from the traces of barium which remain attached to the ulcers, and which show up in the photographs. In front of and behind such lesions there may be marked enterospasm. From a study of such a series of photographs one can gain much valuable information, and indications as to treatment.

Macroscopically *the stools always contain mucus*. On microscopical examination of the stool the characters of the cellular exudate are nothing like as characteristic as in cases of acute bacillary dysentery, and everything depends on the state of affairs in the colon. Red blood corpuscles may be present, but are frequently absent. Mucus is invariably present, also—in cases of chronic infection with Flexner's bacillus—much undigested starch. Desquamated columnar epithelial cells form an important element in the cellular picture, whilst if abscesses are present in the wall of the colon, the stools may be loaded with pus cells. Macrophages may be present, but are much less numerous than in the acute bacillary stool.

The isolation of dysentery bacilli from such a stool is often an exceedingly difficult matter, and failure to isolate them by no means invalidates the diagnosis of chronic bacillary dysentery. Manson-Bahr, Perry and the late Sir Patrick Manson (1922) advocate at least five platings. The fæces should be collected on the tip of a sterile swab, and then thoroughly emulsified in 10 c.c. of saline. The emulsion is then spread with a platinum loop in a spiral manner, using progressively smaller quantities of emulsion for each successive plate. In this way a satisfactory distribution of colonies is ensured, without which recognition of suitable colonies becomes impossible. Fletcher and Jepps (1924) record several such cases where repeated examination of the stools during life failed to show dysentery bacilli, but where culture from the contents of the mucous retention cysts in the gut at post-mortem yielded many colonies of dysentery bacilli. The stools may have to be

repeatedly plated before the causative organism is found. Sometimes the administration of a saline aperient before the stool is collected for plating will assist.

In cases where the stool has to be sent to a distant laboratory, the use of the solution advocated by Teague and Clurman (1916) in connection with the examination of stools of cases of typhoid fever is recommended by Fletcher and Jepps. About one part of fæces is emulsified in two parts of a solution of 30 per cent glycerine in sterile 0·6 per cent saline. Fletcher and Jepps record that in such emulsions Shiga's bacillus may be recovered up to 29 days later as compared with an extreme limit of 3 days in plain fæces, whilst Flexner's bacillus survived up to 42 days in the glycerine emulsion as against an extreme limit of 9 days in plain fæces. In connection with a small epidemic of dysentery due to Shiga's bacillus fifty miles away from the nearest town, the medical officer on the spot knew of Teague and Clurman's method, and sent specimens by post emulsified in the glycerine solution; the specimens when received were 6, 7, and 8 days old respectively, yet Shiga's bacillus was isolated from each of them. (It may be mentioned, however, that this solution rapidly destroys the vegetative forms of *Entamœba histolytica*, and is detrimental in the examination of suspected amœbic stools.) An alternative solution which has been advocated by Dudgeon (1919), and which he states to be even better than Teague and Clurman's method, is to emulsify one part of the fresh fæces in an equal volume of N/33 caustic soda solution. In using Teague and Clurman's solution it is important to note that the glycerine used must be free from any trace of acidity.

Secondary infections may be present in the case of patients suffering from chronic bacillary dysentery. The sufferer from this condition is no more exempt than anyone else from infection with *E. histolytica*; indeed Fletcher and Jepps suggest that possibly *E. histolytica* cannot penetrate the mucosa of the gut until the *B. dysenteriæ* or other agent has caused a superficial breach of the mucosa. Secondary invasion of the ulcers may occur with other bacteria, of chief importance amongst which are the *B. pyocyaneus*, *B. asiaticus*, *B. fæcalis alkaligenes*, *B. mucosus capsulatus*, and others, a subject to which we shall return later. Where a case of chronic bacillary dysentery has improved under vaccine therapy to a certain point and then remains stationary, it is often advantageous to again plate the stool and examine the cultures for secondary organisms which may have come to infect the ulcers, and to prepare and use an autogenous vaccine of such organisms.

The blood agglutination reaction against Shiga's and Flexner's bacilli by the Widal technique often affords useful information. A positive agglutination at a titre of 1 : 50 to Shiga's bacillus may be considered diagnostic of a past or present infection with that bacillus, and one of 1 : 160 to be diagnostic of infection with Flexner's bacillus. During recent years this test has been applied as a routine examination to all patients admitted to the Carmichael Hospital for Tropical Diseases in Calcutta, no matter from what disease they were suffering, and the number of

persons who give a positive agglutination at 1 : 160 to Flexner's bacillus—although not suffering from dysentery or diarrhœa—is very surprising. This is a still further indication of the widespread character of infections with the bacillus of Flexner in India ; it is probable that quite the majority of Indian children pass through the course of an infection with this bacillus in early life.

In estimating the condition of the endocrine system the basal metabolism may be tested as a rough guide in this matter. The muddy complexion and the test for the adrenal white line will afford an indication of adrenal insufficiency. Or the activity of the adrenals may be tested by observations on the blood-sugar, pulse, etc., after injections of adrenalin or insulin.

Prognosis.

In the severe cases of intractable bacillary dysentery in debilitated patients the prognosis is very bad. Such patients, as a rule, follow a steadily downward path and die in a condition of extreme asthenia. In the mild cases, and especially in the neurasthenic type, the prognosis is good, *provided that the medical man can gain the confidence and co-operation of the patient.* If this is not done the patient wanders from one consultant to another seeking help which is not obtained, 'suffering many things at the hands of many physicians' and perhaps even more at the hands of surgeons and gynæcologists. It is in such patients that the inverse of the Coué dictum holds good : 'every day and in every way, I get worse and worse.' These patients require an infinite amount of tact, patience and care on the part of the medical attendant.

Chronic Bacillary Dysentery. Treatment.

(*a*) *Severe Cases.*

In severe cases, and especially in debilitated cases, the patient must be put to bed and kept there, and be made to use the bed-pan. Here rest to the ulcerated gut is imperative. The patient should not be starved, but on the other hand he should not be sickened with a chronic milk diet. If the infection is due to the bacillus of Flexner—as is most frequently the case—there will be intolerance to carbohydrates, and proteins should be made use of such as milk, meat extracts, chicken jelly, etc. It is essential to keep the bowels opened regularly, and a dose of liquid paraffin may be given every evening. Warmth is very important in the case of such patients and they should be warmly clad, whilst a hot water-bottle to the abdomen is often very comforting. Fruit is often a valuable addition to the dietary, and ispaghul is very useful in the treatment of the condition.

The value of *rectal irrigations* in such cases has been much disputed. Fletcher and Jepps (1924) consider them of but little value in the debilitated type of patient which they were called upon to treat. They may make the patient more

comfortable, but they do not reach the whole of the ulcerated areas in sufficient quantity to be of use. 'Many of the solutions employed for injection,' they write, 'appear to aggravate the inflammation which it is sought to cure. Quinine douches are commonly employed for the treatment of chronic dysentery, but our experience of rectal injections of quinine in malaria has shown that they are most irritating. There is no objection to warm soothing inactive solutions if they ease pain, and it is legitimate to employ irritating injections, such as silver nitrate and quinine in selected cases, with the object of promoting a beneficial inflammation, but they should not be used (as they often are) indiscriminately for long periods.'

On the other hand Manson-Bahr (1925) considers such irrigations of special value in the treatment of these cases. Ellsworth and Wheatley (1923) have demonstrated by the aid of *x*-rays that the entire colon, and sometimes even the lower part of the ileum, can be distended with an enema when it is properly given; but the use of such injections is restricted in consequence of the unsatisfactory results of faulty administration.

The following details of technique for such injections are given by Manson-Bahr :—

The apparatus required is (*a*) a cylindrical glass funnel, 1½ inches in diameter, and graduated to hold 10 ozs. of fluid; (*b*) three feet of rubber tubing of half-inch diameter, which should be firmly secured to the constricted end of the glass funnel by tape; (*c*) a bulbous glass connection for joining the rubber tubing to the rectal tube; (*d*) a rectal tube which should consist of a stout catheter at least ⅜th of an inch in diameter with a big round terminal opening.

The solution used may be any one of the following. It is far better to use bland and non-irritant than irritant fluids :—

Sodium chloride	4 dr. to the pint of water.
Sea water	
Sodium bicarbonate	4 dr. to the pint of normal saline.
Eusol, or similar preparation ..	5 ozs. to the pint of saline.

The patient's bowels should first be well cleared by a dose of castor oil administered on the previous evening, and on the morning of irrigation only the lightest breakfast should be allowed. A large enema of sodium bicarbonate, 1 dr. to the pint, should be given half an hour before the irrigation in order to clear out the bowel. The apparatus is then fitted together, securely tied, and sterilized. Rubber gloves should be worn by the operator, if possible, in order to avoid infecting himself, and the irrigating fluid should be given at a temperature of 100° to 110°F.

If the patient is sufficiently robust the knee-elbow position is best, but in much debilitated patients this is not advisable. The foot of the bed should be raised slightly to facilitate the flow of fluid. In severely debilitated

patients it is best to place the patient on a waterproof sheet with the buttocks well padded with tow or wool. The rectal tube is well greased with vaseline, the apparatus filled with the irrigating fluid, and the tubing constricted whilst the rectal tube is gently inserted for a distance of about 3 inches. The rectal tube should not be inserted for a further distance, as it may kink, or even cause perforation of the ulcerated gut, and the so-called ' high rectal tube ' is useless. The funnel is now raised to about one foot above the anus and the fluid run in at the rate of about one inch level per minute, by alternately raising and lowering the funnel for a distance of about two feet. The patient should be encouraged to retain the fluid for as long as he can. Lateral pressure on the buttocks aids in the retention of the fluid, especially when the patient feels that he has taken all that he can manage. The injections may be given daily or on alternate days.

Intestinal antiseptics do not appear to be of much value in these severe cases but salol and pulv. ipecac. co. may be given by the mouth. Serum treatment is useless. If vaccine treatment is adopted, it is necessary to proceed with extreme caution, since too large a dose may cause the whole condition to flare up. The initial dose with a vaccine of Shiga's bacillus should not exceed a dose of 5 million, and with Flexner's bacillus a dose of 10 million. The treatment of secondary infections of the gut is often important.

In general, the treatment of these severe cases consists in adequate nursing, and seeing that the patient has a sufficiently nourishing diet with adequate vitamines. Cæcostomy, followed by daily irrigation of the entire colon with warm boracic solution, may be of value in the treatment of such patients as are not too debilitated to stand the shock of operation.

(*b*) *Mild Cases and Carriers.*

The first thing, if possible, is to get the patient into hospital and put to bed. This will give rest to the ulcerated colon, and afford opportunities of obtaining fresh material for laboratory examination, sigmoidoscopy, a barium meal and radiography, etc. It is a mistake to try and treat these cases as out-patients, as one wants them under full control and observation. With regard to diet, two things are important : that the patient should not be starved, and that he should not get sick to death of milk. In Flexner bacillus infections the patient should be kept on a more or less protein diet.

Nursing is important, a careful recording of the temperature, reporting the number and character of the stools, seeing that the patient avoids chills and gets adequate nutrition. Patient, nurse and doctor should work together harmoniously and with confidence in each other.

Serum treatment in these cases is useless, but *bacteriophage* treatment may prove very valuable. A dose of 1 c.c. is given on an empty stomach every day

for three days. Some of our cases have done very well on this treatment, but it seems to be very important to secure a potent and selected brew of bacteriophage.

Vaccine therapy is especially indicated in these cases. In the case of a Shiga bacillus infection it is very necessary to go cautiously; an initial dose of only 5 million organisms should be given, and the dose gradually raised to 50 million or so. In Flexner bacillus infections the initial dose may be 10 million organisms, and the patient may be gradually worked up to 100 to 150 million. The injections should be given twice a week or so, and intradermally, not subcutaneously. Reaction will be shown on the temperature chart and in the character of the stools. If there is a sharp febrile reaction or an attack of diarrhœa following after the injection, this is an indication that the dose of vaccine is probably too high, and it should be reduced, or the same dose be repeated at the next injection.

As adjuvants to this line of treatment iodine may first be mentioned. In many of these chronic intestinal conditions there is a deficiency in the iodine intake and hence a condition of hypothyroidism. It may be given either intravenously, in doses of 3 to 8 minims of the tincture well diluted with saline, or by the mouth, 5 minims in a little milk. Scott's method of calcium and parathyroid treatment is very useful for some of these cases which are probably associated with parathyroid deficiency; it consists in giving parathyroid extract, gr. $\frac{1}{10}$ twice a day, and cachets of calcium lactate, 15 to 20 grains three times a day after food. This treatment is especially appropriate if there is any indication of gastric or duodenal lesions as complications.

The condition of the bowels must be kept regular. If necessary a dose of liquid paraffin may be given every evening. To combat stasis a well-fitting abdominal belt may be necessary, and often gives the patient great comfort. Abdominal massage along the direction of the colon will often do far more for the patient's recovery than any surgical interference.

In the neurasthenic type of case endocrine therapy is indicated to combat the endocrine insufficiency. Desiccated thyroid gland should be given in very small doses, gr. $\frac{1}{6}$ to gr. $\frac{1}{4}$, on an empty stomach twice a day. In administering adrenalin and pituitrin, it is best to begin by giving these drugs hypodermically, so that one gets the patient under their full influence, before changing to oral administration. A daily hypodermic injection of 0·2 c.c. of 1 : 1,000 liquor adrenalin with 0·5 c.c. of liquor pituitrin may be given daily for three days. A change is then made to oral administration, and gr. $\frac{1}{4}$ to gr. $\frac{1}{2}$ of suprarenal extract, with gr. $\frac{1}{4}$ to gr. $\frac{1}{2}$ of post-pituitary extract is added to the prescription of thyroid extract and given twice daily. It may also prove advisable to add gr. 2 of gonad extract to the above prescription. The practitioner should remember that all these endocrine preparations are very hygroscopic, that they contain much

protein, and are liable to decompose on storage and in wet weather. The endocrine treatment should be continued for from 3 to 6 weeks.

Alcohol as a rule is contra-indicated, but if the patient is restless and sleepless bromides or other sedatives may prove useful.

To sum up, the successful treatment of these cases entirely depends upon making a most careful assessment of the conditions and factors present, and in securing the confidence and co-operation of the patient. It is surprising how well many of these neurasthenic patients do under such conditions.

CHAPTER VII.

Chronic Amœbiasis and the *Entamœba histolytica* Carrier.

At one time it was thought that *Entamœba histolytica* caused amœbic dysentery and hepatic abscess and nothing else. The carrier condition was supposed to be an instance of almost perfect symbiosis between parasite and host; the carrier showed no symptoms, but was chiefly a danger to others. Since the Great War, however, and within recent years our views of the carrier condition have been considerably modified, and we now regard intestinal infection with *E. histolytica* as being usually associated with symptoms of amœbic colitis, and amœbic dysentery and amœbic hepatitis as uncommon complications of amœbic colitis. The carrier may show either constipation or irregularity of the bowels; he is a potential danger to himself and to others; secondary organisms may invade his blood-stream through the ulcers produced in his gut; whilst the entamœbæ themselves may get into his liver, and set up anything varying from a mild hepatitis to acute liver abscess.

It may be asked whether *E. histolytica* is by itself capable of invading the uninjured mucosa of the colon. During the last few years a certain amount of evidence has been brought forward to show that this parasite may occasionally live free in the lumen of the gut (where it possibly feeds upon bacteria), without invading the mucosa. The work of Sellards and Leiva (1923*a*), which has already been commented on, shows that intestinal stasis together with a fluid condition of the contents of the colon may be important contributory factors to the invasion of the gut. It is possible that *E. histolytica* can only invade the mucous membrane of the colon in the presence of intestinal stasis and where some other organism—such as the *Bacillus dysenteriæ*, the paradysentery bacilli, or even *Trichuris trichiura*—has already caused a breach in the continuity of the mucosa.

The degree of ulceration in the carrier state varies very much, and with it the degree of intensity of the intestinal symptoms. There is a curious idea which is still very prevalent that a 'histolytica carrier' is a person who is carrying the *cysts* of *E. histolytica* in his intestine, such a person often being erroneously referred to as a 'cyst carrier'. As Dobell and O'Connor (1921) point out, this confusion of thought is as illogical as it would be to consider a person infected with hookworms as an 'egg carrier'. The patient infected with hookworms passes their ova in his

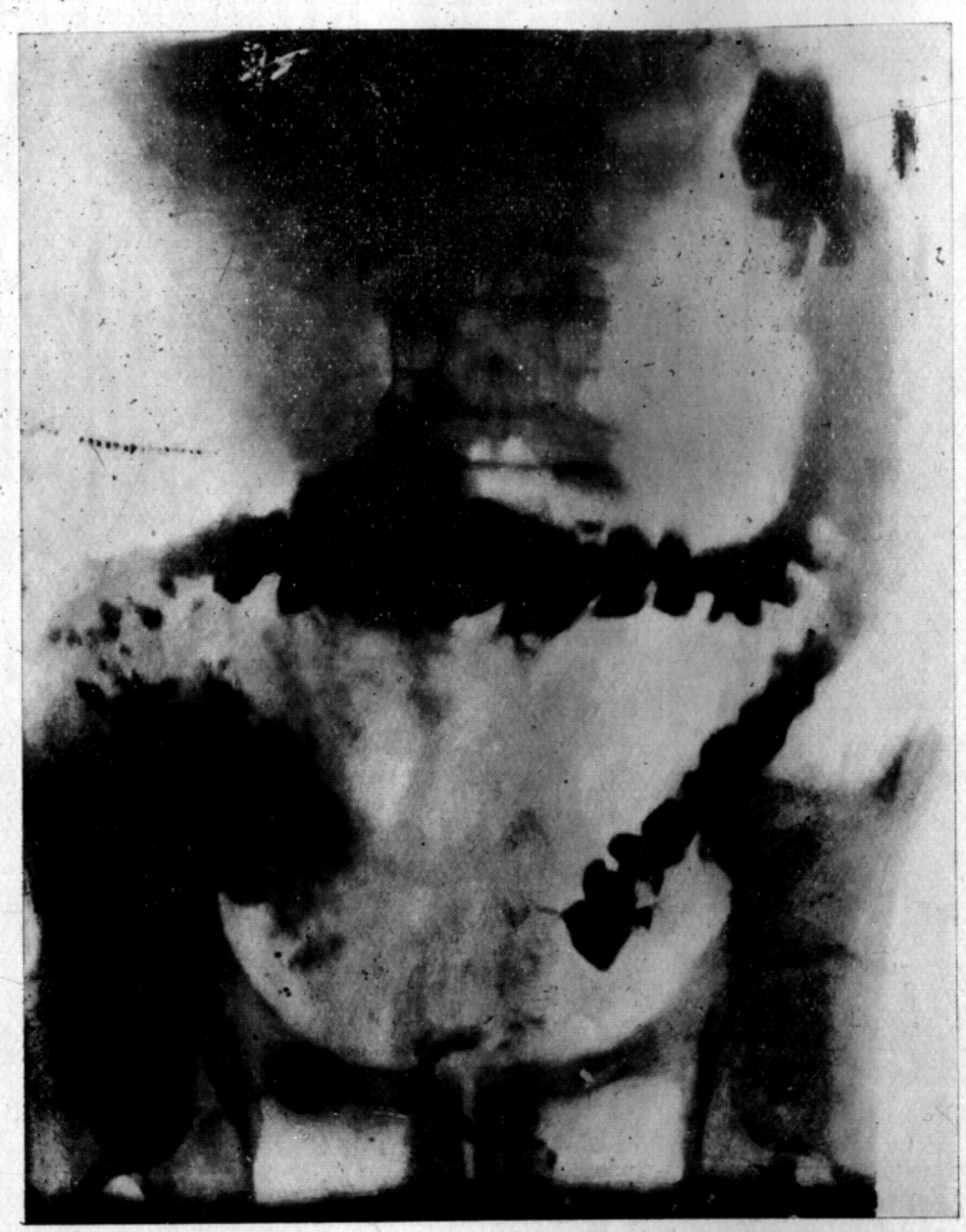


FIG. 25. Anglo-Indian male, 33 years. Chronic, relapsing amœbic dysentery: attacks in 1916, 1922, and 1926. The last attack had lasted off and on for six months prior to his admission to hospital. Stools formed or semi-formed with adherent mucus and blood. Charcot-Leyden crystals and cysts of *Entamœba histolytica* present. No dysentery bacilli isolated on repeated cultures. No helminthic ova seen.

Skiagram 24 hours after a barium meal. Patchy ulceration at the hepatic flexure.

FIG. 26. Amœbiasis with severe symptomatology. Skiagram after a barium meal, showing general intestinal ulceration, especially of the hepatic flexure.

(After Vallarino, 1924.)

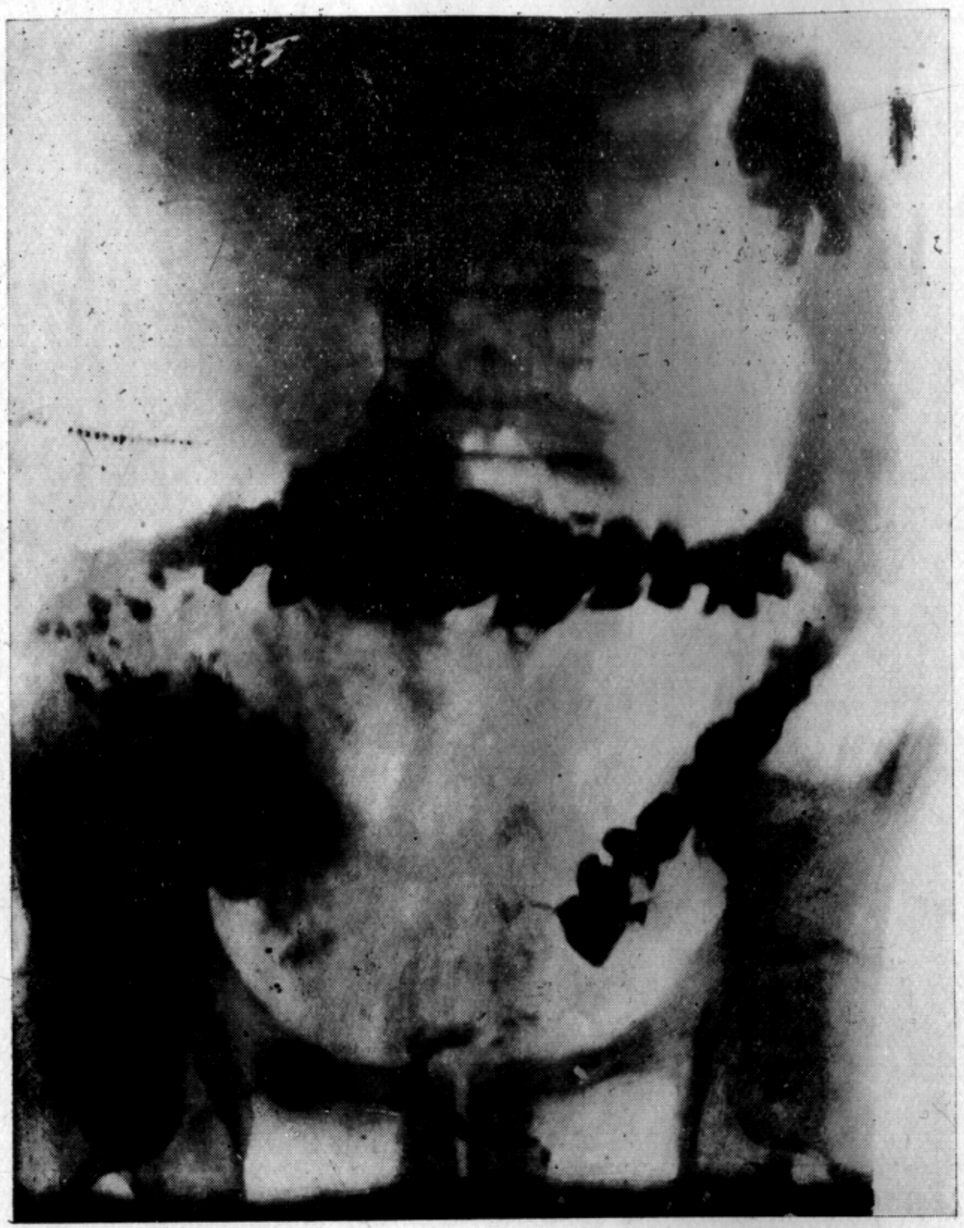


FIG. 25. Anglo-Indian male, 33 years. Chronic, relapsing amœbic dysentery: attacks in 1916, 1922, and 1926. The last attack had lasted off and on for six months prior to his admission to hospital. Stools formed or semi-formed with adherent mucus and blood. Charcot-Leyden crystals and cysts of *Entamœba histolytica* present. No dysentery bacilli isolated on repeated cultures. No helminthic ova seen.

Skiagram 24 hours after a barium meal. Patchy ulceration at the hepatic flexure.

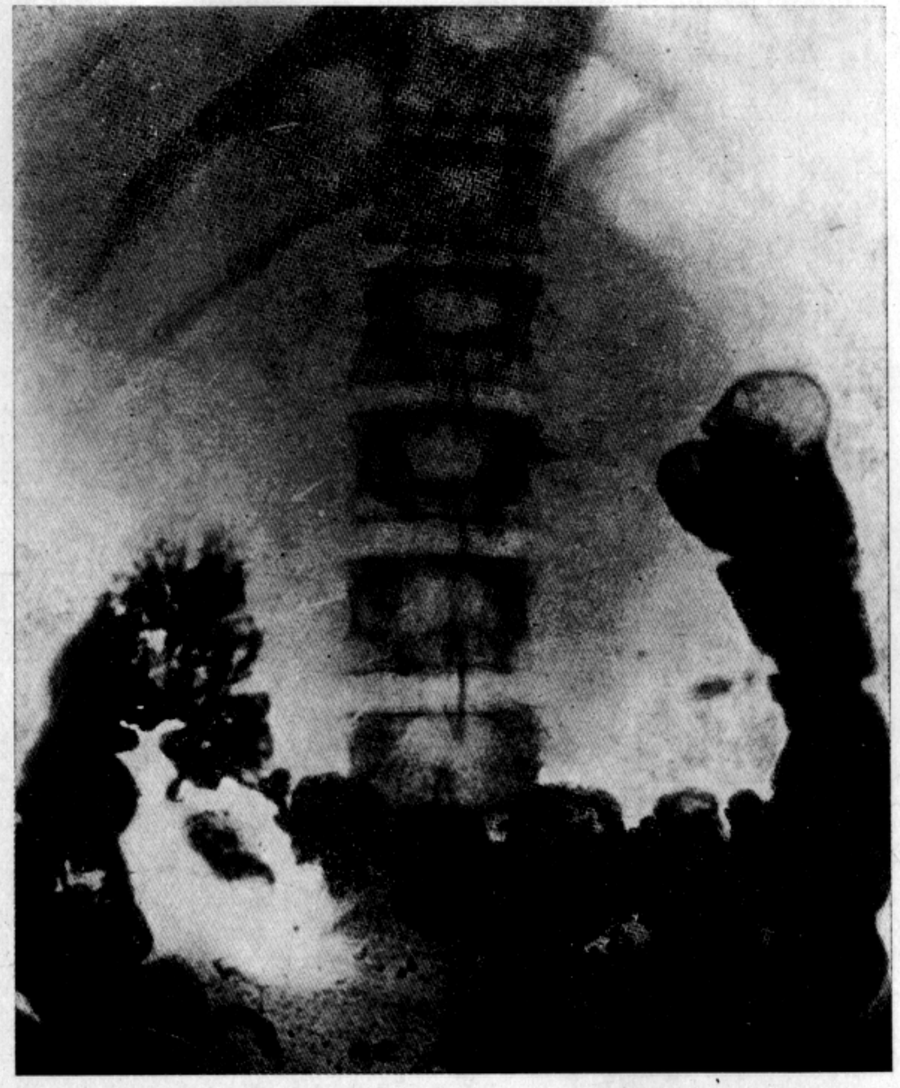


FIG. 26. Amœbiasis with severe symptomatology. Skiagram after a barium meal, showing general intestinal ulceration, especially of the hepatic flexure.

(After Vallarino, 1924.)

FIG. 27. Slight amœbic infection with light symptomatology and no history of dysentery. Slight patchy ulceration of cæcum and hepatic flexure. Appendix patent.

(After Vallarino, 1924.)

stools; similarly the 'histolytica carrier' has active, motile, vegetative *E. histolytica* living in and at the expense of the mucous membrane of his colon, and from these vegetative forms are derived the cysts which are passed in his formed stools. Should such a person contract bacillary dysentery or diarrhœa due to non-amœbic causes he may commence to pass scanty motile vegetative forms of *E. histolytica* in his stools, a source of considerable confusion to the inexperienced laboratory worker. Finally, should the local resistance of such a carrier be unduly reduced from extraneous causes, he may go down with an attack of true amœbic dysentery.

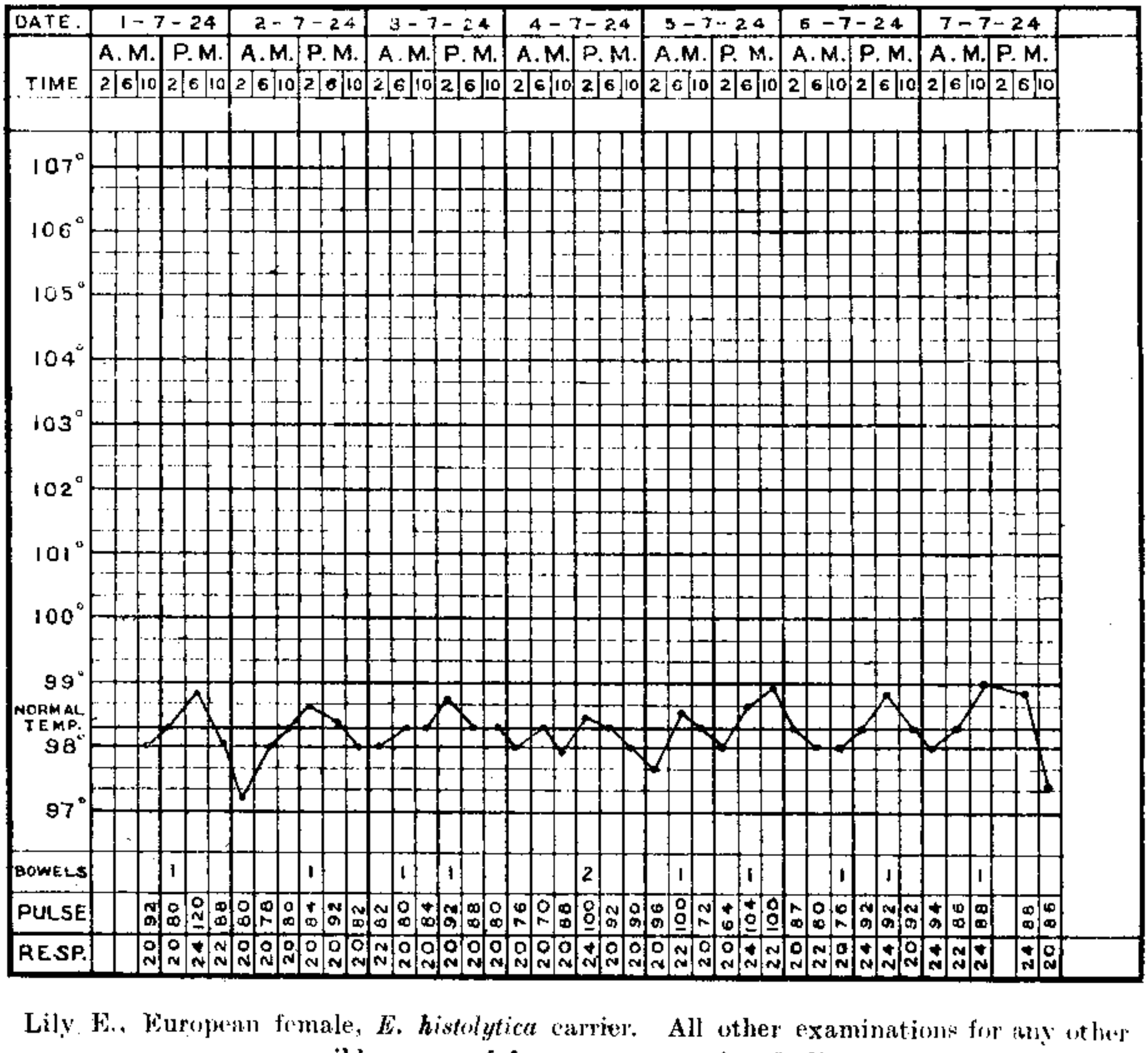
The degree of ulceration of the colon mucosa in the carrier state varies very considerably, but it is surprising how extensive it can be in the absence of symptoms. Musgrave (1910) and Bartlett (1917) record quite extensive ulceration of the colon, unaccompanied by symptoms. Armitage (1919) records a very interesting case of a patient who had never had any symptoms of dysentery, but was a contact carrier of *E. histolytica*; he acquired a typical liver abscess, and when this was cured an amœbic abscess of the brain developed, from which he died. During the war in Mesopotamia six lascars were accidentally suffocated in the bottom of a barge where they had lit a fire and closed the hatches before going to sleep. On post-mortem examination one of the six showed two small ulcers in the cæcum, each about the size of a round four anna bit, with numerous *E. histolytica* present in the cæcal contents, and also in nests in the submucous tissue of the cæcal wall, as seen in sections. A second showed a small ulcer in the region of the splenic flexure, with cysts of *E. histolytica* in the gut contents, and vegetative forms present in sections of the gut wall. Both these men were on the active list; they had not recently been in hospital, and would have been classified as being in ordinary good health. A case is recorded in the war literature of an officer who was on the active list and suddenly died from perforation of the cæcum. At autopsy amœbic infection was found to be the cause. The reason for the usual absence of definite intestinal symptoms in the carrier state is probably because the lesions are usually limited to the cæcum and the ascending colon.

Signs and Symptoms of the Carrier State.

Clinically, we are wont to recognize two well marked types of *E. histolytica* carriers: the first, the lean, thin—sometimes cadaverous—individual with a muddy complexion, and usually neurasthenic. His food assimilation is inadequate; he tends to be faddy and irritable; he is vaguely ill without knowing what is wrong with him; he is habitually constipated and always taking drugs to cure the constipation. The second type is the fat and jovial *bon viveur* who is apt to suffer from rather chronic morning diarrhœa, especially if he has had a 'short' drink or two at the club the previous evening, apt to get a little fever, and occasionally to feel vague pains in his liver.

Together with minor ulceration of the colon mucosa goes a train of ill-defined symptoms, the elements of which may be presented as follows :—

(*a*) *Irregularity in the state of the bowels.* The *E. histolytica* carrier has usually marked irregularity in the state of the bowels. Marked constipation may be a symptom, so that purgatives may have to be taken daily. This is especially seen in the adult European female where a previous attack of amœbic dysentery has been followed by visceroptosis. On the other hand there may be constipation for two or three days, followed by a morning of diarrhœa with frequent stools ; the lower



Lily E., European female, *E. histolytica* carrier. All other examinations for any other possible cause of fever gave negative findings.

down the colon the greater the tendency to looseness of the bowels. Some patients may have two or three stools every morning, often with adherent mucus on them, and then be comfortable for the rest of the day.

(*b*) *Pain*, usually described as vague and colicky, and not infrequently setting in half an hour or so after meals. This may be associated with lesions of and sometimes adhesions in the hepatic and splenic flexures, whilst hyperchlorhydria may sometimes be present.

(*c*) *Fever* of a low, erratic and irregular type, often not perceived by the patient, and only to be detected by taking a four hourly temperature chart, the temperature showing occasional rises to 99° or 99·6°F., sometimes with a daily rise, suggestive of early amœbic hepatitis, but without any localizing symptoms in the liver. The temperature chart shown above is such an instance ; it is of a European female patient, aged 17, who was a carrier of *E. histolytica*, where all attempts to find any other cause for the low fever failed, but where combined bismuth and emetine treatment cured the fever. The fever is often associated with considerable lassitude, coming on in the evening.

If we are to understand the ætiology of these symptoms it must be remembered that the ulcerations are usually situated in the cæcum and ascending colon, sometimes at the hepatic flexure, more rarely in the splenic flexure, and most rarely of all in the pelvic colon and rectum. When a peristaltic wave starts it is often blocked at these ulcerated sites, with the result that the intestinal contents are dammed back into the cæcum, which becomes full, and is frequently easily palpable, with a good deal of gurgling. If this condition is not relieved the cæcum becomes enormously distended and empties every second to fourth day with a sharp attack of diarrhœa. The intestinal stasis leads to the production of such putrefactive epd products as indol and skatol, and these may be found in excess in the urine. Absorption of these toxins from the gut leads to :—

(1) A condition of chronic indigestion, as the toxins cause pyloric spasm (which is frequently very well seen in skiagrams of such cases) and hyperchlorhydria. These cases are frequently mistaken for duodenal or gastric ulcers, and not infrequently operated on without relief of the symptoms. Sometimes however the gastric functions are depressed and hypochlorhydria is present.

(2) Depression of the general metabolic functions, the patient becoming slack, irritable and frequently neurasthenic.

(3) Stimulation of the blood-vessels and involuntary muscles, with the onset of such symptoms as asthma, urticaria, giant urticaria, etc. (We do not claim for a moment that these conditions are always due to *E. histolytica* infection, but in many such patients, examination of the stools will show the carrier condition to be present, and emetine treatment will clear up the asthma or urticaria.)

With the cæcal stasis there is very apt to be a patent appendix containing fæcal matter, the mucous membrane of which may from time to time be catarrhally inflamed. Many of these patients show the scar of an appendicectomy operation, but complain that the operation has not cured their symptoms.

In the stout, jovial type of carrier, intestinal stasis is much less marked, but signs of active disease are rather more pronounced. He will have two or three loose stools each morning, and a certain grade of fever up to 99·6°F. towards evening. It is particularly in this type of case that there is danger of embolism, either of

E. histolytica into the portal circulation or of streptococci into the general circulation.

These patients appear to run a more definite risk of liver abscess than do the other type.

With ulceration present in the gut it is obvious that embolism may occur. This may be of different types :—

(1) *Amœbic showers.* We do not think that the medical profession in this country has as yet properly appreciated the frequency of a low grade of hepatitis due to *E. histolytica* infection in the carrier state. It is probable that in most *E. histolytica* carriers amœbæ from time to time make their way into the portal blood-stream and get into the liver. Clark (1924) records that at post-mortem examination of 186 persons who had died from amœbic dysentery, 95 persons—or 51 per cent—showed major or minor amœbic lesions of the liver. Solitary abscesses were present in 40 patients, and multiple abscesses in 55. Sir Leonard Rogers (1925) found that the incidence of cirrhosis of the liver in 1,600 autopsies held in Calcutta was 5·91 per cent as against a corresponding figure of 1·3 per cent for 1,000 post-mortems held in London ; after a full discussion of the possible causes for this large excess in the Bengal figures he concludes that it is mainly due either to direct infection of the liver with *E. histolytica* and chronic irritation, or else to the absorption of poisonous principles from the gut in cases of amœbic ulceration of the colon. It is probable, indeed, that in the majority of persons suffering from *E. histolytica* infection of the colon, repeated small infections of the liver occur. Usually these are not attended by any symptoms ; sometimes there may be a mild grade of hepatitis, associated with low fever, but not with abscess formation ; more rarely there is actual liver abscess.

(2) *Streptococcal showers.* Streptococci are normally present in the contents of the colon, but are of non-hæmolytic type. If the stool of a 'healthy' carrier be plated on Conradi-Drigalski medium their colonies can be isolated as very minute, translucent, dew-drop-like colonies. Every one of the sweepers at the Calcutta School of Tropical Medicine is a 'healthy' carrier of *E. histolytica*, and in none of them have we been able to isolate hæmolytic streptococci, though non-hæmolytic strains are frequently present. On the other hand, if the stool of a carrier with vague symptoms be plated, hæmolytic strains of streptococci—corresponding to the *Streptococcus anginosus* of Andrewes—are frequently isolated. These may escape from the ulcerated gut through the ulcers into the blood-stream and cause various types of lesions. Thus there may be brachial or sciatic neuritis, myositis, such as lumbago or wry-neck, mono-articular synovitis or even multiple synovitis of several small joints, such as those of the hand, whilst—very exceptionally—they may produce duodenal ulcer. If the modern view of the production of duodenal ulcer be accepted, that it is due to toxic or bacterial embolism from some focus, such as burns or a septic dental socket, then we must realise that chronic amœbic

ulceration of the colon may also—though very rarely—give rise to it. These streptococcal infections of the blood-stream may produce a fairly severe grade of anæmia. The streptococci can only very rarely be isolated on blood culture, since their presence in the blood-stream is intermittent and they are very scanty. They are excreted by the kidney, however, and may set up a pyelitis or give rise to inflammation which ends in calculus formation.

The best way to isolate these streptococci is to take a 25 c.c. specimen of urine from the patient by catheter direct into a small sterile flask. The flask itself is then placed for 24 hours in the warm incubator. Next day the growth of streptococci will be found as tiny wisps or flocculent balls, and can be subcultured on blood-agar to test whether it is a hæmolytic strain or not.

(3) To complete the picture we must add that *streptothrix infection* of the blood-stream may occur, though it is very rare. The species present is generally the *Discomyces asteroides* of Eppinger, and it causes a portal pyæmia or—more rarely—a cerebral abscess.

A condition which is not infrequently associated with chronic intestinal amœbiasis is leucoderma. In these cases it would seem that, with the change in the bacterial flora of the gut associated with the amœbic infection, the precursors from which the melanin of the body is ultimately produced are absent, and hence leucoderma results. In all cases of leucoderma it is important to examine the stools for *E. histolytica* infection, since, if it is found and treated, this may lead to cure of the leucodermic state.

Finally, owing to his lowered state of general resistance, the chronic *E. histolytica* carrier is more liable than is the healthy individual to the onset of intercurrent disease, such as bacillary dysentery, kala-azar, cholera, etc.

The Diagnosis of the Carrier State.

In addition to a careful record of the patient's history and symptoms, abdominal examination should be carried out. In many of these cases the cæcum and ascending colon, or sometimes the sigmoid flexure, will be found to be thickened and definitely palpable.

The sigmoidoscope is not as useful in the chronic amœbic carrier state as in subacute, and especially chronic and relapsing amœbic dysentery, since the ulceration usually affects the upper part of the colon. A few small sea-anemone-like ulcers with white or yellow sloughs attached to their bases may be found sometimes, however.

Radioscopy is of special value in these cases, both from the point of view of diagnosis and of getting information as to the extent of the lesions and the portions of the colon affected. An excellent account of the radiographical findings in such cases is that given by Vallarino (1924). He points out that a series of photographs taken after a barium meal are better than photographs taken after administration

of a large enema of barium salt, as under the latter circumstances the fluid is forced against the direction of peristalsis and abnormal appearances may result, whereas after the barium meal the barium fills the lumen of the gut naturally and remains in any small pockets of ulceration. The whole of the colon should be photographed in a series of photographs taken 12, 18, 24 and 30 hours after the barium meal. He records finding defects in all cases of amœbic infection associated with definite symptoms. The bowel loses its normal contour in the part affected and a mottled area is found instead, the extent of the mottling depending on the degree of ulceration present. The majority of the lesions were found in the cæcum and ascending colon, next in frequency in the sigmoid flexure, less often in the transverse and descending colon. The lesions in the carrier state are often minimal, consisting of small scattered patches of defect in the cæcum and ascending colon, in which the barium lodges and remains after the rest of the meal has passed on.

Laboratory Diagnosis.

Here, in the first place, it is of the utmost importance that the stools shall be as fresh as possible, for the cysts of *E. histolytica* commence to degenerate in the passed fæces and, with the exception of a proportion of the mature cysts, may all have degenerated within a few hours and be no longer recognizable.

The macroscopic character of the stool will vary with the intestinal state of the patient, but *in all cases there is visible mucus.* In the lean type of carrier the stool is usually a hard, formed one, with streaks of mucus over the scybalous masses. In this case the mucus should be examined and the fæcal matter near it. The findings here usually will be both large and small cysts of *E. histolytica* and Charcot-Leyden crystals, but on plating streptococci are not found as a rule. In the other, the stout type of carrier, the stool is frequently a mucoid and diarrhœic one. Here one will usually find a few pre-cystic or even small motile vegetative forms of *E. histolytica,* cysts at all stages of development and generally of small size, and Charcot-Leyden crystals. In these cases streptococci are usually numerous and are frequently of hæmolytic type.

The laboratory worker should never be content with a single negative finding. Emulsions must be made in both saline and iodine, for in the former the characteristic chromatoid bars of the cyst of *E. histolytica* are unmistakable, and in the latter nuclear detail stands out. The examination of stools for the cysts of *E. histolytica* is not easy, and the more experienced the laboratory worker the more difficult he recognizes such a procedure to be. The mere presence of entamœbæ or of entamœbic cysts of any type in the stool does not constitute evidence of *E. histolytica* infection ; it is necessary to be certain that the entamœbæ or cysts are those of *E. histolytica.* And to the laboratory worker who is still uncertain as to the identification of the cyst of *E. histolytica* we would recommend two procedures : the first the careful study of Dobell and O'Connor's *Intestinal Protozoa of Man,*

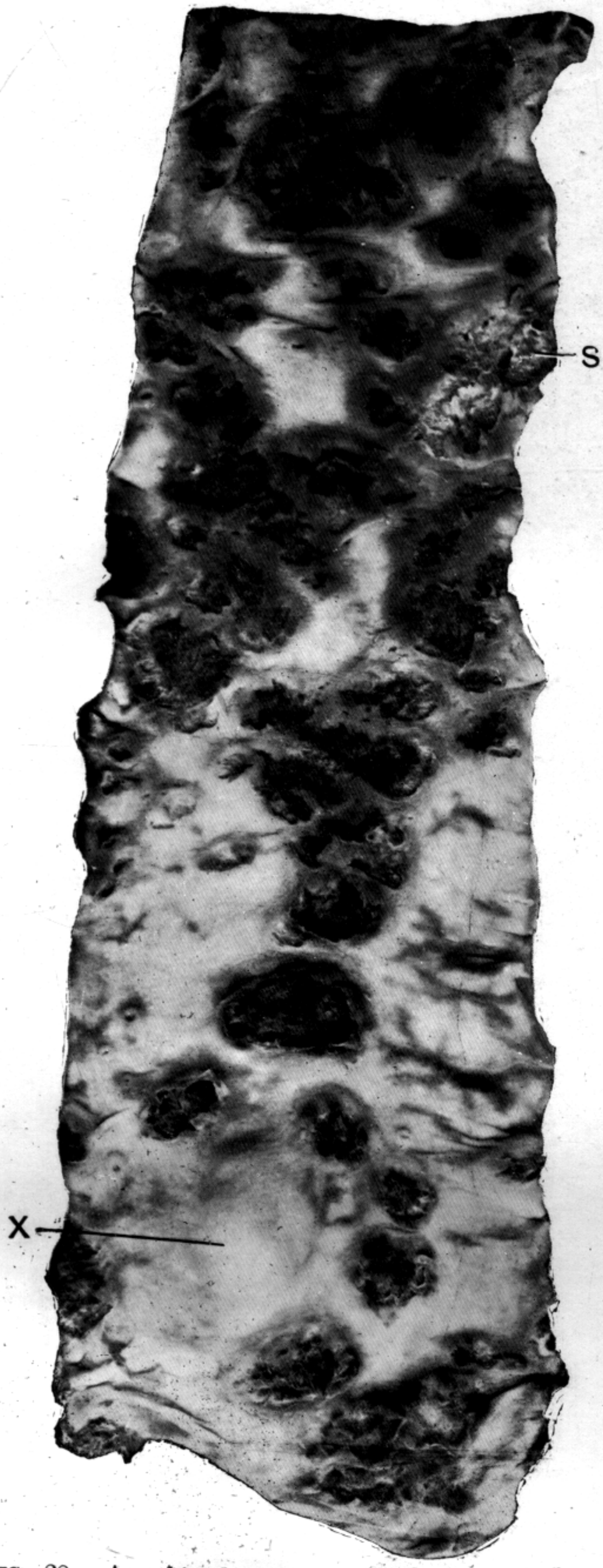


FIG. 28. Amœbic dysentery. Thinning and ballooning of intestinal wall at point marked X in descending colon. The black sloughs have been scraped away from the two ulcers marked S, exposing the yellow base.

(After Fletcher and Jepps, 1924.)

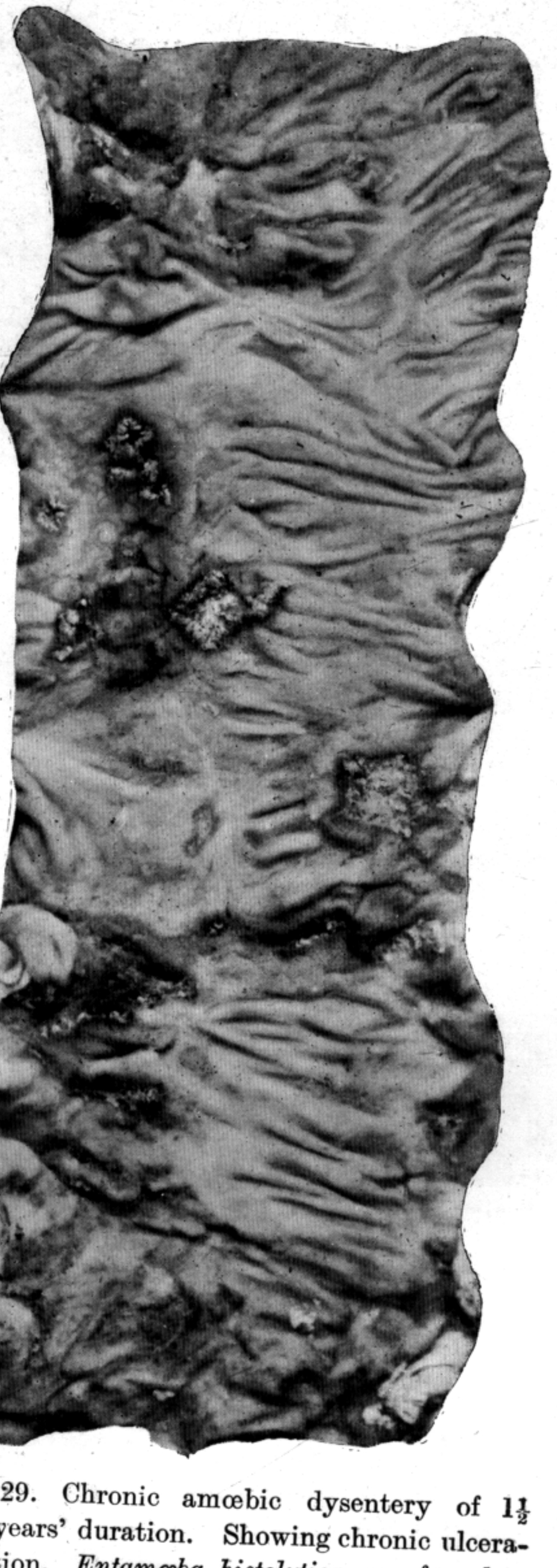


FIG. 29. Chronic amœbic dysentery of 1½ years' duration. Showing chronic ulceration. *Entamœba histolytica* was found in scrapings from the ulcers. No dysentery bacilli were isolated. There was great thickening of the intestine in places, and the *appendices epiploicæ* were much enlarged.

(After Fletcher and Jepps, 1924.)

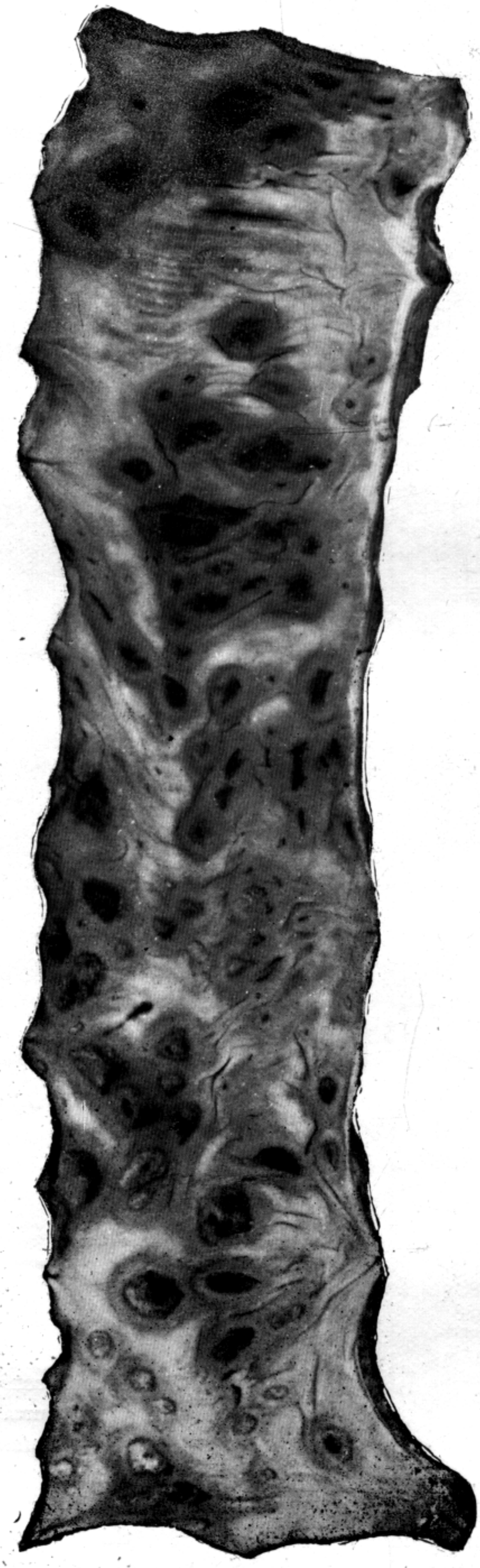


FIG. 30. Amœbic dysentery. Healing ulcers in the rectum.
(After Fletcher and Jepps, 1924.)

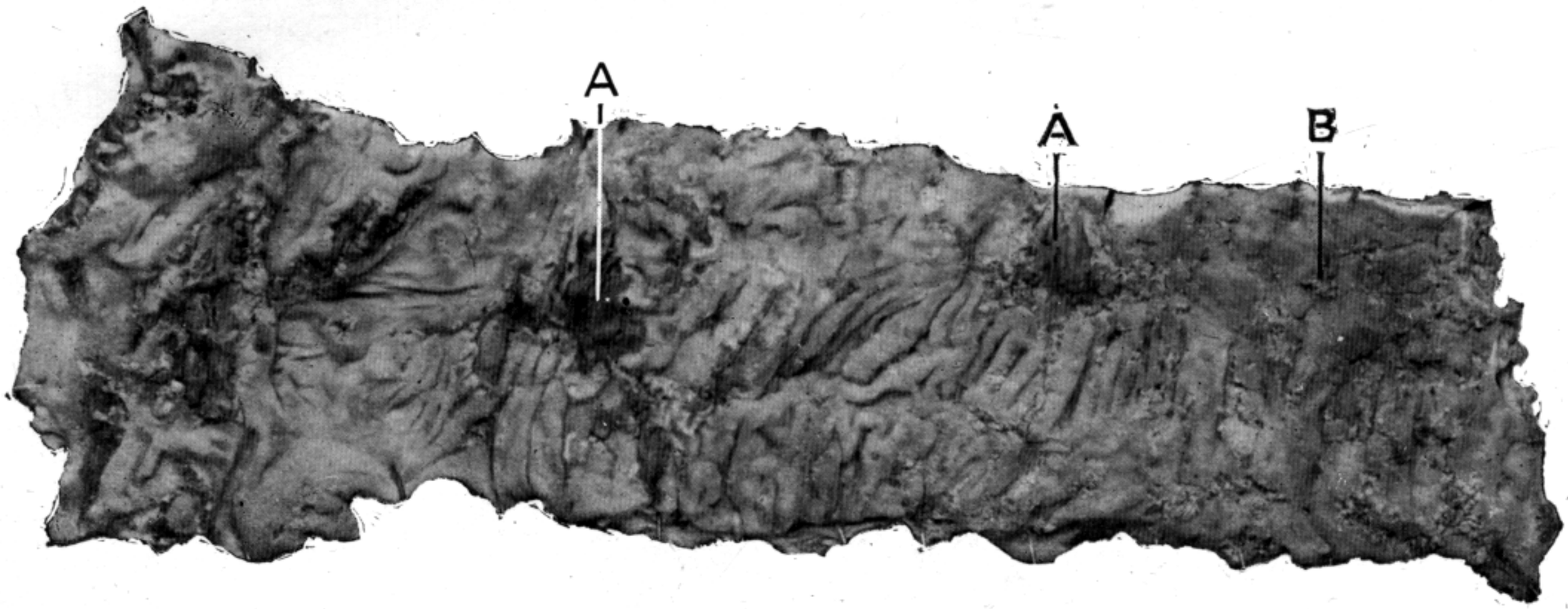


FIG. 31. Mixed bacillary and amœbic dysentery. Descending colon, showing several dark, amœbic ulcers (marked A) and bacillary catarrh (marked B). History of repeated attacks of dysentery. The ascending colon was much thickened and contained numerous ulcers of the amœbic kind, while there was bacillary catarrh in the descending colon and rectum. There was a large amœbic abscess in the right side of the liver. *B. dysenteriæ*, Flexner, was isolated from the stools and *Entamœba histolytica* found in them the following day. (After Fletcher and Jepps, 1924.)

and the second the repeated and careful examination of the stools of sweepers, in which sooner or later typical cysts of all the four common intestinal entamœbæ of man will be encountered. The study of such material is an education in itself.

A good way of preparing the iodine emulsion for study in such cases is to grind up a portion of the stool in the iodine solution with a pestle and mortar, and then to centrifuge the emulsion so made. The supernatant fluid is then thrown away, and a tiny particle of the deposit picked up in a capillary pipette and emulsified in a small drop of saline on the slide, then covered with a cover-slip. By this method the cysts stand out very clearly, stained with iodine, against a colourless background.

The Cyst of Entamœba histolytica.

The pre-cyst of *E. histolytica* is smaller than either the vegetative or the encysted forms, thus constituting the ' minuta ' phase of the parasite's life-history (Fig. 14). The amœba in the lumen of the gut is considerably smaller than the vegetative form in the tissues, and this Dobell ascribes to a probable reduction in size by division. The amœba rounds up and becomes motionless, withdrawing all its pseudopodia into the body. All ingested red blood corpuscles are thrown out, whilst the nucleus becomes large relatively to the size of the body. At this stage it is very difficult to distinguish the pre-cyst of *E. histolytica* from the pre-cyst of *E. coli*.

In the pre-cyst of *E. histolytica*, however, the nucleus remains true to its ' histolytica ' characters ; it is invisible in saline, and when stained with iodine or in an iron-hæmatoxylin preparation shows the fine central karyosome and the thin deposit of chromatin on the inner aspect of the nuclear membrane.

A cyst wall is next secreted which is definitely thinner than that of *E. coli*. The nucleus is at first single and its diameter measures about one-third of that of the cyst. The most characteristic feature of the cyst of *E. histolytica* next appears, i.e., the laying down in the cytoplasm of chromatoid substance. According to Malins Smith (1918) chromatoid substance is present in 27 per cent of the cysts of *E. histolytica*, but Dobell (1919, p. 48) regards this as a serious under-estimate and considers that possibly a majority of cysts of *E. histolytica* contain chromatoid substance. The chromatoid substance is not fine, feathery and like splintered glass as in the cyst of *E. coli*, but massive. It is laid down in the form of large rods, bars, chunks and masses. Its visibility in saline varies considerably. Sometimes the chromatoid bars are so brightly refractile and stand out with such very great prominence that they are the most brilliant feature of the cyst when seen in saline. Sometimes, however, they are less refractile and less conspicuous. In iodine the chromatoid substance does not show up at all ; there is a palish area where the chromatoid bars lie less deeply stained than is the rest of the cyst. In iron-hæmatoxylin the chromatoid substance stains an intense jet black.

The amount of glycogen present in the cyst of *E. histolytica* varies, but there is never the enormous glycogen vacuole so characteristic of the bi-nucleate phase

Plate IV.

Cysts of the chief intestinal protozoa of man, as seen in a saline emulsion of the stool.

Figs. 1 to 6. Cysts of *Entamœba histolytica.*

Fig. 1. Mono-nucleate cyst with small glycogen vacuole.

„ 2. Mono-nucleate cyst showing two chromatoid bars and a glycogen vacuole.

„ 3. Tetra-nucleate cyst showing two chromatoid bars.

„ 4. Tetra-nucleate cyst in phase of early degeneration, with chromatoid substance not visible.

„ 5. 'Minuta' type of cyst with small glycogen vacuole.

„ 6. 'Minuta' type of cyst with two chromatoid bars.

Figs. 7 and 8. Degenerated cysts in a stale stool, showing progressive vacuolation of the cytoplasm, and breaking up of the nucleus and chromatoid substance.

„ 9 to 11. Cysts of *Entamœba coli.*

Fig. 9. Typical cyst at the bi-nucleate phase, showing the enormous glycogen vacuole.

„ 10. Typical mature 8-nucleate cyst. Nuclei at different levels within the cyst.

„ 11. Giant and aberrant type of cyst of irregular shape with 16 nuclei. These constitute a rare finding.

Figs. 12 and 13. Cysts of *Endolimax nana.* Note their thin cyst wall and the refractile volutin granules.

„ 14 and 15. Cysts of *Iodamœba bütschlii.* Note the thick cyst wall, irregular shape, dull grey glycogen vacuole and refractile volutin granules.

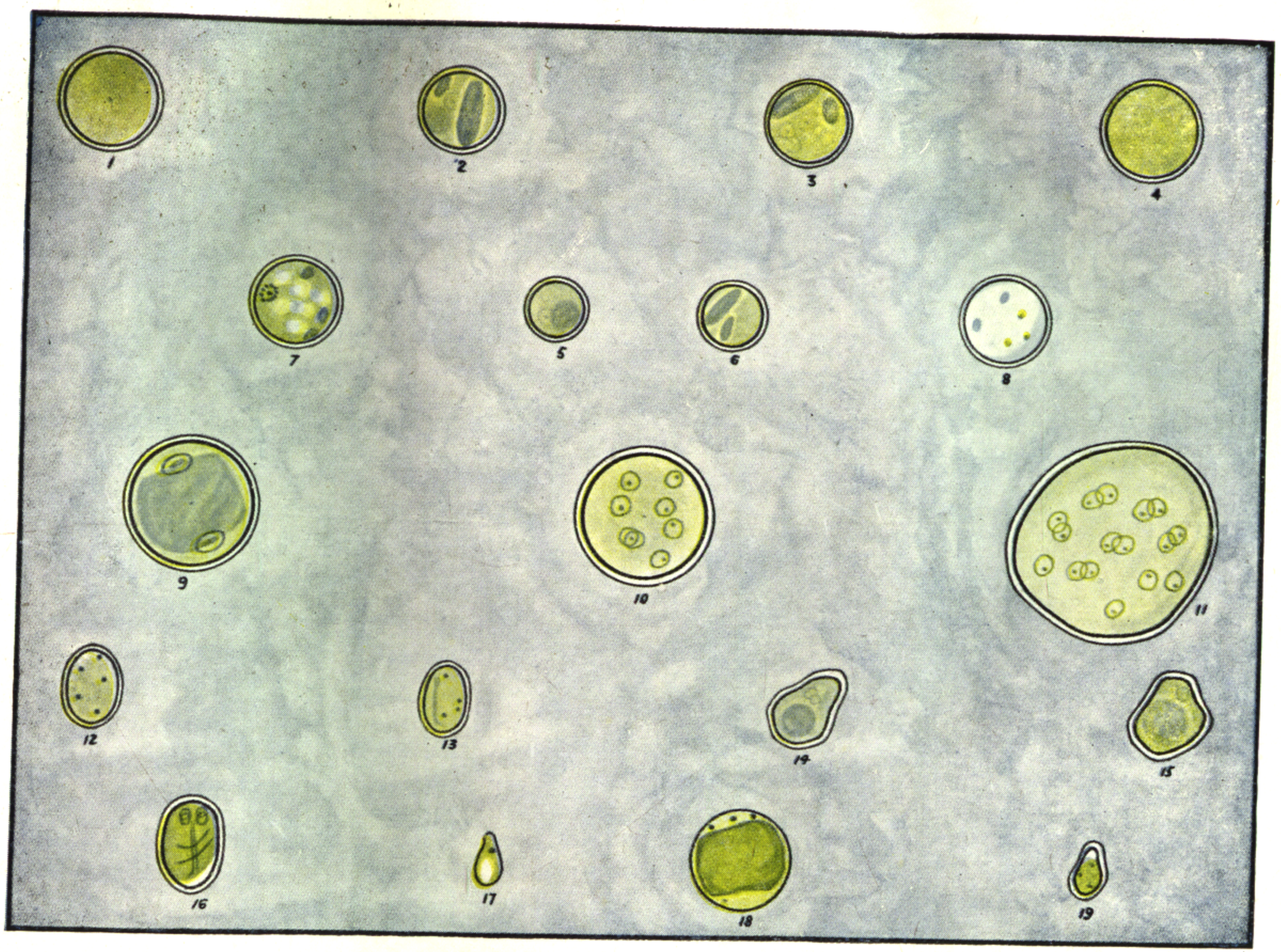
Fig. 16. Cyst of *Giardia intestinalis* at 4-nucleate phase.

„ 17. Pear-shaped, large yeast, for comparison.

„ 18. *Blastocystis hominis,* for comparison.

„ 19. Cyst of *Chilomastix mesnili.*

PLATE IV.



of the cyst of *E. coli*. In the mono-nucleate phase the cyst of *E. histolytica* may show a small glycogen vacuole, more commonly perhaps the glycogen is diffuse and stains as a diffuse brown area within the cyst in iodine. Glycogen can hardly be regarded as characteristic of the cyst of *E. histolytica*.

The nucleus next divides into two and then into four nuclei, and the cyst becomes mature (Fig. 14). As it does so the amount of glycogen seems to diminish and little or none is seen at the adult tetra-nucleate phase.

The adult cyst is a very characteristic structure. It has a smooth, thin cyst wall and is usually spherical—sometimes a little oval—in shape. The large and massive chromatoid bars are its most distinguishing features and they often stand out with very great prominence in saline. The nuclei are invisible in the saline preparation, but are well seen in the iodine preparation, and remain true to 'histolytica type' with fine central karyosome and thin peripheral deposit of chromatin on the nuclear membrane.

When seen in iodine the cyst tends to have a smooth hyaline look, which is in marked contrast to the beaded or granular appearance of the cyst of *E. coli*. Further, in the iodine preparation, the contents of the cyst often appear as if confused, so to speak, owing to the pale areas where the chromatoid substance is alternating with the more deeply staining other portions of the cyst.

With regard to variations a definite glycogen vacuole of small size is sometimes seen, but usually only at the mono-nucleate phase. It is to be noted that the chromatoid substance disappears gradually from the cyst after it has left the body, and not infrequently one encounters cysts which appear to have no chromatoid substance at all. Such cysts when seen in saline are often difficult to identify, since they show no structure within the cyst wall. In the iodine preparation of the same stool, however, the nuclei show up well.

Several authors have claimed that in the cyst of *E. histolytica* nuclear division sometimes overshoots the mark and a cyst with 8 nuclei is formed. This, however, must be very exceptional. Dobell says that he has never encountered an 8-nucleate cyst of *E. histolytica*, whilst the writers also have never come across such a finding in man.

With regard to size Dobell recognizes at least four different 'races' of *E. histolytica* with cysts whose mean diameters are 6·6 μ, 8·3 μ, 11·6 μ and 13 μ to 15 μ. It is important to note that the cyst of *E. histolytica* may be very small indeed; it is frequently as small as 6 μ in diameter and may even be as small as 5 μ in diameter. The cyst findings in the stool in the case of an infection with *E. histolytica* are more varied than in the corresponding case of an *E. coli* infection, and in a formed stool one encounters cysts at all phases, mono-, bi- and tetra-nucleate. Only some 53 per cent of cysts seen in the formed stool are at the mature tetra-nucleate stage.

Plate V.

Cysts of the chief intestinal protozoa of man, as seen in an iodine emulsion of the stool.
(The same cysts as in Plate IV.)

Figs. 20 to 27. Cysts of *Entamœba histolytica.*

Fig. 20. Mono-nucleate cyst with glycogen vacuole.

„ 21. Mono-nucleate cyst with glycogen vacuole and faintly showing chromatoid bars.

„ 22. Mature tetra-nucleate cyst with two chromatoid bars.

„ 23. Mature cyst in stale stool; chromatoid substance used up.

„ 24. 'Minuta' type of cyst at mono-nucleate phase.

„ 25. 'Minuta' type of cyst with two faintly showing chromatoid bars.

Figs. 26 and 27. Degenerating cysts with progressive vacuolation of the cytoplasm and nuclear fragmentation.

„ 28 to 30. Cysts of *Entamœba coli.*

Fig. 28. Typical cyst at the bi-nucleate phase, with an enormous glycogen vacuole.

„ 29. Typical mature 8-nucleate cyst.

„ 30. Giant and aberrant cyst with 16 nuclei.

Figs. 31 and 32. Cysts of *Endolimax nana.*

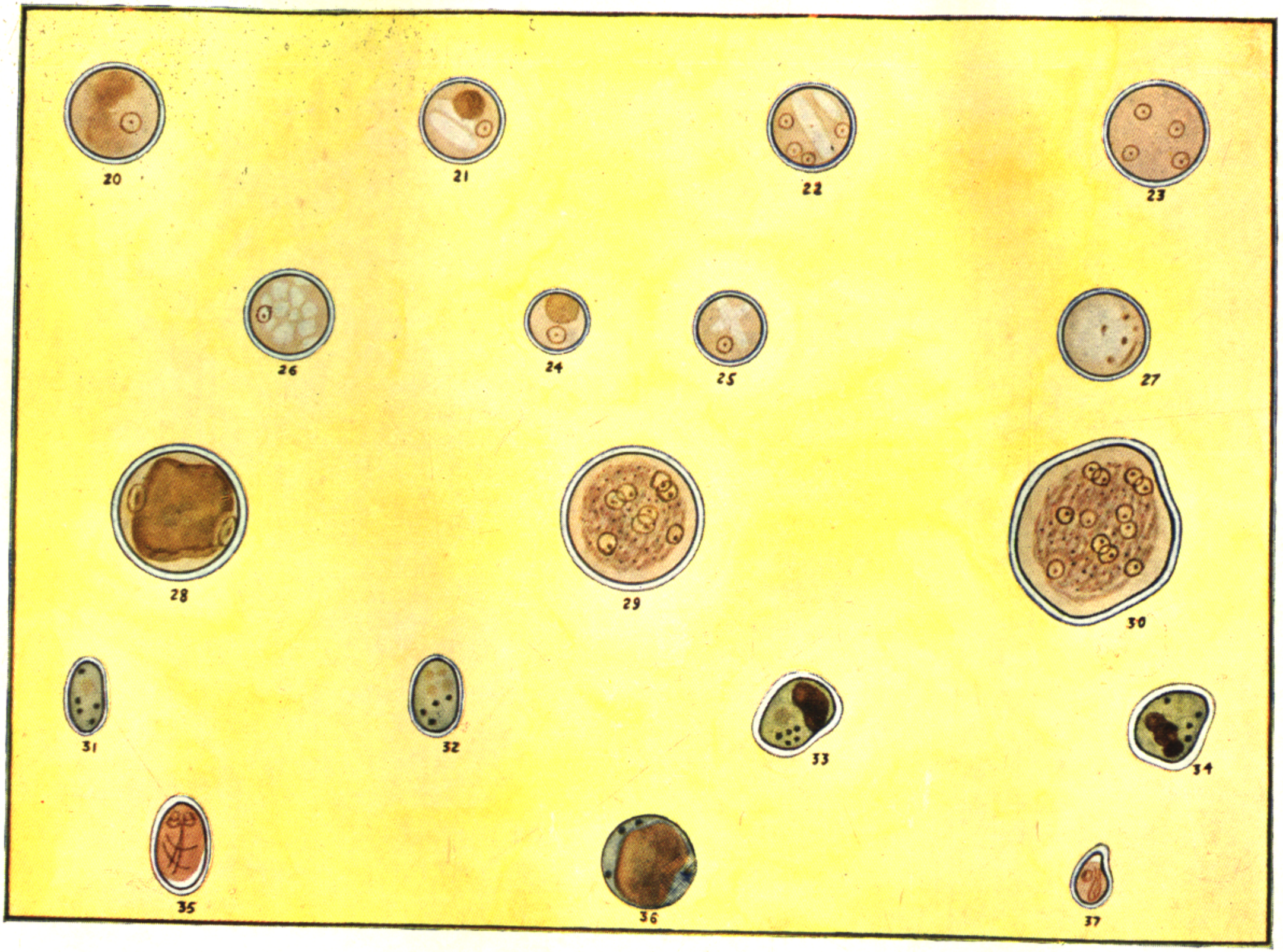
„ 33 and 34. Cysts of *Iodamœba bütschlii.* Note the very deeply staining glycogen vacuole.

Fig. 35. Cyst of *Giardia intestinalis* at 4-nucleate phase.

„ 36. *Blastocystis hominis*, for comparison.

„ 37. Cyst of *Chilomastix mesnili.*

PLATE V.



The cysts of *E. histolytica*, with the exception of some 50 per cent or so perhaps of mature tetra-nucleate cysts, degenerate slowly in the passed stool (Fig. 14). The nucleus breaks up and now becomes visible in saline as a distorted ring of brightly refractile chromatin beads. The chromatoid bars disintegrate, and any glycogen present becomes more and more diffuse and progressively less in amount. Vacuoles of a spherical type appear in the cytoplasm of the cyst, become larger and larger and fuse together. Ultimately we are left with little more than the thin cyst wall as a capsule containing an almost empty space within which lie a few remnants of the cytoplasm and chromatinic dots. Such degenerated cysts are very frequent in stale stools and it is almost impossible to diagnose them; the writers have frequently known them to be mistaken for *Blastocystis hominis*.

Mature cysts of *E. histolytica*, however, are relatively resistant. They will survive for several weeks outside the body of man if kept moist and cool. They will live for weeks in damp fæces or water without showing any conspicuous change except the loss of their chromatoid substance. Dobell states that the number of viable cysts in such a preparation steadily diminishes, after a fortnight only a few isolated survivors are present, but exceptionally some cysts may survive for five weeks. They are susceptible to heat, and if kept at body temperature die within a few days, whilst desiccation also rapidly kills them. The wall of the dead cyst becomes permeable to watery stains, and hence the use of the 1 per cent eosin test for viability of the cysts, those which are still viable not taking the stain, whereas the dead ones do.

The tyro in stool examination is usually content to merely look for 'cysts'; the more experienced worker knows how difficult the diagnosis of species may be; the worker who has had considerable experience begins to appreciate the difficulties which are encountered with aberrant forms and degenerated cysts. A thin emulsion which will allow of clear definition, a good lens, and patience are the three chief pre-requisites for accuracy; and the laboratory worker who has not examined more than 1,000 stools is still a tyro at identification. The chromatoid bars are the most characteristic feature of the cyst of *E. histolytica*, but they rapidly break down in the cysts in passed fæces. As pointed out by Yorke and Adams (1926), during the early mono-nucleate phase of the cyst the amount of glycogen present may be fairly considerable, but as the cyst matures the glycogen is used up and there is little or none in the mature tetra-nucleate cyst. On the other hand as the cyst matures the chromatoid substance becomes more and more prominent, and it is probable that all mature tetra-nucleate cysts contain chromatoid substance. When the cyst is passed in the fæces, however, the chromatoid substance immediately starts to disintegrate and is the first structure to disappear within the cyst; hence in a stool which is a little stale the cysts may fail to show chromatoid substance. In such cases one has to rely on the invisibility of the nuclei in saline and their

typical ' histolytica ' type of structure as seen in the iodine preparation for identification.

One final point may be noted. If a stool shows numerous entamœbic cysts, almost all of which are tetra-nucleate, the infection present is either one with *E. histolytica* or with *E. nana*, since the tetra-nucleate phase of the cyst of *E. coli* is the rarest phase of this parasite encountered. The cyst of *Endolimax nana* is readily identified by (*a*) its usual presence in very great numbers in the stool; (*b*) its oval to circular shape and small size, although many cysts of *minuta* type of *E. histolytica* may be as small in diameter; (*c*) its bright volutin granules, which are usually prominent; and (*d*) its faintly greenish tinge in iodine as compared with the smooth hyaline brown appearance of the cyst of *E. histolytica*.

The presence of Charcot-Leyden crystals in the stool is an added factor in diagnosis. These have already been described on p. 52 and need here be no further commented on. Further search of the same stool or of more stools from the same patient will almost always show the presence of *E. histolytica* infection in such cases.

It only remains to add that the diagnosis of *E. histolytica* carriers from material sent through the post is an easy matter. The medical attendant should make a fine emulsion of a small and typical portion of the stool in a large volume of the iodine solution mentioned with a pestle and mortar. This emulsion is then poured into a glass specimen tube, which is tightly corked, the cork being luted with wax. The tube is then suitably packed and sent by post. On receipt in the laboratory the emulsion is centrifuged and the deposit examined for cysts of *E. histolytica*. The cysts are well preserved in such an emulsion and can be identified as long as two weeks later.

Cultural Examination of the Stool.

Even if *E. histolytica* in its vegetative or encysted form be found, the laboratory worker's duty is by no means over. *It should be an invariable rule that every stool examined should be plated.* We are accustomed to make two cultures from every stool: (*a*) for dysentery bacilli on a plate of McConkey's medium; and (*b*) for streptococci on Conradi-Drigalski medium. If this be done as a routine the importance of mixed infections will come to be realized. The routine method of examination for *B. dysenteriæ* has already been dealt with, but we may here deal with (*b*).

The Isolation of Streptococci from the Stool.

The culture-medium used is a Conradi-Drigalski one, which is prepared as follows:—

Nutrose	.. ..	1 gm. (or Casein 1 gm.)
Agar	.. ..	2 gms.
Broth	.. ..	100 c.c.

Autoclave for half an hour for melting, and then filter to clear. Then to every litre add 1 c.c. of a 10 per cent solution of sodium carbonate, 1·5 per cent lactose, 1 c.c. of crystal violet solution (strength 0·1 per cent) and 10 c.c. of Teichmann's litmus solution.

Sterilize in the Arnold sterilizer for ten minutes on two successive days. The medium is used in Petri dishes in the same way as McConkey's medium, the plates being streaked in the same manner.

Streptococcal colonies on this medium show up as very fine tiny dew-drop-like growths, and may be either lactose fermenters or non-lactose fermenters. The colonies should be subcultured on blood-agar to test whether the strain is hæmolytic or not. Vaccines can then be prepared from the hæmolytic strains.

An alternative method of securing hæmolytic streptococci from such patients is to incubate a catheter specimen of the urine, as described above.

The concomitant streptococci which are so frequently present in the colon of the *E. histolytica* carrier probably lead to an alteration in the pH of the small ulcers in which the entamœbæ lie, as most of them are lactose fermenters and produce lactic acid. This acidity favours the growth of vegetative *E. histolytica* and also hinders the action of emetine, which is required in a very much stronger solution to be effective in an acid environment than in an alkaline one.

The whole bacterial flora of the gut in fact seems to be changed in the presence of *E. histolytica* infection. On a McConkey plate the stool usually yields a large number of small colonies, both of lactose fermenters and non-lactose fermenters. Streptococci and small yeasts predominate ; also late lactose fermenters, and lactose fermenters quite different from those in a healthy stool are present in considerable numbers, sometimes also the *B. proteus*. A suggestive culture showing such a bacteriological picture should lead the laboratory worker again to search the patient's stools for *E. histolytica*, and its value should not be neglected.

The prognosis in the case of the *E. histolytica* carrier is good provided that the medical attendant understands the state of affairs which is present, and can gain the confidence and co-operation of the patient. If the condition is not eradicated, however, the prognosis is not good, for the course of health in an untreated *E. histolytica* carrier is frequently one of steady deterioration until he falls a prey to some secondary disease or—in the case of the European—has to be invalided from the tropics.

Treatment.

We have tried out all or almost all of the newer remedies for the carrier state, and in the end have fallen back upon emetine again, because no other drug has given us such consistently good results. For some reason emetine when administered hypodermically to the carrier is far less efficacious than when administered by the mouth, and the oral administration of bismuth emetine iodide is the line of treatment which has given us the best results. In general

the patients may be divided into two groups: (*a*) those in whose cases hæmolytic lactose-fermenting streptococci cannot be isolated from the stool; and (*b*) those in which they are present. In the latter group of cases autogenous vaccine therapy is indicated in addition to oral administration of bismuth emetine iodide.

The *E. histolytica* carrier who is under treatment need not be kept in bed, as the ulcers are small and indolent, but he should take matters quietly whilst under emetine treatment. Diet is not important but it should be light and nutritious. For European patients milk, eggs, bread, soups, fish and boiled meats may be given. In the case of Indians the rice given should be of the better grades as these are more digestible; *suji* chupatties are useful, and the less indigestible dâls, such as *mung* and *mussoor*. The patient should not be starved, but be given a wholesome and easily digestible diet. With regard to alcohol 'short' drinks and cocktails should be absolutely tabooed, for nothing proves so irritating to the ulcerated gut.

Bismuth emetine iodide was first introduced in the treatment of amœbiasis by Dale in 1916. It is a brick-red powder which should contain not less than 26 per cent of emetine. The keratin coated or stearin coated pills and the compressed tablets are useless as they are nearly always passed *per rectum* unchanged, and the drug—in spite of its nauseating qualities—should be given in powder or in cachet form. It must pass through the stomach without ionizing, and is best given on an empty stomach. Patients vary very much in their ability to retain the drug, but we have found that with the following plan there is very little vomiting, and most patients can take the complete course of treatment without discomfort.

Half an hour before retiring to bed the patient is given either 6 to 10 minims of tinct. opii, or—better—Omnopon (Roche) gr. $\frac{1}{6}$th. After he is in bed, and as he is getting drowsy the nurse or attendant administers the dose of bismuth emetine iodide gr. 2* suspended in 2 drachms of liquid paraffin. This course is given every night for 10 or, if the patient will stand it, 12 days. Anything less than 10 days seems

---

* Adult male European patients can frequently take gr. 3 without discomfort, but few Indian patients can tolerate more than gr. 2.

An alterrative preparation which the junior writer has recently been using a good deal, which gives excellent clinical results, and apparently good results with reference to the eradication of the infection is Alcresta Ipecac. (Lilly and Co.) It is stated that each tablet of this preparation contains the alkaloids emetine and cephaline from 10 grains of ipecacuanha (U. S. P.), the alkaloids being held in absorption by hydrated aluminium silicate. It is claimed that after ingestion the tablets disintegrate, but that the absorption compound passes unchanged through the stomach and releases the alkaloids only in the alkaline intestinal secretions, so that there is no vomiting. For acute amœbic dysentery, the makers recommend 2 or 3 tablets three times a day. The junior writer has had no experience with this preparation in the treatment of acute amœbic dysentery, but it appears to be of considerable value in the treatment of the *E. histolytica* carrier. Two or three of the tablets may be given each night for ten or twelve days, and a preliminary dose of opium or omnopon is not usually necessary.

to be useless, and short intermittent treatments seem to do more harm than good. After the end of treatment all emetine is suspended, and one now commences examination of the stools to see whether the infection has or has not been eradicated. If possible, as is often the case with European or better class Indian patients, the best plan is to examine one stool a week for six—or preferably eight—weeks.

During the course of treatment a mild emetine diarrhœa may set in about the 6th or 7th day, but this should not be allowed to interrupt the course of treatment, which must at all costs be continuous, if it is to be effective. Children as a rule tolerate bismuth emetine iodide well.

We have not as yet been able to analyse our hospital figures for the last six years, but we believe that quite the majority of *E. histolytica* carriers can have their infection eradicated by this course of treatment. If the treatment fails to eradicate the infection, the stools should be repeatedly plated or catheter specimens of the urine cultured for hæmolytic lactose-fermenting streptococci. If these are found an autogenous vaccine is prepared and a course of injections, commencing with 10 million and rising to 50 million, is given during the next three weeks. When this has been completed and the streptococcal infection of the gut has been brought under control or eradicated, the patient is next given a second course of bismuth emetine iodide on lines exactly similar to the first course. This line of treatment will eradicate the infection in quite the majority of cases which prove resistant to the first course of treatment.

It may even be necessary to give three courses of bismuth emetine treatment, with long intervals between them.

Where bismuth emetine iodide fails, it is the custom of the junior author to prescribe a course of stovarsol treatment—one tablet daily for ten days. In quite a number of cases which fail to respond to bismuth emetine iodide, this succeeds; on the other hand it frequently fails, though it usually improves the patient's general condition very much. Or kurchi or yatren may be tried.

During treatment, and especially after treatment, the patient's bowels must be kept regular, and a daily dose of liquid paraffin may be necessary every night. In the thin type of patient with intestinal stasis, abdominal massage and endocrine therapy (as described in the section on chronic bacillary dysentery) may be required. Ispaghul and bael sherbet are also useful as demulcents.

We are convinced that the successful treatment of the chronic *E. histolytica* carrier is not the terribly difficult business that it was generally supposed to be shortly after the Great War.

APPENDIX.

TABLE VI.

Morphology of the Human Entamœbæ.

	Entamœba coli.	*Entamœba histolytica.*	*Endolimax nana.*	*Iodamœba bütschlii.*	*Dientamœba fragilis.*	*Entamœba gingivalis.*
VEGETATIVE FORMS.						
Size ..	20 to 40 μ .. Never less than 10 μ	20 to 30 μ .. Sometimes less than 10 μ	6 to 12 μ ..	9 to 15 μ ..	8 to 9 μ ..	10 to 20 μ
Motility ..	Sluggish	Very active if fresh ..	Sluggish	Fairly active ..	Very active ..	Active if fresh.
Ectoplasm ..	Scarcely seen ..	Well seen. $\frac{1}{3}$rd of parasite.	Scarcely seen ..	Well seen in motile amœba.	Very clear ..	Only well defined in actively motile amœba.
Pseudopodia..	Blunt: rounded: consist mostly of endoplasm.	Thin, finger-like, if fresh: later are lobose. Consist only of ectoplasm.	Blunt	Blunt: consist of clear ectoplasm.	Fragile: leaf-like. When moving amœba resembles a snail.	Round: lobose.
Colour and appearance in fresh state.	Like 'ground glass' ..	Glassy: clear: greenish or yellowish.	Greenish ..	Rather refractile ..	Fragile ..	Greenish.
R. B. Cs ..	Are never ingested ..	Any entamœba containing ingested R. B. Cs. is *E. histolytica.*	Never ingested ..	Never ingested ..	Never ingested ..	Never ingested: but the greenish hyaline masses may look like them.
Endoplasm ..	Densely granular: packed with bacteria, yeasts, debris of	Finely granular. Shows only included R. B. Cs. Sometimes	Full of food particles.	Full of bacteria and food particles.	Granular but fragile. Contains bacteria and food particles.	Full of bacteria: vacuoles: and hyaline greenish

Bacteria ..	Are freely ingested ..	Are never ingested (except in culture, when it freely ingests bacteria): bacteria parasitise the dying amœba in stools.	Are ingested ..	Are ingested ..	Are ingested ..	Usually packed with bacteria.
Vacuoles ..	Often numerous: usually seen as clefts or cracks in endoplasm.	Scanty; spherical; defined.	Many; well seen ..	Numerous ..	Often present ..	Crammed with vacuoles.
Nucleus (unstained)	Conspicuous as a clear, large, bright round or oval ring.	Usually invisible ..	Invisible ..	Not seen	Two nuclei: well seen.	Not conspicuous.
Nucleus (stained)	Coarse type with much chromatin. Big excentric karyosome: halo around: clear space with chromatin grains: thick ring deposit of chromatin on nuclear membrane.	Delicate type with scanty chromatin. Central small karyosome: halo: clear space free from chromatin; thin ring deposit of chromatin on nuclear membrane.	Blob-like. Much chromatin. Chromatin mass in bizarre forms inside nuclear membrane.	Large. Much chromatin. Big central nucleolus: clear zone with chromatin dots: nuclear membrane well defined.	Two nuclei alike. Nuclear membrane well seen. Big central star-shaped cluster of chromatin.	Well marked central karyosome: halo: clear space: ring-like thick deposit of chromatin on nuclear membrane.
Multiplies by..	Binary fission probably. (Not yet described.)	Binary fission only ..	Probably binary fission.	Probably binary fission.	Not known ..	Binary fission only.
Pre-cyst ..	'Minuta phase.' Spherical: clear: single nucleus. 12 to 17 μ Three races in size.	'Minuta phase.' Spherical: clear: single nucleus. 5 to 14 μ Four races in size.	Very small, 5 to 8 μ. Very clear and transparent. Single large nucleus.	Thick cyst wall. Volutin grains and iodophilic body forming.	Not known. (It rapidly becomes very vacuolated and degenerated when passed in stools.)	Not known.
Encystment ..	Glycogen vacuole often very prominent, especially at 2-nucleate stage. Chromatoid bodies very rare: only in 5% of cysts. 4-nucleate phase rarely seen.	Glycogen vacuole varies; sometimes marked in early phase, but soon disappears. Chromatoid bodies seen early. Coarse and highly refractile. Nucleus relatively large to cyst.	Straightforward nuclear multiplication to 2- and 4-nucleate stages. Glycogen vacuole and chromatoid bodies very rare.	'Iodine cyst' ..	Not known ..	Not known.

APPENDIX—*concld.*

TABLE VI—*concld.*

Morphology of the Human Entamœbæ.

	Entamœba coli.	*Entamœba histolytica.*	*Endolimax nana.*	*Iodamœba bütschlii.*	*Dientamœba fragilis.*	*Entamœba gingivalis.*
Adult Cyst ..	Usually spherical. Sometimes ovoid. 8-nucleate.	Spherical. 4-nucleate.	Oval or spherical. 4-nucleate.	Quite irregular shapes. 1-nucleate. ..	Not known ..	Not known.
Size ..	15 to 22 μ. Three races.	6 to 18 μ. Four races.	About 8 μ ..	9 to 12 μ ..	....	....
Glycogen ..	May be faint traces ..	Has disappeared ..	None	Deeply staining glycogen vacuole or vacuoles.	....	....
Chromatoid Bodies.	Very rare : only seen in 5% of cysts.	Big : coarse : and most characteristic. Massive.	Very rarely seen : filamentous.	None	....	....
	Fine feathery : like 'splintered glass.' (Sometimes seen at the bi-nucleate phase.)	Seen in majority of all cysts, if specimen is fresh.		Refractile volutin granules however.	....	....
Nuclei ..	'Coli type': (as above).	'Histolytica type': (as above).	The 4 nuclei are often clustered together near one pole.	Excentric : in cytoplasm outside glycogen vacuole.	....	....
Frequency ..	87% of *E. coli* cysts seen in stools are 8-nucleate.	53% of *E. histolytica* cysts seen in stools are 4-nucleate.	4-nucleate forms by far the most common. Cysts usually numerous when present.	Cysts usually numerous when present.	....	....
Variations ..	16-nucleate big cysts.	....	8-nucleate cyst has been noted.	Cysts vary much in shape and size. Very rarely glycogen vacuole may be absent.	Rarely only one nucleus present.	....

CHAPTER VIII.

Streptococcal Infections Secondary to Bacillary Dysentery.

THERE are three clinical conditions in the practice of medicine in the tropics which we believe to be frequently—or usually—due to secondary streptococcal infection of the gut following after an original infection with the bacillus of Flexner. These are :—

1. The 'mucous disease' of infancy.
2. Sprue and hill-diarrhœa, which diseases especially attack Europeans and only rarely Indians.
3. A condition of pernicious-like anæmia in young adult Indians, often associated with an asthenic diarrhœa. The *sutika* of Indian women during the puerperium is a good example of it.

Our reasons for regarding the last two conditions as due to a secondary infection of the ulcerated gut with streptococci after a primary Flexner bacillus infection are (*a*) the frequency with which hæmolytic streptococci can be isolated from the urine or stools of such patients ; (*b*) the frequency with which the sera of such patients give a strong agglutination reaction, to a titre of 1 : 160, against the bacillus of Flexner ; and (*c*) the number of cases of chronic diarrhœa, due to infection with the bacillus of Flexner, which we have seen pass into one or other of the above conditions. The senior author, for example, at the time of writing has a case of chronic Flexner bacillus infection in a young European female patient, who was gradually passing into a typically pre-sprue condition, with pale, copious and frothy evacuations, whilst *x*-ray examination of the gut after a barium meal shows enormous distension of the gut.

It is only occasionally that the bacillus of Flexner can be isolated from the stools of such patients. Usually in fact, the original infection with the bacillus of Flexner has disappeared, but the ulcers have become secondarily infected with a hæmolytic streptococcus infection which spreads up and down the mucosa of the gut.

SPRUE.

Ætiology.

Sprue is essentially a disease of the European who has been in the tropics for a long time, but there is no question that occasional cases occur among Indians—

especially among those of the better class. It is a chronic intestinal disease, with periods of remission and relapses, characterized by ulcerations of the tongue and mouth, atrophy of the intestinal mucosa of the whole of the intestine, and the passage of large, frothy, pale-coloured stools. It is usually seen in Europeans or Anglo-Indians who are more than 30 years of age, and females seem to be more susceptible to it than males.

There have been many theories as to the causation of sprue which have been put forward, and these may be considered briefly first :—

1. *The vitamine deficiency theory.* This has been stressed by Elders (1919) and Nicholls (1918) in Ceylon where the disease is very prevalent. McCarrison (1919) has produced a sprue-like condition in monkeys fed upon a vitamine-free diet, the intestinal lesions resembling those found in sprue in man. On the other hand sprue is essentially a disease of the well-to-do European in the tropics, and there seems to be no real evidence that it is due to deficiency in vitamines.

2. *The fungoid theory.* Manson-Bahr (1914*a*) in Ceylon isolated a fungus from tongue scrapings, as well as in the œsophageal, gastric, and intestinal mucus at post-mortems on sprue cases, and the same organism was cultivated from the spleen, liver and kidneys. It was not found in the mucus or contents of the intestinal canal in fatal cases of diarrhœa other than sprue.

Ashford (1915, 1915*a*, 1915*b*) in Porto Rico isolated a similar organism from the fæces of patients with sprue and called it *Monilia psilosis*. He claimed that when cultures of this organism were injected into the tongue of rabbits there resulted a gaseous diarrhœa, gradual emaciation and death ; also that such cultures are intensely toxic to white rats and mice when injected intraperitoneally. Michel (1918), using emulsions of this *Monilia psilosis* as an antigen, obtained positive complement-deviation in the sera of no less than 400 cases of sprue. Anderson (1917) conducted an exhaustive enquiry into the normal and abnormal fungi of the fæces. He claims that 'wild yeasts' are very commonly present in the fæces of normal individuals, but that the pathogenic variety obtained from the stools of sprue patients differs entirely from these 'wild yeasts', and he has re-named the organism *Parasaccharomyces ashfordi*. Dold and Fischer (1918) claim to have experimentally produced sprue by feeding white mice and monkeys with cultures of a similar organism.

On the other hand Manson-Bahr (1923) records that all his attempts to produce sprue experimentally in animals with such an organism failed, as also did similar attempts by Breinl and Priestley on dogs. Further, the same author also records that he has frequently failed to isolate *Monilia* from sprue cases seen in London. The junior author, whilst at Shillong, isolated an organism roughly corresponding in its morphology and sugar reactions to the so-called *Monilia psilosis* of Ashford from three cases, but all three strains proved absolutely non-pathogenic to white rats and guinea-pigs, whether on feeding or intraperitoneal injection. Two of these

patients were treated by an autogenous vaccine prepared by autolysing cultures of this fungus on the lines suggested by Michel, and both recovered. One of them was a European female of about 35, who was in such an extremely critical condition that her husband, who had just landed at Karachi from Mesopotamia, was wired for to come immediately. This patient was treated solely by dieting and injections of the autolysed *Monilia* vaccine and made such a brilliant recovery that three months later she won the ladies' singles tennis championship at Shillong.

The term '*Monilia*' has been so much abused in the literature, that, in passing, we would like to point out that the organism described by Ashford is probably an *Endomyces* allied to the *Oïdium albicans* of thrush.

Whilst such *Endomyces* organisms are undoubtedly frequently present in the stools of sprue patients, yet they are sometimes absent, and despite the claim of Gonzalez-Martinez (1920) that it has been fully proved that *Parasaccharomyces ashfordi* is the ætiological agent of sprue, we regard such fungi as secondary invaders of the gut in sprue. They may be responsible perhaps for the fermentation and frothiness of the stools.

3. *The streptococcal theory.* Rogers (1914), as the result of successful treatment of sprue cases with an autogenous oral streptococcal vaccine, suggested that sprue was due in the first instance to an oral infection with an organism of *Streptococcus viridans* type, the infection passing from the mouth down the alimentary canal. The organism was non-hæmolytic, but positive complement-deviation was obtained with it when the sera of sprue patients was tested. One of the most remarkable patients treated by Sir Leonard Rogers was an elderly Scot, a business man who had retired from Calcutta, and gradually developed sprue in Aberdeen. This patient reversed all the accepted canons of treatment. He came out from Scotland to Calcutta to be treated by Sir Leonard in Calcutta, and as he did not do well in the climate of Calcutta during the hot weather, he was sent to Shillong, where he came under the treatment of the junior author. He was treated at first with an autogenous streptococcal vaccine and improved up to a certain point; an autogenous autolysed *Endomyces* vaccine was then added to the streptococcal vaccine. The patient made a sound recovery and the junior writer heard from him from Scotland three years later that he was in excellent health.

There can be no doubt that some patients suffering from sprue do very well when treated with autogenous *Endomyces* or streptococcal vaccines; on the other hand others do not, and the correlation is a partial one. Possibly these injections merely act as would any injection of a foreign protein. In the case of the lady tennis player referred to above the reactions after injection were always very severe, so much so that the utmost caution had to be employed in increasing the dose.

4. *The post-Flexner bacillus infection view.* In the experience of the senior author these cases usually begin as an infection with the bacillus of Flexner. This

does not cause dysentery in these patients, so much as an initial diarrhœa, which may be of 'hill-diarrhœa' type or a chronic diarrhœa contracted in the plains. The blood agglutination reactions frequently show the previous existence of this Flexner bacillus infection. A secondary streptococcal infection of the ulcers next sets in and persists and spreads up and down the gut, just as in ringworm of the skin the lesions are often secondarily invaded with a streptococcus which leads to a spreading streptococcal dermatitis or 'eczema.' This leads to inflammation, scarring and atrophy of the mucosa, whilst the original infection with Flexner's bacillus is killed out. These patients with diarrhœa due to the bacillus of Flexner are often wrongly given milk with quantities of carbohydrates, such as the patent foods, and they are particularly intolerant to carbohydrates; as a result the indigestion is still further increased. With pancreatic failure—probably due to the action of toxins from the gut on the pancreas—still further intolerance to carbohydrates develops. Finally the *Endomyces* infection sets in as a terminal infection, similar to what so frequently happens in cases of pulmonary tuberculosis.

Symptomatology.

With the symptomatology of sprue we will deal only very briefly, since the subject is so very well described in text-books on tropical medicine. An admirable account is given by Manson-Bahr (1923, 1925).

The onset of the disease may begin with an acute diarrhœa, with 'hill-diarrhœa', or—much more commonly—with an insidious diarrhœa. This tends especially to affect the patient in the early morning, and he passes 2 or 3 stools early each morning, light yellow in colour and containing mucus. By degrees the stools become larger, more frothy and paler in colour, and the patient is now passing 2 or 3 copious and frothy stools early every morning and is relatively comfortable for the rest of the day, but is tired and listless.

Loss of appetite next sets in, followed by indigestion and acid eructations, and the patient tends to gradually confine himself to a diet of liquids or semi-solids only. There is now rapid and progressive loss of weight.

With the onset of the characteristic lesions of the mouth and tongue the condition passes from what one may term the pre-sprue state into established sprue. The mouth becomes sore and salivation incessant, whilst the patient cannot touch any hot food and deglutition is painful. The tongue becomes red and glazed, and aphthous ulcers form on the tongue, the lips, pharynx, etc.

These are the outstanding symptoms, upon which clinical diagnosis is based. Turning to the signs of the disease:—

The *tongue* is red and glazed and resembles raw beef. Small aphthous ulcers are frequently present on the tongue, gums and lips. These are frequently situated on the tongue opposite the second molar tooth. The mouth is intensely tender,

and the patient cannot stand spiced or hot foods, acids or alcohol. There is often a burning pain in the region of the œsophagus on swallowing, indicating that ulcers are also present in the œsophageal mucosa. The patient has by now become emaciated and worn out physically ; he is usually rather irritable, and the complexion has assumed a peculiar lemon-like or muddy tinge.

The abdomen is swollen and frequently ballooned around and above the umbilicus. Its wall is thin. The intestines are intensely distended, so that the abdomen has a peculiar boggy feel on palpation. Peristalsis is frequently visible through the abdominal wall.

The stools are very large, of a faintly yellowish white colour, frothy and full of gas. On microscopic examination numerous fatty acid crystals are seen, and sometimes soaps. They are loaded with yeasts and bacteria. Mucus and epithelial debris are rarely present.

The urine is loaded with indican and urobilin.

The blood by degrees comes to present the picture of a pernicious anæmia. The red cell count may be from 1 to 3 millions, or even lower. The colour index, however, is often below 1. The leucocyte count is reduced, from 6,000 to 3,000 per c.mm., and there is an increase in the number of mononuclear and eosinophile leucocytes.

Autopsy. At autopsy on such patients the body is seen to be extremely emaciated, and the skin loose, atrophic, dry and harsh. Œdema of the feet is usually present. On opening the abdomen the liver is found to be greatly reduced in size. The intestines are greatly distended and full of fæces ; in the upper part of the small intestine the contents may be bile-stained, but lower down they are white in colour. Sidney Martin and Blyth (quoted by Manson-Bahr, 1923) have shown that bile pigment is still present in the stools, but that it is present in the form of a colourless compound, leucobilin, which is a reduction product of hydrobilirubin. If an extract be made with 90 per cent alcohol of an almost colourless sprue stool and the filtrate be exposed to air, a white colourless fluid results, which slowly becomes oxidized to a yellow colour and gives the spectrum of hydrobilirubin.

The small and large intestine are greatly distended and the walls so thin as to be diaphanous. The serous coat is generally healthy, but the muscular coat is almost completely atrophied. The internal surface of the bowel is coated with a thick layer of grey tenacious mucus which conceals patches of congestion, erosion, and even ulceration, together with smooth thin-scarred cicatricial patches. The villi and glands are eroded and in many places completely destroyed. Here and there minute spherical indurations, about the size of a pin's head and surrounded by a congested areola, can be felt in the mucous membrane. On cutting into these one finds them to be cyst-like dilatations of the follicles, filled with a mucoid, gummy or muco-purulent material. The erosive lesions are usually most marked towards the lower end of the ileum and the upper part of the colon, but the entire

alimentary tract may be affected in patches from the mouth to the anus. The tongue, mouth, œsophagus and stomach usually show small minute ulcers.

Endocrine glands. The thyroid shows a condition of hypothyroidism and fibrosis with loss of colloid secretion. There is hyperplasia of the alveolar epithelium, but without secretion. The pancreas is small and fibrosed, with changes in the secretory epithelium.

On cultivation of the gut contents no Flexner bacilli are isolated, but hæmolytic strains of streptococci and *Endomyces* are frequently isolated.

Diagnosis.

In diagnosis one relies on (1) the morning diarrhœa; (2) the enormous frothy clay-coloured stools; (3) the characteristic glazed ulcers of the tongue, gums and lips; (4) the great and progressive emaciation; and (5) the boggy, blown out abdomen. The tongue lesions are very characteristic. In hill-diarrhœa, which we regard as due to infection with the bacillus of Flexner, there are no oral lesions and no abdominal distension; this condition however may develop into sprue. In the severe anæmia of Indians associated with asthenic diarrhœa there are no mouth lesions, the abdomen is shrunken and concave and not ballooned; the stools are not frothy, but large and yellow in colour. In chronic pancreatitis there are no mouth lesions, there is localized tenderness in the epigastrium, and the stools are loaded with fat and show Cammidge's crystals.

Among the *complications* of sprue one may mention the sudden onset of very severe attacks of diarrhœa persisting throughout the day; these exhaust the patient's strength very rapidly. Meteorism is perhaps a symptom rather than a complication; it may be very severe and make the patient very uncomfortable. Insomnia may be severe and require treatment. With the atrophy of the cardiac muscle from the absorption of toxins, cardiac failure may threaten, whilst true pancreatitis and true pernicious aplastic anæmia may set in.

The *prognosis* in sprue is always serious, but not too bad if one can secure the full co-operation and obedience of the patient. Treatment requires the fullest and most cordial co-operation of the patient, nurse and doctor alike; it calls for patience and perseverance on the part of patients who are often irritable and peevish, and the doctor must rule with a firm hand and stand no nonsense.

Treatment.

General. The fullest co-operation must be secured from the patient. The extreme gravity of the disease should be explained to him and its dangers pointed out, also the hopefulness of the outlook if he will obey orders. Otherwise he will be asking for pickles or bloater paste. Any case of more than the mildest severity must be kept in bed and carefully nursed.

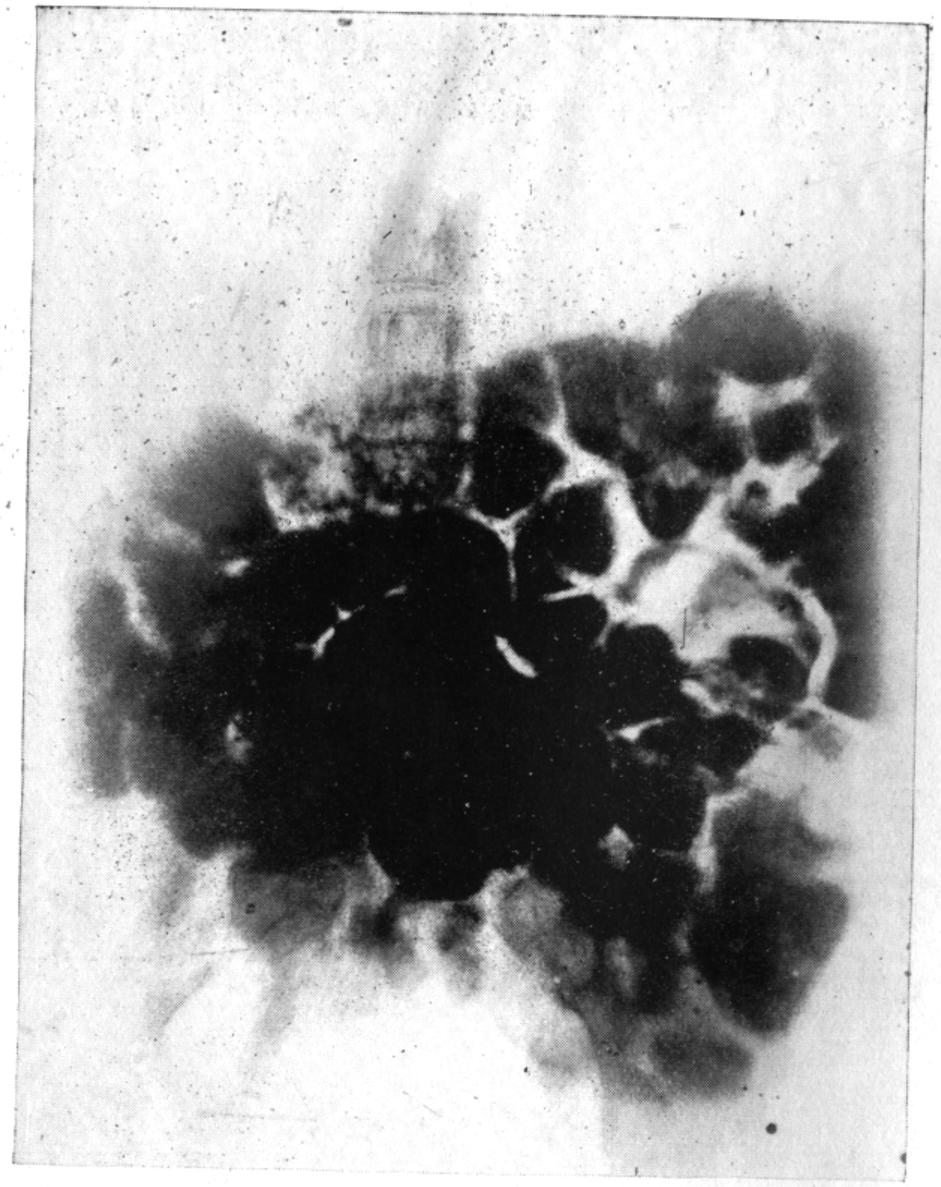


FIG. 32. Anglo-Indian female, 40 years. Chronic dyspepsia and diarrhœa off and on with copious stools for 8 years. Tenderness over cæcum and descending colon. Admitted in 1926, when the bacillus of Flexner was isolated from the stools. Readmitted October 1927, with a sprue-like condition present. Twelve examinations of the stool failed to show any helminthic ova, protozoa or dysentery bacilli. *Bacillus capsulatus* and a *Monilia*-like organism present.

Skiagram taken 24th October, 1927, showing the ballooning and doughiness of the small intestine characteristic of sprue.

FIG. 33. Same patient as in Fig. 32. Skiagram taken 10 hours after a barium meal. Marked ballooning of the cæcum.

Diet. No end of special diets have been recommended for sprue. Thus we have the milk cure, the raw meat cure and the fruit cure. The strawberry supply of India is a very limited one, but we should think that most of it is consumed by sprue patients, who are often put to considerable expense to secure this delicacy. Change of climate is often an advantage, but not essential. The patient should not be sent on the voyage from India to England unless he is in a condition to stand it, for one can rarely obtain a suitable diet for a sprue patient on board ship, and fresh milk is unprocurable.

As the Flexner bacillus infection has usually died out in these cases, milk is not contra-indicated, and on the whole we prefer a general milk diet, supplemented by proteins. The milk must be fresh cow's milk if possible, and if the patient can afford it—as is usually the case—he will do well to purchase his own cow. The milk should not be boiled but given fresh in small repeated feeds, $2\frac{1}{2}$ or 3 pints during the 24 hours. If the patient is very debilitated night feeds may be necessary. On the other hand the patient should not be nauseated with milk, and chopped raw meat, liver, liver soup and fruit may be added. Bananas are well tolerated by such patients as a rule and papaya is useful on account of the ferment which it contains. Fresh bael fruit (*Ægle marmelos*) is spoken of by Manson-Bahr as being almost a specific for the disease, and it is best taken raw, mixed with sugar. Apples and pineapples are not well tolerated by sprue patients.

Medicinal Treatment.

The number of different 'specific' medicinal 'cures' for sprue is even larger than the number of dietary 'cures' which have been advocated. The use even to-day of powdered cuttle-fish bones and crabs' eyes shows that the medical profession has still an innate tendency to rely upon the miraculous.

Alkalies—such as sodium bicarbonate in large doses, 1 to 3 drachms a day in water—have their advocates. We cannot say that we have seen much benefit follow their use.

Yellow sun-baked santonin is undoubtedly of value in some cases. It must be of a rich yellow colour and well oxidized; the white powder is useless. It is given in 5 grain doses dissolved in a teaspoonful of olive oil twice or three times a day for a week. If the patient does not show any signs of improvement at the end of a week there is no use continuing with it.

Calcium and parathyroid. H. H. Scott (1923) believes that the essential condition underlying the causation of sprue is a deficiency in the calcium content of the blood due to defective action of the parathyroids. Occasionally, it is stated, tetany has been observed in sprue cases. We believe this calcium deficiency to be a result of rather than the cause of the disease, and that the correlation is a partial one. Scott's treatment consists in a very strict diet—usually a diet of fresh milk only—and in administering desiccated parathyroid extract, gr. 1/10th twice a day

and calcium lactate, gr. 10 to gr. 15 three times a day after food. There is no doubt that a few patients rapidly improve on this line of treatment.

Specific Treatment.

Here everything depends on the bacteriological findings, and the stools should be repeatedly plated. If the bacillus of Flexner is found—though this is not usually the case—bacteriophage may be administered, or an autogenous vaccine prepared and given.

Hæmolytic streptococci may be isolated either from the stool on plating, more frequently by culture of the urine by the method previously described, and most frequently from the ulcers on the tongue or gums. An autogenous vaccine should be prepared from such strains and given in doses of 5 million as the initial dose and gradually increasing the dose every 3rd day up to 50 millions.

It may be necessary to add an autolysed *Endomyces* vaccine to the streptococcal one, especially in cases which improve to a certain point, and then remain stationary. As the technique for the preparation of an autolysed vaccine is not generally known we may describe it here briefly.

A twenty-four hours' growth of the *Monilia* strain isolated on Sabouraud's agar is taken. Measure the square area of the growth in sq. cms. with a steel rule. Add an equal number of c.c. of sterile distilled water. E.g., if the area of growth is 4 cms. by 1·5 cms., then the square area of growth is 6 sq. cms., and 6 c.c. of sterile distilled water should be added. This gives an emulsion of approximate strength 1 c.c.= 4,000 million organisms.

Next thoroughly emulsify the growth in the distilled water. Pipette off the emulsion into a sterile test-tube, and incubate this at 37°C. for 48 hours. The distilled water dissolves the yeasts and gives an autolysed vaccine. Add 0·5 per cent carbolic acid to kill the growth, and dilute for use to 1 c.c.= approximately 100 millions. Dosage, 10 million to begin with, rising gradually to 100 million.

Local Measures.

It is very important in all cases of sprue to pay special attention to the hygiene of the mouth and teeth. The patient should use a mouth-wash of thymol or listerine as a routine measure. The ulcers may be painted with a solution of optochin, 1 : 1,000—which we have found to be far and away the best application in these cases—or with glycothymoline. At night glycerine-borax should be applied to them. If there is severe oral pain the local application of cocaine, 5 gr. to the oz., may be necessary before meals in order to enable the patient to take food. For œsophageal pain 3 to 5 minims of 1 : 1,000 adrenalin may be swallowed before the meal.

Complications.

The acute attacks of diarrhœa must be combated, and liquor opii sedativus may be necessary, or even starch and opium enemata may have to be given ; (for an adult the formula for such an enema is 1 drachm of tincture of opium in 10 ozs. of starch mucilage). For the constipation which so often sets in after an acute

attack of diarrhœa, soap and water enemas should be given and castor oil emulsion. In obstinate cases the constant use of liquid paraffin and abdominal massage may be useful. Constipation is particularly distressing to these patients, as it increases the abdominal distension and is associated with the passage of large, firm, white, pasty stools.

The muscular pains associated with the disease are best treated by massage and injections of pilocarpine, gr. 1/10th to gr. 1/5th t.d.s. For the abdominal and intestinal colic, hot wet packs may be given for two hours every morning and evening, and are very soothing. If cardiac failure threatens, digifortis (Parke Davis & Co.), 3 to 5 minims, may be given hypodermically twice or three times a day.

For the severe anæmia Manson-Bahr especially recommends hypodermic or intramuscular injections of arsenite of iron (Squire's liquid extract in 10 minim doses, or the Burroughs & Wellcome preparation), given at intervals of three days. Sprue patients do not tolerate iron and arsenic well by the mouth. The hæmoglobin index must be taken from time to time.

For the dyspepsia and flatulence Manson-Bahr (1925) recommends large doses of sodium bicarbonate. The same author also stresses the value of nutrient enemata or suppositories, given every four or six hours, and states that, if tolerated, they are most valuable aids to nutrition.

Stimulants are very bad for sprue patients. Mental worry is perhaps one of the worst foes of the sprue patient, and such patients usually do better when in hospital than when surrounded by over-anxious relatives.

II. The Pernicious Anæmia and Asthenic Diarrhœa of Indians.

This is a condition seen as a rule in young Indian adults of either sex, as the result of debilitating conditions, and predisposed to by chronic bacillary dysentery infections. The *sutika* of Indian women in the puerperium is an example of it. The condition of pernicious-like anæmia may or may not be associated with an asthenic diarrhœa.

Ætiology. As shown by its excretion in the urine, the micro-organism underlying and causing this condition is a hæmolytic streptococcus. It may apparently be derived from several different septic foci : such as carious teeth, the gums in pyorrhœa alveolaris, a primary or secondary gastric or duodenal ulcer, the site of ankylostome bites, or chronic bacillary infections of the colon. The streptococcus can be recovered on plating the stools sometimes, more usually by culture of the urine, whilst the blood serum frequently shows an agglutination to Flexner's bacillus at a titre of 1 : 160.

Symptoms and Signs.

The patient has a pale, muddy complexion which may be compared to the Indian *huldi* or tumeric. Slight œdema is frequently present. The tongue is

flabby and resembles wet blotting-paper. The conjunctiva is pale and the sclerotic coat of the eye dead white. The lips are dead white, also the nails. There is palpitation and dyspnœa on the slightest exertion. The appetite is poor, and chronic indigestion is present. The bowels may either be constipated or there may be a chronic and wasting diarrhœa, or constipation and diarrhœa may alternate with one another.

Blood. The blood picture shows a severe grade of anæmia, with a red cell count of from 1 to 3 million per c.mm. The hæmoglobin index is 1 or more. The leucocytes range from 4,000 to 6,000 per c.mm., with a diminution in the percentage of polymorphonuclears, and a relative increase in the mononuclears and eosinophiles. Abnormal red cells may be present or the normal red corpuscles may show chromatin dots. Normoblasts are frequently encountered and occasionally gigantoblasts.

Severe anæmia of aplastic type is much rarer. Here the red cell count is reduced to less than 1 million, and the function of the bone marrow is almost entirely destroyed. The leucocyte count is extremely low, being usually from 200 to 500 per c.mm. The hæmoglobin value is about unity. No abnormal red cells are seen as a rule, owing to the defective action of the bone marrow.

Autopsy. At post-mortem examination in such cases a condition of pernicious anæmia is found. The liver shows a deposit of iron. The heart is small and atrophic, the bone marrow red and œdematous and extending into the shaft of the long bones. In the aplastic type the bone marrow may have almost completely vanished.

Treatment.

The prognosis in these cases is always serious, but with appropriate treatment is perhaps less serious than was formerly the case. For the aplastic cases but little can be done, for the activity of the bone marrow has been almost completely destroyed, and only Heaven can supply new organs.

General. The regular routine and hours of a hospital are essential for proper treatment, though the patient need not necessarily be kept in bed.

Diet is important. The iron of the body is taken in the form of pyrollol bases, obtained from the chlorophyll of vegetables, so chopped spinach is very useful in these patients. Bile-salts increase the permeability of the intestinal epithelium to pyrollol bases and hinder the growth of streptococci in the gut, and hence liver should be given. It is best administered chopped up fine and very lightly grilled—as nearly raw as possible. Liver soups are also useful. Milk and milk foods may be used and the diet must contain a sufficiency of vitamines.

Specific Treatment. Here every attempt must be made to get at the underlying focus from which the streptococcal infection is coming. The teeth should be most carefully examined for caries and pyorrhœa, and radiographs of the teeth

may be necessary. A series of *x*-ray photographs of the entire intestinal tract after a barium meal may be necessary to look for gastric or duodenal ulcer or for chronic ulceration in the colon. The hæmolytic streptococcus responsible may be recovered from the teeth, or from the urine, or on plating the stool. If isolated, an autogenous vaccine should be prepared and vaccine therapy instituted, starting with a dose of 5 million organisms and working up to a dose of 50 million.

As adjuvants, in the first place iodine may be indicated, as the iodine absorption is often low in such patients. It may be given either intravenously (5 to 10 minims of the tincture well diluted with saline), or orally in milk. A remedy which the junior author has found very useful in the early treatment of such cases, and to tide over the interval between the admission of the patient to hospital and the isolation of the streptococcus in the laboratory is Hæmostyl (Roussel). This is stated to be a serum prepared from horses which are bled ; after an intensive bleeding, the horse's blood is examined at regular intervals, and it is again bled at the moment when examination of the blood shows the most intense hæmopoietic reaction present. The collected serum is sterilized by five heatings at 55°C., and this is called Hæmostyl. It is put up in ampoules for hypodermic administration and in the form of a syrup for oral administration. A dose of 10 c.c. may be given orally daily or on alternate days.

Blood transfusions are usually useless in these cases, since, even if the right type of blood be used after blood group testing, the hæmolysins present will destroy this new blood and severe reactions are apt to follow.

As the patient begins to recover on vaccine therapy iron arsenite may be given hypodermically, as described under the treatment of sprue.

Complications. If cardiac failure threatens, digifortis should be given, 3 to 5 minims hypodermically, two or three times a day. For cramps, which are often present in such cases, massage and warmth to the limbs are indicated. Purpura may be a complication and may require injections of calcium, etc. The bowels should be kept open if there is constipation by liquid paraffin, etc. Ox bile is probably the best intestinal antiseptic to use in such cases and may be prescribed as Burroughs, Wellcome and Co.'s 'Tabloid' Fellis bovini purificati, gr. 4 to gr. 8, two or three times a day.

Red wines act as both stimulants and sedatives in such cases and may be given in the evening.

CHAPTER IX.

Prophylaxis against Dysentery.

UNDER the heading of prophylaxis, under conditions as they at present exist in India, there is unfortunately but little to be said. Were it not for the fact that direct sunlight rapidly kills the *B. dysenteriæ* and that complete desiccation is lethal to the cyst of *Entamœba histolytica*, dysentery would probably be the most prevalent disease of the tropics. Moisture is the one essential for the spread of both infections, and we are far from certain that water-carriage conservancy is the best method of conservancy for cities in the tropics. The rural *ryot* who passes his stool on to the surface of a sun-baked field is doing far less harm than is popularly supposed. It is when such fæces are washed down by a fall of rain into the nearest tank or well or stream that trouble begins. And, as matters now stand in India, it is practically certain that every inhabitant of this peninsula will continue to be continuously exposed to infection for the whole of his life. Even in temperate zones infection may readily be acquired. Dysentery is a part—a very important part, indeed—of the price that India pays for her neglect to develop a 'sanitary conscience.'

Where one is dealing with a controlled community, as in the Army, in hostels or similar institutions, and in jails, it has been shown by Cunningham (1923) that a large measure of control can be exercised by *the daily macroscopic examination of the stools of all individuals concerned.* The stool of every individual in the community is examined every day for the presence or absence of mucus for eight—or preferably ten—days. Those men who show mucus in their stools are then segregated, and laboratory examination of their stools repeatedly carried out. If they are found to be carriers appropriate treatment is instituted, and they are required to give a clean negative laboratory record before they are returned to the general community. On examining the stools of 3,460 individuals in four jails in Eastern Bengal once only by this method 411 or 11·88 per cent were found to contain mucus or mucus and blood; but on repeated examination of the stools of the same persons for ten days the percentage rose to 22·8 and it was found that at least eight examinations were necessary to detect all carriers. 'I am convinced,' he writes, 'that we have in the method which I advocate, that is the systematic *macroscopic* examination of the stools, a really practical means of dealing with the carrier problem as far as dysentery is concerned. By this means I maintain that the vast majority of the latent, and

therefore dangerous carriers, can be separated from any community which is sufficiently under control to permit of a daily examination of their stools. Large numbers of cases can be examined in a comparatively short time and the technique does not call for any special skill on the part of the medical attendant.'

In one particular and very sickly community where this method was systematically adopted the 'latent dysentery index' was found to be 30·9 per cent. Those showing mucus in their stools were segregated, and an examination of the case histories showed that no less than 97 per cent of the cases of dysentery which had occurred came from this group of persons, those with healthy stools only contributing 3 per cent of the admissions for dysentery. On segregation and treatment of the carriers the dysentery which had been so prevalent fell very rapidly in incidence. Further, the method is not only applicable to controlled populations; it will help the medical practitioner to assess whether his convalescent dysentery patient is or is not a danger to the household.

In general, prophylaxis against dysentery can be summed up in the one word 'cleanliness.' Carriers being the most important source of infection, the stools of all who have to do with the handling of foodstuffs should be repeatedly examined. Unfortunately this is rarely practicable. In 1920 a small outbreak of cholera occurred in the nurses' quarters in the Medical College Hospital, Calcutta. The junior author, who was in charge of the cholera ward at the time, made a determined effort to secure the stools of all servants in the nurses' quarters for examination. This was immediately followed by a strike. These men were quite willing to have their blood taken for an agglutination test against the *Vibrio choleræ*, but not to let samples of their stools be taken.

If there is reason to suppose the water-supply to be infected, it should be chlorinated. Chart 1 shows the immediately beneficial effect of such a measure. One of the most important measures is *the most rigorous attention to the cleanliness of latrines*. If there is much dysentery about antiseptics should be used most liberally in the latrines, and those using them be made to wash their hands with an antiseptic lotion after visiting the latrine. Deep trench latrines, where the fæces are protected from the action of strong sunlight, are dangerous. A campaign against flies is also part and parcel of anti-dysentery measures, though the housefly is probably not as important in the conveyance of dysentery as the human carrier. Vegetables and all other food which is taken raw must be properly washed in a weak permanganate solution. The kitchen being the chief source of infection, in a mess or hostel the most rigorous measures must be taken to ensure cleanliness in the kitchen, whilst the stools of the cooks should be repeatedly examined to ensure that they are not carriers.

During the Great War rigorous measures had to be taken against dysentery in many theatres of war. In Egypt and Palestine it was found that the addition of a certain amount of oil to the daily dietary was a useful measure, as it lessened

the amount of intestinal irritation produced by sand and an unsuitable dietary. In France special dysentery hospitals were opened and all cases of dysentery—and in some of the commands, all cases of diarrhœa—were segregated in them. In June 1918, forward dysentery centres were opened in field ambulances near the firing line, and orders were issued that all soldiers whose stools showed the presence of mucus or pus should be diagnosed as 'dysentery', whether the bacteriological examination yielded positive results or not. Three consecutive negative examinations of the formed stools of all convalescent cases were insisted on before the men were returned to the firing line. The patients concerned had separate eating, sleeping and latrine accommodation. They wore hospital clothing as a mark of distinction at all times, and were permitted to attend physical drill and all recreations in common with other patients, but not the general canteens. In the case of every discharged dysentery patient a special notification had to be sent with the discharged patient to the unit concerned that he had been suffering from dysentery, together with a certificate to the effect that examination of the formed stools on convalescence had given negative results.

Dobell, Gettings, Jepps and Stephens (1918), on examination of 1,300 persons from the different war fronts, found the following incidence of *E. histolytica* carriers:—

France	..	..	..	8·37	per cent
Salonika	..	..	..	18·92	,, ,,
Egypt	..	..	..	18·96	,, ,,
Gallipoli	..	..	..	23·07	,, ,,
Mesopotamia	..	..	..	20·51	,, ,,

whilst Malins Smith (1919) showed that the incidence of *E. histolytica* carriers amongst healthy British recruits in the United Kingdom was 5·6 per cent. Towards the close of the war, attempts were made in many areas to isolate and treat all *E. histolytica* carriers in the different units concerned, but this procedure had to be abandoned as it proved too costly and too troublesome. It should be noted that 'relapses' of both bacillary and amœbic dysentery in reality are frequently due to re-infections, for the patient, having been cured and his infection eradicated, only too frequently returns to the same environment in which he previously contracted dysentery and is again exposed to the risk of re-infection.

Vaccines.

The high toxicity of the dysentery bacilli—and especially of Shiga's bacillus—has greatly militated against the use of vaccines prophylactically against bacillary dysentery. Early in the Great War Dean and Adamson (1916) suggested the use of a vaccine in which the dysentery bacilli were killed by the addition of eusol; this was found to be so toxic, however, that it was abandoned. Later Græme

Gibson (1917) tested the current Japanese method of giving vaccine and antiserum simultaneously, but found that, although the local reactions were mild, the production of antibodies was not well marked. It was concluded that the serum had not only neutralized the toxin of Shiga's bacillus, but also its antigenic properties. Accordingly, Gibson introduced a method of giving a vaccine of Shiga's bacillus together with *absorbed* anti-Shiga serum, whilst a vaccine of Flexner's bacillus could be added to this. This 'sero-vaccine' was issued in twin-conjoined phials, one containing the vaccine and the other the antiserum. The doses given were as follows:—

1*st dose.* Vaccine, 0·25 c.c., containing 500 million organisms, *plus* serum 0·1 c.c.

2*nd dose.* (Given ten days later.) Vaccine, 0·5 c.c., containing 1,000 million organisms, *plus* serum 0·2 c.c.

The local reactions after these injections produced a painful lump, but constitutional reactions were mild, and on a limited basis of statistics Gibson claimed favourable results with this sero-vaccine. It was largely used in France during the later stages of the war. A somewhat similar method was used in Germany and Austria during the war under the name of Boehncke's 'Dysbakta' (Boehncke, 1917).

The use of vaccines hypodermically against bacillary dysentery indeed has not as yet been tested on a sufficiently large scale to warrant any conclusions as to the value of such a procedure. In places where Flexner bacillus infections are common the use of an anti-Flexner bacillus vaccine might definitely be of value. Vaccines against Shiga's bacillus are in general too toxic to use, but fortunately infections with this organism are much less common than those with Flexner's bacillus.

It may be added that Perry and Coppinger (1925) state that vaccines of Shiga's bacillus prepared from anaërobic cultures are much less toxic than vaccines prepared from cultures grown aërobically. They advocate a mixed vaccine prepared from anaërobically grown Shiga's bacillus and aërobically grown Flexner's bacillus.

Oral Vaccines. 'Bilivaccin.'

In 1924 Dr. H. Plotz of the Institut Pasteur, Paris, read a paper before the Royal Society of Tropical Medicine and Hygiene in London, by Professor Besredka (Besredka, 1924) on the subject of 'local immunity in infectious diseases.' Besredka points out that the skin of a guinea-pig can be immunised against the bacillus of anthrax, and that the guinea-pig is immune to anthrax—no matter by what route the organism is introduced—only if its epidermis has been successfully vaccinated. Following on this line of thought he suggests the possibility of producing a local immunity in the mucosa of the intestinal tract by oral

administration of anti-cholera, anti-typhoid and anti-dysentery vaccines. Experiments with mice and rabbits showed that a solid immunity could be produced by the ingestion of heated cultures of the bacilli concerned. Nicolle and Conseil (1922) vaccinated two Europeans by making them swallow killed cultures of dysentery bacilli, and 15 and 18 days later, respectively, made them swallow living cultures. Neither developed dysentery, whereas two unvaccinated control persons who swallowed the same cultures died.

The oral use of vaccines appears to have been tested first in connection with an outbreak of dysentery among troops at Versailles in July 1923. Of 546 soldiers vaccinated by the mouth the dysentery incidence was 7·69 per cent, as against an incidence of 26·86 per cent among 1,070 unvaccinated controls. An epidemic of dysentery broke out in Petrograd in July-August 1923. On the 3rd August the Inspector of Hygiene orally vaccinated 1,000 of the exposed persons with a vaccine of dead Shiga, Flexner and Hiss strains. The subsequent incidence of dysentery was 0·3 per cent amongst the vaccinated and 3·17 per cent amongst the 1,768 unvaccinated controls.

In order to secure more intimate contact of the swallowed vaccine with the intestinal mucosa Besredka then went on to advocate the previous administration of ox bile. This increases the absorptive power of the mucosa for the large protein molecules of the vaccine, and should increase the immunity conferred. The technique now adopted—Besredka's now well-known 'bilivaccin'—is to give on three successive days before breakfast, first a dose of bile, followed by a pill containing the desiccated vaccine. The bilivaccin was first tested in connection with an outbreak of typhoid fever in the Pas de Calais. The incidence of typhoid subsequently proved to be 2·3 per cent among 173 vaccinated individuals, as against 7·7 per cent among 650 unvaccinated persons. Besredka finally claimed that the new method was harmless, safe and effective.

His paper at the Royal Society of Tropical Medicine met with a very mixed reception. It is hardly necessary to say that it aroused the greatest interest, but there were many critics. Dr. Ledingham criticized his results with *B. anthracis* and reported that several workers who had tested the oral vaccination had had completely disappointing results. Colonel D. Harvey, R.A.M.C. considered that subcutaneous inoculation of vaccine was more suitable than oral administration of tablets in the Army. Dr. F. H. Teale stated that in his experimental animals the immunity conferred by oral vaccination was not greater than that resulting from subcutaneous inoculation. Dr. W. E. Gye mentioned that ox bile might produce severe diarrhœa in rabbits, and his results with the method had had completely negative results.

Since the publication of Besredka's (1922) first paper on bilivaccin, almost innumerable reports have been published on the method. Most of these suffer from the one and almost invariable fallacy introduced into such experiments; the vaccine comes into use when the epidemic is declining from natural reasons and

the decline in the epidemic is then attributed to the use of the vaccine. The literature on this subject is now very large, but it is in such a state of confusion that it almost defies analysis. Reference may be made, however, to a few of the more important subsequent papers.

Nicolle and Conseil (1922) record the results of anti-dysentery vaccination by different methods among French troops in Tunis on a large scale. Subcutaneous vaccination was found to produce such severe reactions that the men who were vaccinated had to be given sick leave. Intravenous injections of vaccine were followed by violent reactions, and this method is quite unsuitable. In 5 Europeans oral immunisation protected against the infection, when living cultures were subsequently swallowed. Kanai (1922), however, working at the Lister Institute with the bacillus of Shiga, only succeeded in demonstrating a very low form of immunity by the oral method, whereas by the subcutaneous route, using killed cultures, he obtained evidence of solid immunity in rabbits.

Besredka's method was adopted by the League of Nations for experimental trial on a large scale, and was extensively tested on Greek refugees after the Græco-Turkish War by Gauthier (1924). This worker first used vaccine subcutaneously, but found that the reactions were very severe and abscesses sometimes followed. He then used vaccine by the oral route, administering it to 29,880 persons. Unfortunately the majority of persons vaccinated could not be followed up. An epidemic of bacillary dysentery having broken out in the island of Hydra, oral vaccination was resorted to both by way of prophylaxis and for the treatment of actual cases ; the epidemic is reported to have ceased as a result.

Pascal (1924) records the history of bacillary dysentery in 1923-24 in an asylum at Chalons-sur-Marne. Towards the end of 1923 an epidemic broke out, with 65 cases among the 256 inmates—incidence 22·72 per cent. In April 1924, a second outbreak occurred with 9 cases, 2 of which proved fatal. The remaining occupants —399 in number—were now all given oral vaccine, and only 3 of them—0·75 per cent—contracted the disease. The authors consider these figures very suggestive, but it is obvious that there are many possible sources of error in the comparison of sets of figures for one year with those for another.

Lesbre and Verdeau (1924) report that killed cultures of Shiga's bacillus are extremely toxic to rabbits on oral administration, and 2 out of 6 animals to which big doses were given died within 3 to 5 days. Results with regard to immunity were inconclusive. Enlows (1925) found that the mortality among vaccinated rabbits was lessened if cultures not more than 6 hours old were used, and suspensions of dried organisms given. Protection against lethal doses of living organisms was shown by 57 per cent of 107 rabbits immunised by oral vaccines. He concludes that the method gives 'some' protection and is worthy of further trial.

Costa, Boyer and van Deiuse (1925) record the use of Besredka's vaccine in

Dutch Navy. The whole crew, consisting of 348 men, were given 1 c.c. doses of vaccine orally daily on three consecutive days; there were no disagreeable symptoms, and the epidemic was suddenly arrested.

Seyfarth (1925) records an interesting incident among Greek refugees in camp at Phaleran; 340 refugees were vaccinated by the mouth and transferred to a new barrack alongside those occupied by other refugees among whom dysentery was epidemic. They drank the same water, which was much fouled and was doubtless the source of the dysentery, but the new-comers were not affected.

Vaz (1925) concludes that it is possible to immunise rabbits successfully against the bacillus of Shiga by the oral route, but that a large number of deaths occur among animals so treated, death being due to the action of the toxins present in the killed cultures. Two strains tested gave a high degree of protection. The serum of the immune animals shows antitoxic, but not agglutinating power. Otten and Kirschner (1925), working with experimental rabbits, conclude that oral administration of the vaccine gives better protection than its subcutaneous use, but that the immunity is not limited to the intestinal mucosa. Alivisatos and Jovanovic (1926) show that in immunised rabbits the duration of the immunity is not indefinite; it lasted up to 30 days, but not to 45. They conclude that the immunity is not an antitoxic one, and that it is at its height 4 days after the cessation of the feeds. They point out that in epidemic bacillary dysentery among men all that is required is a relative immunity over a short period of exposure to infection, and this they think that oral vaccination will achieve.

Fulton and Berry (1927) tried oral vaccination against Flexner's bacillus on infants under 2 years of age in the United States. A vaccine containing 400 million each of five different bacillary strains—total 2,000 million bacilli per c.c.—was given every month in the milk feed on three successive days to 107 infants, leaving 399 untreated infants as controls. The frequency of bacillary dysentery in the two groups, however, was identical, and the oral administration of the vaccine appeared to have no protective action at all. These authors note that the production of agglutinins in rabbits by vaccination is no guarantee that the vaccine will afford protection to human beings.

Maitra and Basu (1926) tested the bilivaccin method in four jails in Bengal. In all, oral vaccine was administered to 1,136 prisoners with no unpleasant effects, either immediate or remote. Two strains were used: (*a*) a mixed bacillary emulsion of Shiga and Flexner strains from strains locally isolated in Calcutta. With this the subsequent incidence of dysentery was as follows:—

Number vaccinated	627
Cases of dysentery among the vaccinated	18 or 2·88 per cent.
Unvaccinated controls	4,516
Cases of dysentery among the unvaccinated	237 or 5·2 per cent.

(*b*). The second strain used was Bilivaccin-Shiga prepared by La Biotherapie of France, according to Besredka's formula. Results with this were as follows :—

Number vaccinated	509
Cases of dysentery among the vaccinated	11 or 2·16 per cent.
Unvaccinated controls	1,053
Cases of dysentery among the unvaccinated	47 or 4·46 per cent.

These workers conclude that these figures are distinctly promising and that the matter should be tested on a larger scale.

It will be seen from the above brief account that opinion is very divided as to the value of oral administration of vaccines against bacillary dysentery, and it is at present quite impossible to give any decision as to whether this method should be employed or not. It seems at least to have the merit of being harmless in man, for all reports are in accordance in stating that no ill effects have followed it. The whole matter must at present be considered as being still *sub judice*.

It only remains to add that the method of administration advocated by Besredka is as follows :—Two hours before the first meal of the day, a tablet containing 20 cgms. of desiccated bile is administered orally, followed by a dose of 100 milliards of dysentery bacilli killed by heat. No food is allowed for two hours after the dose, and the same treatment is given on two further consecutive days—three days in all.

Bacteriophage may prove to be a most useful agent in prophylaxis against bacillary dysentery, if a suitable strain of full potency for the locality concerned can be obtained, and d'Herelle and Malone (1927) suggest that contaminated water-supplies may be inoculated with bacteriophage, and persons exposed to infection be treated with it orally by way of preventing their contracting the infection.

REFERENCES.

ACTON, H. W. (1918) .. .. The significance of Charcot-Leyden crystals in the fæces as an indication of amœbic colitis. *Indian Journ. Med. Res.*, Vol. VI, p. 157.

ACTON, H. W. (1921) .. .. On the behaviour of *Paramecium caudatum* towards the cinchona alkaloids. *Ibid.*, Vol. IX, p. 339.

ACTON, H. W., CHOPRA, R. N. and BOYD, T. C. (1923). .. The reduction of amino-acids into simpler natural bases (amines) by the *B. dysenteriæ* (Shiga). *Ibid.*, Vol. X, p. 837.

ACTON, H. W. and KNOWLES, R. (1924) On the dysenteries of India. *Indian Med. Gaz.*, Vol. LIX, p. 325.

ALIVISATOS, G. P. and JOVANOVIC, M. (1926). Experimenteller Beitrag zur peroralen Immunisierung des Kaninchens gegen Ruhr. *Centralbl. Bakt.*, Vol. XCVIII, p. 311.

ALLEN, W. (1921) .. .. The effect of emetine on *E. histolytica* in the stools. *Journ. Pharm. and Exp. Therapy*, Vol. XVI, p. 21.

ALLEN, W. (1922) .. .. The effect of emetinized blood and serum from man and cat on pathogenic entamœbæ in stools. *American Journ. Trop. Med.*, Vol. II, p. 195.

ANDERSON, H. W. (1917) .. .. Yeast-like fungi of the human intestinal tract. *Journ. Infect. Dis.*, Vol. XXI, p. 341.

ANDERSON, J. (1921) .. .. A study of dysentery in the field. *Lancet*, Vol. II, p. 998.

ANDREWES, F. W. (1923) .. .. Bacillary Dysentery. In *History of the Great War. Medical Services. Pathology.* London. p. 319.

ANDREWES, F. W. and INMAN, A. C. (1919). A study of the serological races of the Flexner group of dysentery bacilli. *Medical Research Council, Special Report Series*, No. 42. London.

Annual Reports of the Public Health Commissioner with the Government of India, 1919—1924. Calcutta.

ARMITAGE, F. L. (1919) .. .. Amœbic abscess of the brain with notes on a case following amœbic abscess of the liver. *Journ. Trop. Med. and Hyg.*, Vol. XXII, p. 69.

ASHFORD, B. K. (1915) .. .. A Monilia found in certain cases of sprue. Preliminary note. *Journ. American Med. Assoc.*, Vol. LXIV, p. 810.

ASHFORD, B. K. (1915*a*) .. .. Relation of the genus Monilia to certain fermentatic conditions of the intestinal tract in Porto Rico. *Ibid.*, Vol. LXIV, p. 1893.

ASHFORD, B. K. (1915*b*) .. .. Is sprue a moniliasis of the digestive tract? *American Journ. Trop. Dis. and Prevent. Med.*, Vol. III, p. 32.

BARTLETT, G. B. (1917) .. .. Pathology of dysentery in the Mediterranean Expeditionary Force. *Quart. Journ. Med.*, Vol. X, p. 185.

BESREDKA, A. (1922) .. .. Immunité générale par immunisation locale. *Bull., Inst. Pasteur*, Vol. XX, pp. 473, 513.

BESREDKA, A. (1924) .. .. Local immunity in infectious diseases. *Trans. Roy. Soc. Trop. Med. and Hyg.*, Vol. XVII, p. 346.

BOECK, W. C. and DRBOHLAV, J. (1925) The cultivation of *Endamœba histolytica*. *American Journ. Hyg.*, Vol. V, p. 371.

BOECK, W. C. and STILES, C. W. (1923) Studies on various intestinal parasites (especially amœbæ) of man. *Bull. No.* 133. *Hyg. Lab.*, Washington.

BOEHNCKE (1917) .. .. Rurschiitzimpfung im Kriege. *Med. Klin. Berlin*, Vol. XIII, p. 1083.

BROWN, H. C. (1919) .. .. Further observations on the standardization of bacterial suspensions. *Indian Journ. Med. Res.*, Vol. VII, p. 238.

BROWN, H. C. (1922) .. .. Observations on the amœbicidal action of conessine. *British Med. Journ.*, Vol. I, p. 993.

BROWN, H. C. and KIRWAN, E. W. O' G. (1915). Standardization of bacterial suspensions by opacity. *Indian Journ. Med. Res.*, Vol. II, p. 763.

BRUG, S. L. (1919) .. .. De entamœben van de rat. *Geneesk. Tijdschr. v. Nederl.-Indië*, Vol. LIX, afl. 4 (1919).

BRUMPT, E. (1909) .. .. Démonstration du rôle pathogéne du *Balantidium coli*, enkystement et conjugaison de cet infusoire. *C. R. Soc. Biol.*, Vol. LXVII, p. 103.

BRUMPT, E. (1913) .. .. *Précis de parasitologie.* 2nd edition. Paris.

CAWSTON, F. G. (1922) .. .. Emetine injections. *British Med. Journ.*, Vol. II, p. 661.

CHANDLER, A. C. (1928) .. .. The prevalence and epidemiology of hookworm and other helminthic infections in India. Part XII. General summary and conclusions. *Indian Journ. Med. Res.*, Vol. XV, p. 695.

CHOPRA, R. N. and GHOSH, B. N. (1922). The therapeutics of emetine. *Indian Med. Gaz.*, Vol. LVII, p. 248.

CHOPRA, R. N., GUPTA, J. C., DAVID, J. C. and GHOSH, S. (1927). Observations on the pharmacological action of conessine, the alkaloid of *Holarrhena antidysenterica*. *Ibid.*, Vol. LXII, p. 132.

CLARK, H. C. (1924) .. .. The distribution and complications of amœbic lesions found in 186 post-mortem examinations. *Proc. Internat. Conf. Health Problems in Trop. Amer.*, Boston, Mass., p. 365.

COSTA, S., BOYER, L. and VAN DEIUSE, F. (1925). Vaccination antidysentérique (bacille de Flexner) collective, par la voie digestive. *C. R. Soc. Biol.*, Vol. XCIII, p. 122.

CUNNINGHAM, J. (1923) .. .. Some observations on dysentery. *Indian Med. Gaz.*, Vol. LVIII, p. 358.

CUTLER, D. W. (1918) .. .. A method for the cultivation of *Entamœba histolytica*. *Journ. Path & Bacter.*, Vol. XXII, p. 22.

DALE, H. H. and DOBELL, C. (1917) .. Experiments on the therapeutics of amœbic dysentery. *Journ. Pharm. and Exp. Therapy*, Vol. X, p. 399.

DEAN, H. R. and ADAMSON, R. S. (1916). A preliminary note on a method of preparation of a non-toxic dysentery vaccine. *British Med. Journ.*, Vol. I, p. 611.

DE CASTRO, A. B. and DEUSKAR, V. N. (1927). Some observations on dysentery in Port Blair, Andaman Islands. *Indian Med. Gaz.*, Vol. LXII, p. 667.

DEEKS, W. E. (1914) .. .. Emetine in amœbic dysentery. *Ann. Trop. Med. and Parasit.*, Vol. VIII, p. 353.

D'HERELLE, F. and MALONE, R. H. (1927). A preliminary report of work carried out by the Cholera Bacteriophage Enquiry. *Indian Med. Gaz.*, Vol. LXII, p. 614.

DOBELL, C. (1919) .. .. *The Amœbæ living in Man.* London.

DOBELL, C. (1921) .. .. A report on the occurrence of intestinal protozoa in the inhabitants of Britain. *Medical Research Committee, Special Report Series,* No. 59. London.

DOBELL, C., GETTINGS, H. S., JEPPS, M. W. and STEPHENS, J. R. (1918). A study of 1,300 convalescent cases of dysentery from home hospitals. *Ibid.*, No. 15. London.

DOBELL, C. and HARVEY, D. (1923) .. Amœbic Dysentery. Chapter XI in *History of the Great War. Medical Services. Pathology.* London.

DOBELL, C. and LAIDLAW, P. P. (1926) .. The action of ipecacuanha alkaloids on *Entamœba histolytica* and some other entozoic amœbæ in culture. *Parasitology,* Vol. XVIII, p. 206.

DOBELL, C. and LAIDLAW, P. P. (1926*a*) On the cultivation of *Entamœba histolytica* and some other entozoic amœbæ. *Ibid.*, Vol. XVIII, p. 283.

DOBELL, C. and LOW, G. C. (1922) .. Amœbiasis. Chapter 62 in Byam and Archibald's *Practice of Medicine in the Tropics,* Vol. II. London.

DOBELL, C. and LOW, G. C. (1922*a*) .. Balantidiosis. Chapter 77 in Byam and Archibald's *Practice of Medicine in the Tropics,* Vol. II. London.

DOBELL, C. and O'CONNOR, F. W. (1921) *The Intestinal Protozoa of Man.* London.

DOBELL, C. and STEVENSON, A. C. (1918) A note on the duration of infections with *Entamœba histolytica. Trans. Soc. Trop. Med. & Hyg.*, Vol. XI, p. 168.

DOLD, H. and FISCHER, W. (1918) .. Anatomical findings in experimental sprue. *China Med. Journ.*, Vol. XXXII, p. 125.

DRBOHLAV, J. J. (1925) .. .. Une nouvelle preuve de la possibilité de cultiver *Entamœba dysenteriæ* type *histolytica. Ann. Parasit. Hum. and Comp.*, Vol. III, p. 349.

DUDGEON, L. S. (1919) .. .. The dysenteries: bacillary and amœbic. *British Med. Journ.*, Vol. I, p. 448.

EHRENBERG, C. G. (1838) .. .. *Die Infusionsthierchen als vollkommene Organismen.* Leipzig.

ELDERS, C. .. .. .. Over de Behandeling en de Oorzaken van Indische Spruw en Daarmer waar schigu-lijk ætiologisch Ver wante Symptomem-Complexen. [No date or publisher.] Review in *Trop. Dis. Bull.*, Vol. XIV (1919). p. 121.

ELDERS, C. (1919) .. .. Over Indische Spruw. *Nederl. Tijdschr. v. Geneesk.*, Part 2, No. 21, p. 1683.

ELLSWORTHY, S. W. and WHEATLEY, F. E. (1923). High and low onemata. A mistaken conception. *Boston Med. and Surg. Journ.*, Vol. CLXXXVIII, p. 545.

ENLOWS, E. M. A. (1925) .. .. Vaccination by mouth against bacillary dysentery. *Public Health Rept.*, Vol. XL, p. 639.

FLETCHER, W. (1920) .. .. Capsulate mucoid forms of paratyphoid and dysentery bacilli. *Journ. Roy. Army Med. Corps*, Vol. XXXIV, p. 219.

FLETCHER, W. (1927) .. .. *Annual Report of the Institute for Medical Research, Kuala Lumpur, F. M. S. for* 1926. Kuala Lumpur.

FLETCHER, W. and JEPPS, M. W. (1924) *Dysentery in the Federated Malay States. Studies from the Institute for Medical Research, Kuala Lumpur.* No. 19. London.

FLETCHER, W. and MACKINNON, D. L. (1919). A contribution to the study of chronicity in dysentery carriers. *Medical Research Committee. Special Report Series.* No. 29. London.

FULTON, M. N. and BERRY, G. P. (1927) Agglutination reactions in rabbits following oral vaccination with *Bacillus dysenteriæ*. *American Journ. Dis. Children*, Vol. XXXIII, p. 714.

GAUTHIER, A. (1924) .. .. Essais de vaccinations et de vaccinothérapie par la voie buccale contre la dysenterie bacillaire. *Bull. Acad. Méd.*, Vol. XCI, p. 72.

GIBSON, H. G. (1917) .. .. A new method of preparation of a vaccine against bacillary dysentery which abolishes severe local reactions. Also experiments with this vaccine on animals and men. *Journ. Roy. Army Med. Corps*, Vol. XXVIII, p. 615.

GLAESSNER, K. (1908) .. .. Ueber Balantidienenteritis. *Centralbl. Bakt.*, I. Abt, (orig.), Vol. XLVII, p. 351.

GLYNN, E., BERRIDGE, E. M., FOLEY, V., PRICE, M. and ROBINSON, A. L. (1918). Report upon 2,360 enteritis 'convalescents' received at Liverpool from various expeditionary forces. *Medical Research Committee. Special Report Series.* No. 7. London.

GONZALEZ-MARTINEZ, I. (1920) .. Les méthods de laboratoire dans le diagnostic de la diarrhée chronique des pays chands. *Bull. Soc. Path. Exot.*, Vol. XIII, p. 384.

GREGG, A. J. (1928) .. .. The use of the sigmoidoscope in the diagnosis of dysentery : a clinical lecture. *Indian Med. Gaz.*, Vol. LXII, p. 31.

GUPTA, B. M. DAS (1925) .. .. A note on the cultivation of an Entamœba from a monkey, *Macacus rhesus*. *Ibid.*, Vol. LX, p. 323.

HANCE, J. B. (1927) .. .. The sigmoidoscope as an aid to diagnosis in chronic dysentery and its sequelæ. *Ibid.*, Vol. LXII, p. 496.

HARVEY, D. (1921) .. .. Laboratory methods. Sub-section, Sera and Vaccines. In Byam and Archibald's *Practice of Medicine in the Tropics*, Vol. I, p. 623. London.

HAUGHWOUT, F. G. (1924) .. .. The practical microscopic diagnosis of dysentery. *Bulletins from the Institute for Medical Research, Federated Malay States, No.* 3 *of* 1924. Manila.

HERMITTE, L. C. D., SEN GUPTA, S. C. and BISWAS, T. N. (1926). The therapeutic value of stovarsol administered by mouth in parasitic infections of the bowel, with special reference to its rapidly curative effect in human balantidiosis. *Trans. Roy. Soc. Trop. Med. and Hyg.*, Vol. XX, p. 206.

HOARE, C. A. (1926) .. .. [Infection of kitten by injection of cysts of *Entamœba histolytica per rectum*.] *Ibid.*, Vol. XIX, p. 277.

HUTCHINSON, R. (1923) .. .. The chronic abdomen. *British Med. Journ.*, Vol. I, p. 667.

KANAI, S. (1922) .. .. .. Further experimental studies on immunization against *B. dysenteriæ* (Shiga) and its toxins. *British Journ. Exp. Path.*, Vol. III, p. 158.

KESSEL, J. F. (1923) .. .. Methods of securing amœbæ-free rats for experimental infection with intestinal amœbæ. *Univ. California Publ. Zool.*, Vol. XX, p. 401.

KESSEL, J. F. (1923*a*) .. .. Experimental infection of rats and mice with the common intestinal amœbæ of man. *Ibid.*, Vol. XX, p. 409.

KNOWLES, R. (1925) .. .. Report of Professor of Protozoology. *Ann. Rept. Calcutta Sch. Trop. Med.*, 1924, p. 71.

KNOWLES, R., NAPIER, L. E. and DAS-GUPTA, B. M. (1923). A preliminary note on the relationship of the intestinal protozoa of man to the hydrogen-ion concentration of their environment. *Indian Med. Gaz.*, Vol. LVIII, p. 151.

KOFOID, C. A., SWEZY, O. and BOYERS, L. M. (1925). A report on an investigation of intestinal protozoan infections at Santa Marta, Columbia, in the hospital of the United Fruit Company, with special reference to the incidence of amœbiasis. *Fourteenth Ann. Rep. Med. Dept. United Fruit Co., Boston, Mass.* 1925, p. 140.

LAL, S. M. (1923) .. .. A case of *Fasciolopsis buskii* infection. *Indian Med. Gaz.*, Vol. LVIII, p. 586.

LEDINGHAM, J. C. G. (1920) .. Dysentery and enteric disease in Mesopotamia from the laboratory standpoint. An analysis of laboratory data during the eighteen months ending December 31st, 1918. *Journ. Roy. Army Med. Corps*, Vol. XXXIV, pp. 189, 306.

LESBRE, P. and VERDEAU, A. (1924) .. Essai d'immunisation expérimentale par voie buccale contre la dysentérie à bacillus de Shiga. *C. R. Soc. Biol.*, Vol. XCI, p. 883.

LEUCKART, R. (1861) .. .. Ueber *Paramœcium* (*?*) *coli* Malmst. *Arch. Naturgesch.*, Vol. XXVII, i, p. 81.

LOPEZ, V. J. (1926) .. .. Gastro-enteritis in Alipuram Jail, Bellary. *Indian Med. Gaz.*, Vol. LXI, p. 590.

LYNCH, K. M. (1915) .. .. The rat as carrier of a dysenteric amœba. *Journ. American Med. Assoc.*, Vol. LXV, p. 2232.

MACKIE, F. P. (1922) .. .. Laboratory records from Mesopotamia. *Indian Med. Gaz.*, Vol. LVII, p. 85.

MAITRA, G. C. and BASU, J. B. (1926) .. A trial of oral vaccination against bacillary dysentery in Indian jails. *Ibid.*, Vol. LXI, p. 335.

MALONE, R. H. and BIRD, W. (1927) .. A report on three cases of bacillary dysentery treated with bacteriophage. *Ibid.*, Vol. LXII, p. 373.

MANIFOLD, J. A. (1926) .. .. Important features in the correct diagnosis of dysentery in India. *Journ. Roy. Army Med. Corps*, Vol. LXVI, p. 81.

MANSON-BAHR, P. H. (1914) .. A study of epidemic dysentery in the Fiji Islands with special reference to its epidemiology and treatment.

MANSON-BAHR, P. H. (1914*a*) .. Researches on sprue. *Trans. Soc. Trop. Med. and Hyg.*, Vol. VII, p. 161.

MANSON-BAHR, P. H. (1919) .. The correlation of the pathology and bacteriology of bacillary dysentery. A dissertation on some of the laboratory problems arising in connection with this disease in the Eastern theatres of War. *Journ. Roy. Army Med. Corps*, Vol. XXXIII, p. 117..

MANSON-BAHR, P. H. (1922) .. Dysentery. Chapter III in *History of the Great War. Medical Services. Diseases of the War.* Vol. I. London.

MANSON-BAHR, P. H. (1923) .. Sprue. Chapter CIV in Byam and Archibald's *Practice of Medicine in the Tropics.* Vol. III. London.

MANSON-BAHR, P. H. (1925) .. Manson's *Tropical Diseases.* 8th edition. London.

MANSON-BAHR, P. H. and GREGG, A. L. (1921). Diagnosis by the sigmoidoscope. *Lancet*, I, p. 1121.

MANSON-BAHR, P. H., PERRY, H. M. and MANSON, P. (1922). Bacillary dysentery. Chapter L in Byam and Archibald's *Practice of Medicine in the Tropics*, Vol. II. London.

MARTIN, C. J. and WILLIAMS, F. E. (1918). The chance of recovering dysentery bacilli from the stools according to the time elapsing since the onset of the disease. *British Med. Journ.*, Vol. I, p. 447.

MAYER, M. (1919) .. .. Klinische, morphologische und experimentelle Beobachtungen bei Amöbenerkrankungen. *Arch. f. Schiffs.-u. Trop.-Hyg.*, Vol. XXIII, (No. 10, pp. 177—210).

MCCARRISON, R. (1919) .. .. The pathogenesis of deficiency disease. VII. The effects of autoclaved rice dietaries on the gastro-intestinal tract of monkeys. *Indian Journ. Med. Res.*, Vol. VII, p. 283.

MCDONALD, J. D. (1922) .. .. On *Balantidium coli* (Malmsten) and *Balantidium suis* (sp. nov.), with an account of their neuromotor apparatus. *Univ. California Publ. Zool.*, Vol. XX, p. 243.

MICHEL, C. (1918) .. .. On the use of a Monilia vaccine in the treatment of sprue. *Journ. Infect. Dis.*, Vol. XXII, p. 53.

MUSGRAVE, W. E. (1910) .. .. Intestinal amœbiasis without diarrhœa. A study of fifty fatal cases. *Philippine Journ. Sci.*, (B), Vol. V, p. 229.

NICHOLLS, L. (1918) .. .. The ætiology of sprue. *Indian Med. Gaz.*, Vol. LIII, p. 409.

NICOLLE, C. and CONSEIL, E. (1922) .. Vaccinations préventives par voie digestive chez l'homme dans la dysenterie bacillaire et la fièvre méditerranéenne. *Ann. Inst. Pasteur*, Vol. XXXVI, p. 579.

OTTEN, L. and KIRSCHNER, L. (1925) .. Orale vaccinatie tegen bacillaire dysenterie. *Geneesk. Tijdschr. v. Nederl.-Indië*, Vol. LXV, p. 608.

PASCAL, C. (1924) .. .. Vaccination antidysentérique par voie buccale. *C. R. Soc. Biol.*, Vol. XCI, p. 874.

PERRY, H. M. and COPPINGER, C. J. (1925). Observations on the employment of anaërobically grown *Bacillus dysenteriæ* Shiga as a vaccine. *Journ. Roy. Army Med. Corps*, Vol. XLV, p. 241.

PYMAN, F. L. and WENYON, C. M. (1917). The action of certain emetine derivatives on amœbæ. *Journ. Pharm. and Exp. Therapy*, Vol. X, p. 237.

RAMSAY, G. C. (1923) .. .. The dissemination of human helminthic infections by animals. *Indian Med. Gaz.*, Vol. LVIII, p. 422.

ROGERS, L. (1913) .. .. *Dysenteries : their differentiation and treatment.* Second edition. London.

ROGERS, L. (1914) .. .. Two cases of sprue treated by mouth streptococcal vaccines, and emetine hydrochloride hypodermically *Lancet*, Vol. I, p. 1605.

ROGERS, L. (1921) .. .. *Bowel Diseases in the Tropics.* London.

ROGERS, L. (1925) .. .. Pathological evidence bearing on disease incidence in Calcutta. *Glasgow Med. Journ.*, Vol. XXI, 1, p. 95.

SCOTT, H. H. (1923) .. .. A new theory as to the causation of sprue and the results of treatment based thereon. *Trans. Roy. Soc. Trop. Med. and Hyg.*, Vol. XVI, p. 475.

SELLARDS, A. W. and LEIVA, L. (1923) .. Investigations concerning the treatment of amœbic dysentery. *Philippine Journ. Sci.*, Vol. XXII, p. 1.

SELLARDS, A. W. and LEIVA, L. (1923*a*) The effect of stasis on the development of amœbic dysentery in the cat. *Ibid.*, Vol. XXII, p. 39.

SELLARDS, A. W. and THEILER, M. (1924) Investigations concerning amœbic dysentery. *American Journ. Trop. Med.*, Vol. IV, p. 309.

SEYFARTH, C. (1925) .. .. Infektions krankheiten und ihre Bekämpfung unter den Kleinasiatischen Flüchtlingen in Griechenland, Kreta und Korfu. *Zeitschr. Hyg. u. Infekt.*, Vol. CIV, p. 682.

SINTON, J. A. (1923) .. .. The occurrence of *Balantidium coli* in the fæces of an Indian. *Indian Med. Gaz.*, Vol. LVIII, p. 432.

SMITH, A. M. (1918) .. .. Measurements of and observations upon the cysts of *Entamœba histolytica* and of *Entamœba coli. Ann. Trop. Med. and Parasit.*, Vol. XII, p. 27.

SMITH, A. M. (1919) .. .. A contribution to the question of the number of races in the species *Entamœba histolytica. Ibid.*, Vol. XIII, p. 1.

STITT, A. B. (1922) .. .. *The diagnostics and treatment of tropical diseases.* 4th edition. London.

STRONG, R. P. (1904) .. .. The clinical and pathological significance of *Balantidium coli. Bur. Govt. Lab.*, Manila, Bull. No. 26.

STRONG, R. P. and MUSGRAVE, W. E. (1900). In *Annual Report of the Surgeon-General, U. S. Army for* 1900. Also in *Journ. American Med. Assoc.* (1900), Vol. XXXV, p. 498. (Referred to by Musgrave, W. E. and Sison, A. G., 1914. *Philippine Journ. Sci.*, Vol. IX, p. 243.)

TEAGUE, O. and CLURMAN, A. W. (1916) A method of preserving typhoid stools for delayed examination, etc. *Journ. Infect. Dis.*, Vol. XVIII, p. 653.

THOMSON, J. G. and ROBERTSON, A. (1921) Charcot-Leyden crystals in the stools as an aid to the diagnosis of entamœbic dysentery. *Journ. Trop. Med. and Hyg.*, Vol. XXIV, p. 289.

THOMSON, J. G. and ROBERTSON, A. (1925). Notes on the cultivation of certain amœbæ and flagellates of man, using the technique of Boeck and Drbohlav. *Ibid.*, Vol. XXVIII, p. 345.

UJIHARA, K. (1914) .. .. Studien über die Amöbendysenterie. *Zeitschr. f. Hyg.*,

VALLARINO, J. J. (1924) .. .. Preliminary report on the value of the Roentgen ray in estimating the extent of amœbic infection of the large intestine. *Proc. Internat. Conf. Health Problems in Trop. America,* Boston, Mass., p. 357.

VAZ, E. (1925) .. .. .. Immunização per os contra o B. de Shiga. Contribuição ao estudo da natureza da immunidade. Immunisation per os contre le bacille de Shiga. Contribution à l'étude du mécanisme de l'immunite. *Mem. Inst. de Butantan,* Vol. II, p. 99.

VEDDER, E. B. (1912) .. .. An experimental study of the action of ipecacuanha on amœbæ. *Far East. Assoc. Trop. Med. Trans.,* 2nd Congr. (Hongkong), p. 87. *Journ. Trop. Med. and Hyg.*, Vol. XV, p. 313.

WALKER, E. L. (1913) .. .. Experimental balantidiosis. *Philippine Journ. Sci.*, (B), Vol. VIII, p. 333.

WALKER, E. L. and SELLARDS, A. W. (1913). Experimental entamœbic dysentery. *Ibid.*, (B), Vol. VIII, p. 253.

WARE, F. (1916) .. .. .. The possibility of amœbic dysentery in the dog, and its treatment with emetine. *Journ. Comp. Path. and Therapy,* Vol. XXIX, p. 126.

WATS, R. C., LOGANANDAN, A. D. and CONQUEST, C. N. (1928). Dysentery in Secunderabad. *Indian Med. Gaz.*, Vol. LXIII, p. 13.

WENYON, C. M. (1926) .. .. *Protozoology : a manual for medical men, veterinarians and zoologists.* London. 2 Vols.

WENYON, C. M. and O'CONNOR, F. W. (1916). Memorandum on the carriage of cysts of *Entamœba histolytica* by houseflies, with some notes on their resistance to disinfectants and some other agents. *Medical Advisory Committee,* Mediterranean Area, Alexandria.

WENYON, C. M. and O'CONNOR, F. W. (1917). *Human Intestinal Protozoa in the Near East.* London.

YORKE, W. and ADAMS, A. R. D. (1926) Observations on *Entamœba histolytica.* I. Development of cysts, excystation, and development of excysted amœbæ *in vitro. Ann. Trop. Med. and Parasit.*, Vol. XX, p. 279.

YORKE, W. and ADAMS, A. R. D. (1926*a*) Observations on *Entamœba histolytica.* II. Longevity of the cysts *in vitro,* and their resistance to heat and to various drugs and chemicals. *Ibid.*, Vol. XX, p. 317.

INDEX.

Adrenal deficiency, 113, 115
After-treatment, bacillary dysentery, 95
Agar medium, 70
Age incidence of dysenteries, 16
Agglutination reaction in bacillary dysentery, 83
Agglutination test, 76, **78**
  in bacillary carrier, 118
  with polyvalent serum, 76
Alcresta ipecac, 138
Alkalies in sprue, 149
Amœbiasis, chronic, 124
Amœbic dysentery :
  cellular exudate in, 48
  characters of stools, 45
  chronic, 106
  chronic and relapsing, 40
  complications, 105
  distribution of lesions, 37
  fulminant, 39
  in dry areas, 22
  intestinal stasis in, 35
  Kurchi in treatment, 103
  perforation in, 39, 106
  possible rôle of streptococci, 35
  reaction of stools, 35
  relapsing, 106
  relative incidence of, 20
  sloughs in, 37
  standard treatment for, 100
  stools in, 39
  stovarsol treatment, 108
  symptomatology of, 38
  test for cure, 105
  yatren treatment, 101
Amœbic dysentery, acute :
  aetiology of, 30
  pathology of, 32
  treatment of, 97
Amœbic dysentery and flies, 31
Amœbic hepatitis, 105
Amœbic infection :
  duration of, 33
  incidence of, 31
  mode of transmission, 32
  possible rôle of dog, 32
  possible rôle of rat, 33
  transmission of, 31
Amœbic showers, 128
Amœbic ulceration, 34
Anæmia, pernicious, of Indians, 143
  (*see* also Pernicious anæmia)
Ankylostomiasis, 17
Antiserum therapy, 91
Appendicitis in *E. histolytica* carriers, 127
Arthritis in bacillary dysentery, 96
Ascaris infection, 18
Asthenic diarrhœa of Indians, 113, **161**
Asthma in *E. histolytica* carriers, 127
Atony of gut in bacillary carriers, 114

Bacillary carriers, 24, 109
  agglutination test in, 118
  diagnosis of, 116
  endocrine therapy in, 122
  Europeans, 114
  incidence of, 109
  Indians, 113
  isolation of bacilli from, 117
  neurasthenia in, 115
  pathology of, 110
  symptomatology, 113
  treatment of, 121
  vaccine therapy in, 122
Bacillary dysentery :
  after-treatment, 95
  and carriers, 24
  and flies, 24
  and water-supplies, 23
  bacteriophage treatment, 92
  cell exudate in, 49
  character of stools in, 30
  choleraic, 29

Bacillary dysentery—*continued.*
chronic, 109 (*see* also Chronic bacillary dysentery)
contagion in, 23
distribution of lesions, 37
fever in, 29
findings in stools, 80
fulminant, 29
histopathology of, 28
macroscopic character of stools, 45
medicinal treatment, 93
perforation in, 28
plating the stools, 80
post-mortem findings, 25
predisposing causes, 23
relative frequency of, 20
relative incidence of types, 24
seasonal incidence, 22
secondary invaders in, 65
serological diagnosis, 83
streptococcal infections in, 143
symptomatology, 29
treatment, 89, 119
treatment of complications, 96
vaccine therapy, 83
Bacillary dysentery, acute, 23, 89
diet in, 90
pathology, 25
serum treatment, 91
treatment of, 89
Bacillus aertrycke, 65
—— *albofaciens*, 112
—— *asiaticus*, 66, 118
—— *carolinus*, 66, 73
—— *cloacæ*, 80
—— *coagulans*, 66
Bacillus coli communis :
in blood-stream, 96
in mucous retention cysts, 110
Bacillus diffluens, 66
Bacillus dysenteriæ, 67 (*see* also Dysentery bacilli)
agglutination test, 76, 78
animal inoculation, 81
colonies of, 71
non-agglutinating strains, 75
Bacillus enteritidis, 65
—— *fæcalis alkaligenes*, 66, 70, 73, 118
—— *fæcaloides*, 66
—— *giumai*, 66
—— *lunavensis*, 66
—— *metadiffluens*, 66
Bacillus mobilis, 66
—— *morgani*, 65
—— *mucosus capsulatus*, 118
Bacillus of Shiga, anaërobic culture of, 157
Bacillus paracoagulans, 66
—— *paradiffluens*, 66
—— *pritnitzi*, 66
Bacillus proteus, 65, 70, 137
in entero-colitis of infants, 16
Bacillus pseudo-asiaticus, 66
—— *pseudo-carolinus*, 66
—— *pseudo-morgani*, 66
Bacillus pyocyaneus, 65, 66, 118
and infantile diarrhœa, 16
inhibits *B. dysenteriæ*, 80
vaccine of, 84
Bacillus typhosus, 72, 73
Bacteriophage :
in bacillary carrier, 121
in prophylaxis, 161
treatment by, 92
Bael fruit in sprue, 149
Bael sherbet, 96
Balantidial dysentery, 40
coli exudate in, 52
pathology and symptoms, 40
treatment, 107
Balantidium coli, 61
cultivation of, 63
cyst of, 62
incidence in India, 19
infection in Assam, 19
Barium meal, 117
Bile :
use of in asthenic diarrhœa, 153
use of in bilivaccin, 158
Bilivaccin, 157
large scale use of, 159
mode of administration, 161
results with, 158
testing of, in rabbits, 159
Bismuth :
in amœbic dysentery, 100
in bacillary dysentery, 94
Bismuth emetine iodide, 138
Blastocystis hominis, 52, 58
Blood picture :
in pernicious anæmia of Indians, 152
in sprue, 147
British Army, dysentery in, 1
Broth cultures, 70

Calcium and parathyroid treatment :
in chronic bacillary dysentery, 122
in sprue, 149
Carcinoma of rectum, 17
Carrier : [*see* (*a*) Bacillary carrier ; (*b*) *E. histolytica* carrier]
Carriers, identification of, in communities, 154
Case mortality rates, 8
Cell exudate :
in amœbic dysentery, 48
in bacillary dysentery, 49
in balantidial dysentery, 52
Charcot-Leyden crystals, 52, 130, 136
Children, bacillary dysentery in, 95
Chilodon, in stools, 19
Cholera :
mortality from, 4
simulating dysentery, 18
Choleraic dysentery, 29
Chromatoid substance, 131
Chronic amœbiasis, 124
Chronic amœbic dysentery, 106
Chronic bacillary dysentery :
diagnosis of, 116
pathology of, 110
prognosis in, 119
radioscopy in, 117
rectal irrigations in, 119
secondary infections in, 118
severe cases, 113
symptomatology, 111
treatment, 119
Colitis :
bacterial flora in, 65
membranous, 18
'Collosal' kaolin, 94
Conessine, 104
Conradi-Drigalski medium, 71
use for streptococci, 136
Cultivation :
of *Balantidium coli*, 63
of dysentery bacilli, 72
of *Entamœba histolytica*, 53
Culture media :
Conradi-Drigalski, 71
Endo's, 71
for *Balantidium coli*, 63
for *Entamœba histolytica*, 58
for streptococci, 136
McConkey's, 71
Sabouraud's agar, 74
Cyst :
of *Endolimax nana*, 136
of *E. histolytica*, cultivation of, 60
Cytodiagnosis, 53

Docks' bismuth treatment, 100
Diagnosis :
amœbic dysentery, 45
bacillary carrier, 116
bacillary dysentery, 45, 72
chronic bacillary dysentery, 116
E. histolytica carrier, 129
laboratory, 45
serological, 83
sigmoidoscopic, 43
sprue, 148
Diarrhœa *v.* dysentery incidence, 7
Dientamœba fragilis, 140
Diet :
in amœbic dysentery, 101
in bacillary dysentery, 90
in pernicious anæmia, 152
in sprue, 149
Discomyces asteroides, 129
Dog, possible rôle in amœbiasis, 32
Dosage of vaccines, 87
Dreyer's agglutination method, 78
Dudgeon's solution, 118
'Dyak's hair' sloughs, 37
Dysenteries, age incidence of, 16
Dysentery :
and poverty, 8
and rainfall, 13
and social strata, 8
annual mortality from, 7
as complication of colitis, 20
as terminal infection, 7
case mortality rate, 8
causes of, in India, 19, 25
definition of, 16
diagnosis of, 43
hospital admissions and deaths, 2
in British Army, 1
incidence of, 6
index, 155
in Indian Army, 1
in infants, 16
in jails, 1
laboratory examination of stools in, 45
mixed infections, 41
morbidity due to, 1

Dysentery—*continued.*
mortality due to, 1
other conditions simulating, 16
prophylaxis against, 154
seasonal incidence, 9
sigmoidoscopic appearances in, 43
versus diarrhœa, incidence, 7
Dysentery bacilli : (*see* also *B. dysenteriæ*)
bacteriology of, 64
cultivation of, 72
cultural characters, 70
difficulties in isolating, 79
identification of, 74
in blood-stream, 28
in urine, 28
isolation of, from carriers, 117
morphology of, 68
non-motile, 69
preservation of, 118
proportion of successful cultures, 80
staining reactions, 68
toxins of, 81

Emetine : (*see* also Bismuth emetine iodide)
action of, on *E. histolytica*, 97
toxic effects of, 99
treatment of amœbic dysentery, 99
Endocrine system :
in chronic bacillary dysentery, 115
in sprue, 148
Endocrine therapy, in chronic bacillary dysentery 122
Endolimax nana :
cyst of, 136
morphology of, 140
Endomyces in sprue, 145
Endo's medium, 71
Entamœba coli, 140
—— *gingivalis*, 140
Entamœba histolytica :
action of emetine on, 97
carriers : (*see* below)
cultivation of, 57
cultivation of, from cysts, 60
cyst of, 131
chromatoid bars in, 131
dimensions of, 133
excystation of, 33
glycogen in, 131
infectivity of, 32
resistance of, 30
viability of, 31, 135
degenerative phases, 56
geographical distribution, 31
incidence of infection, 31
ingestion of bacteria by, 60
morphology of, 54, 140
nuclear characters, 55
pre-cyst of, 131
vegetative form, 54
E. histolytica carriers, 124
amœbic showers in, 128
bismuth emetine iodide treatment, 138
colic in, 126
constipation in, 126
diagnosis by post, 136
diagnosis of, 129
diet in, 138
fever in, 127
hepatitis in, 128
incidence of, 156
Kurchi treatment, 139
laboratory diagnosis, 130
leucoderma in, 129
pathology of, 124
prognosis of, 137
radioscopic examination, 129
rôle of, 31
signs and symptoms, 125
stovarsol treatment, 139
streptococcal vaccines, 139
streptothrix infection in, 129
treatment of, 137
types of, 125
Europeans, dysentery in, 8

Fasciolopsis buski, 19
Fever :
in bacillary dysentery, 29
in *E. histolytica* carriers, 127
Fevers, mortality from, 3
Flagella, stain for, 69
Flexner's bacillus : (*see* also *B. dysenteriæ* and Dysentery bacilli)
agglutinability of, 75
colonies of, 74
incidence relative to Shiga's bacillus, 24
sugar reactions, 77

Flies :
and amœbic dysentery, 31
and bacillary dysentery, 24
Fulminant dysentery, 29

Garrow's agglutinometer, 76
Gelatine medium, 70
'Ghost' cells, 51
Giardia intestinalis, 18
Glucose media, 66, 67
Glycogen in *E. histolytica* cysts, 131

Hæmocytometer in standardising vaccines, 86
Hæmorrhoids, 16
'Hæmostyl' in pernicious anæmia, 153
Hanging drop method for motility, 68
Hepatitis, amœbic : (*see* also Amœbic hepatitis)
in *E. histolytica* carriers, 105
Hill-diarrhœa, 112
His bacillus, 75
Holarrhenine, 104
Hypertonic saline, 95
Hypochlorhydria, 115
Hypothyroidism in chronic bacillary dysentery, 115

Indian Army, dysentery in, 1
Indol, tests for, 75
Infantile diarrhœa, 16
Infants, enterocolitis of, 16
Infusions, intravenous, 95
Intestinal antiseptics, 121
Intestinal protozoa in bacillary dysentery, 52
Intestinal protozoal cysts, Plate IV, p. 132, Plate V, p. 134
Intravenous saline, 95
Intussusception, 17
Iodamœba bütschlii, 140
Iodine emulsion of stools, 47
Iodine therapy :
in chronic bacillary dysentery, 122
in pernicious anæmia, 153
Iridocyclitis in bacillary dysentery, 96
Iron arsenite :
in pernicious anæmia, 153
in sprue, 151
Irrigations in bacillary dysentery, 94

Jails, dysentery incidence in, 1

Kala-azar, dysentery in, 18
Kaolin, 94
Kitchens, care of, 155
Kitten, amœbic infection in, 33
Kurchi :
in amœbic dysentery, 103
in *E. histolytica* carriers, 139

Laboratory diagnosis :
amœbic dysentery, 45
bacillary dysentery, 45
E. histolytica carriers, 130
Laboratory examination of stools, 45
Lactose fermenters, 65, 73, Table VI, p. 81
Lactose late fermenters, 65, 73, Table VI, p. 81
Lactose non-fermenters, 65, 73, Table V, p. 78
Latrines, care of, 155
Leucoderma in *E. histolytica* carriers, 129
Litmus milk, 70
Liver in pernicious anæmia, 152

Macrophages, 49
mistaken for *E. histolytica*, 21
Macroscopic inspection of stools, 154
Malaria :
and dysentery, 18
mortality from, 2
Mannite :
fermenters of, 64
non-fermenters of, 64
McConkey's medium, 71
Membranous colitis, 18
Methyl red test, 80
Mixed infections, 41
treatment of, 107
Monilia :
colonies of, 66
culture medium for, 74
Monilia psilosis, 144
Morbid anatomy : (*see* Pathology)
Morbidity from dysentery, 1
Morgan's bacillus and summer diarrhœa, 16
Morphia, use of, 94
Mortality from dysentery, 1
Motility, tests for, 68
Mucous disease of infancy, 143

Neurasthenia in bacillary carriers, 115
Nitroso-indol test, 75
Non-agglutinable strains, 75

Omnopon, 138
Opium, use of, 94
Optochin mouth-wash, 150
Osmo-kaolin, 94, 102

Paradimethyl-amido-benzaldehyde test, 75
Parasaccharomyces ashfordi, 66, 144
Pathology :
  acute bacillary dysentery, 25
  amœbic dysentery, 33
  bacillary carrier, 110
  chronic bacillary dysentery, 110
  E. histolytica carrier, 124
  relapsing amœbic dysentery, 106
  sprue, 147
Perforation :
  in amœbic dysentery, 39, 106
  in bacillary dysentery, 28
Pernicious anæmia :
  and asthenic diarrhœa of Indians, 151
  blood picture in, 152
  complications in, 153
  diet in, 152
  findings at autopsy in, 152
  'Hæmostyl" in, 153
  iodine in, 153
  iron arsenite injections in, 153
  liver in, 152
  ox bile in, 153
  streptococcal vaccines, 152
  streptococci in, 151
  symptoms and signs, 151
  treatment of, 152
Pilocarpine injections in sprue, 151
Plague, mortality from, 5
Polypus :
  formation in bacillary dysentery, 111
  of rectum, 17
Polyvalent antiserum, 91
'Poona-itis,' 22
Post-mortem findings :
  in pernicious anæmia of Indians, 152
  in sprue, 147
Potato medium, 70
Poverty and dysentery, 8
Pregnancy and dysentery, 95
Preliminary agglutination test, 76
Pressor bases, 82
Prognosis :
  in *E. histolytica* carrior, 137
  in sprue, 148
Prophylaxis against dysentery, 154
  bacteriophage, 161
  bilivaccin, 157
  care of kitchen, 155
  care of latrines, 155
  E. histolytica carriers, 156
  examination for carriers, 154
  in the Great War, 155
  macroscopic examination of stools, 154
  oil in dietary, 155
  oral vaccines, 157
  sero-vaccines, 157
  vaccines, 156
Ptomaine poisoning, 18

Quinine, rectal injections, 120

Radioscopy :
  in chronic bacillary dysentery, 117
  in *E. histolytica* carrier, 129
Rainfall and dysentery, 13
Rat as possible transmitter of *E. histolytica*, 33
Rectal irrigations, 119
Red cells, characters of, in amœbic stool, 48
References, 163
Relapsing amœbic dysentery, 106
Relative mortality from different diseases, 3
Respiratory diseases, mortality from, 3

Sabouraud's agar, 74
Saline emulsion of stools, 46
Salol, 94
Santonin in sprue, 149
Schistosoma mansoni, 19
Schmitz bacillus, 75
Seasonal incidence of dysentery, 9
Secondary invaders, 65
  B. albofaciens, 112
  B. coli, 110
  in chronic bacillary dysentery, 118
Serum sickness, 96
Serum treatment of bacillary dysentery, 91
Shiga's bacillus : (*see* also *B. dysenteriæ* and dysentery bacilli)

Shiga's bacillus—*continued.*
sugar reactions, 77
toxins of, 81
vaccines of, 85
vaccines of, dosage, 87
Sigmoidoscope, 43
in amœbic dysentery, 44
in bacillary dysentery, 44
in chronic bacillary dysentery, 116
Sloughs in amœbic dysentery, 37
Social strata and dysentery, 8
Spinach in pernicious anæmia, 152
Spirochætes in stools, 48, 49
Sprue, 143
ætiology of, 143
alkalies in, 149
as sequel to bacillary dysentery, 145
bael fruit in, 149
blood picture in, 147
calcium and parathyroid treatment, 149
care of the mouth, 150
complement deviation in, 144, 145
complications of, 148
diagnosis of, 148
diarrhœa in, 148
diet in, 149
endocrine glands in, 148
iron injections in, 151
milk diet in, 150
Monilia vaccines, 150
Parasaccharomyces ashfordi, 144
pilocarpine in, 151
post-mortem findings, 147
prognosis in, 148
santonin in, 149
stools in, 147
streptococcal theory, 145
streptococcal vaccines in, 150
streptococci in, 150
symptomatology, 146
theories as to causation, 144
tongue in, 146
treatment of, 148
treatment of complications, 150
vaccines in, 84, 150
vitamine deficiency theory, 144
Stains :
for dysentery bacilli, 68
for flagella, 69
Standardisation of vaccines, 85
Stools :
amœbic dysentery, 39
bacillary dysentery, 30, 45
characters of, in amœbic dysentery, 45
chronic bacillary dysentery, 112
cytodiagnosis of, 53
E. histolytica carrier, 130
flora of, in *E. histolytica* infections, 137
iodine emulsion of, 47
laboratory examination of, 45
macroscopic appearance of, 45
pH reaction of, 35
reaction of, 46
saline emulsion of, 46
spirochætes in, 48
sprue, 147
Stovarsol in amœbic dysentery, 103
Streptococcal secondary infections, 143
Streptococcal showers, 128
Streptococcal vaccines :
in *E. histolytica* carriers, 139
in pernicious anæmia, 153
Streptococci, hæmolytic, 35
in amœbiasis, 35
in pernicious anæmia, 151
in sprue, 145
isolation of, from stools, 136
Streptothrix infection in carriers, 129
Strong's bacillus, 75
Sugar reactions, 77
Sulphates in bacillary dysentery, 93
Sutika, 143
Symptoms :
acute bacillary dysentery, 29
amœbic dysentery, 38
bacillary carrier, 113
balantidial dysentery, 40
chronic bacillary dysentery, 111
E. histolytica carrier, 126
pernicious anæmia of Indians, 151
sprue, 146
Syphilitic stricture of rectum, 17

Teague and Clurman's solution, 118
'Terminal dysentery,' 113
'Toad skin' mucosa, 27
Tongue in sprue, 146
Treatment :
acute amœbic dysentery, 97
acute bacillary dysentery, 89

Treatment—*continued.*
balantidial dysentery, 107
chronic bacillary dysentery, 110
E. histolytica carrier, 137
pernicious anæmia of Indians, 152
sprue, 148
Tropical neurasthenia, 115
Tubercular enteritis, 17

Urine, bacteria in, 67
Urticaria, 114, 127

Vaccines :
Bilivaccin, 157
dosage of, 87
in bacillary carrier, 122
in bacillary dysentery, 83
in sprue, 84
Monilia, in sprue, 150
of secondary organisms, 84
oral use of, 157
preparation of, 85
prophylactic use of, 156
sero-vaccine against Shiga's bacillus, 157
Vaccines—*continued.*
Shiga's bacillus, 85, 156
standardisation of, 85
streptococcal, 139
streptococcal in sprue, 150
tests for sterility, etc., 87
use of anaërobic cultures, 157
Viability of *E. histolytica* cyst, 135
Vincent's infection in intestine, 48
Visceroptosis, 114
Vitamines and sprue, 144
Voges-Proskauer reaction, 81

Water-supplies and bacillary dysentery, 23

Yatren :
in amœbic dysentery, 102
in bacillary dysentery, 94
Y-bacillus, 75
Yeasts in amœbic stools, 137

Zettnow's stain for flagella, 69

YATREN 105

Recognised by Medical Authorities as the best remedy for

AMOEBIC DYSENTERY

A sure and safe means against

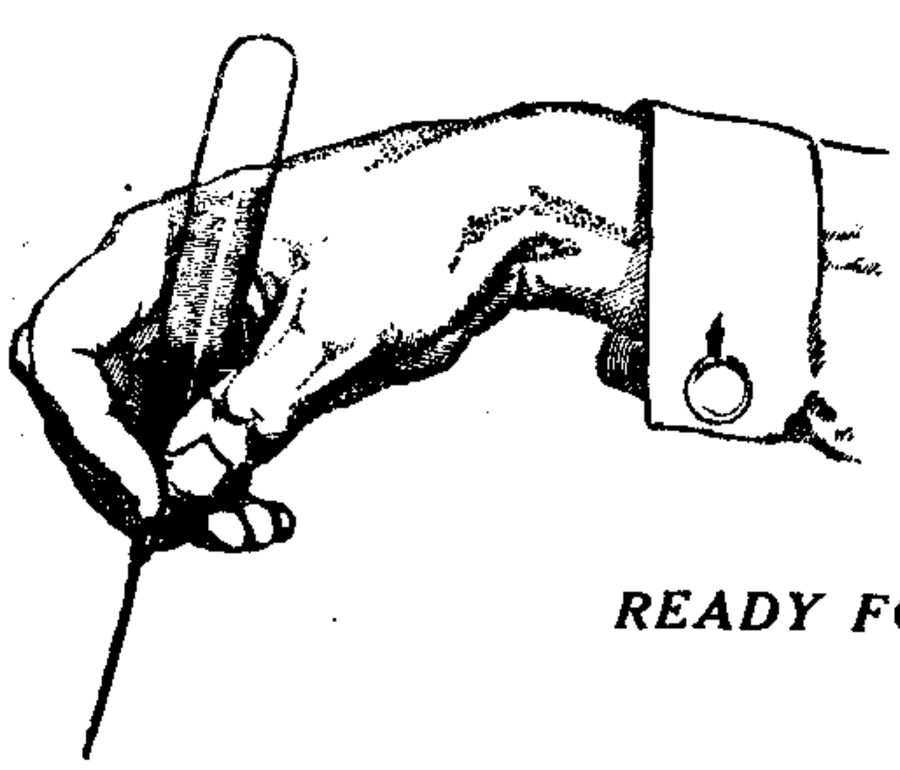
ALLIED INTESTINAL AFFECTIONS

Anti-Dysentery Serum Polyvalent "Original von Behring"

Antitoxic, Bactericidal, State-tested for combating

BACILLARY DYSENTERY.

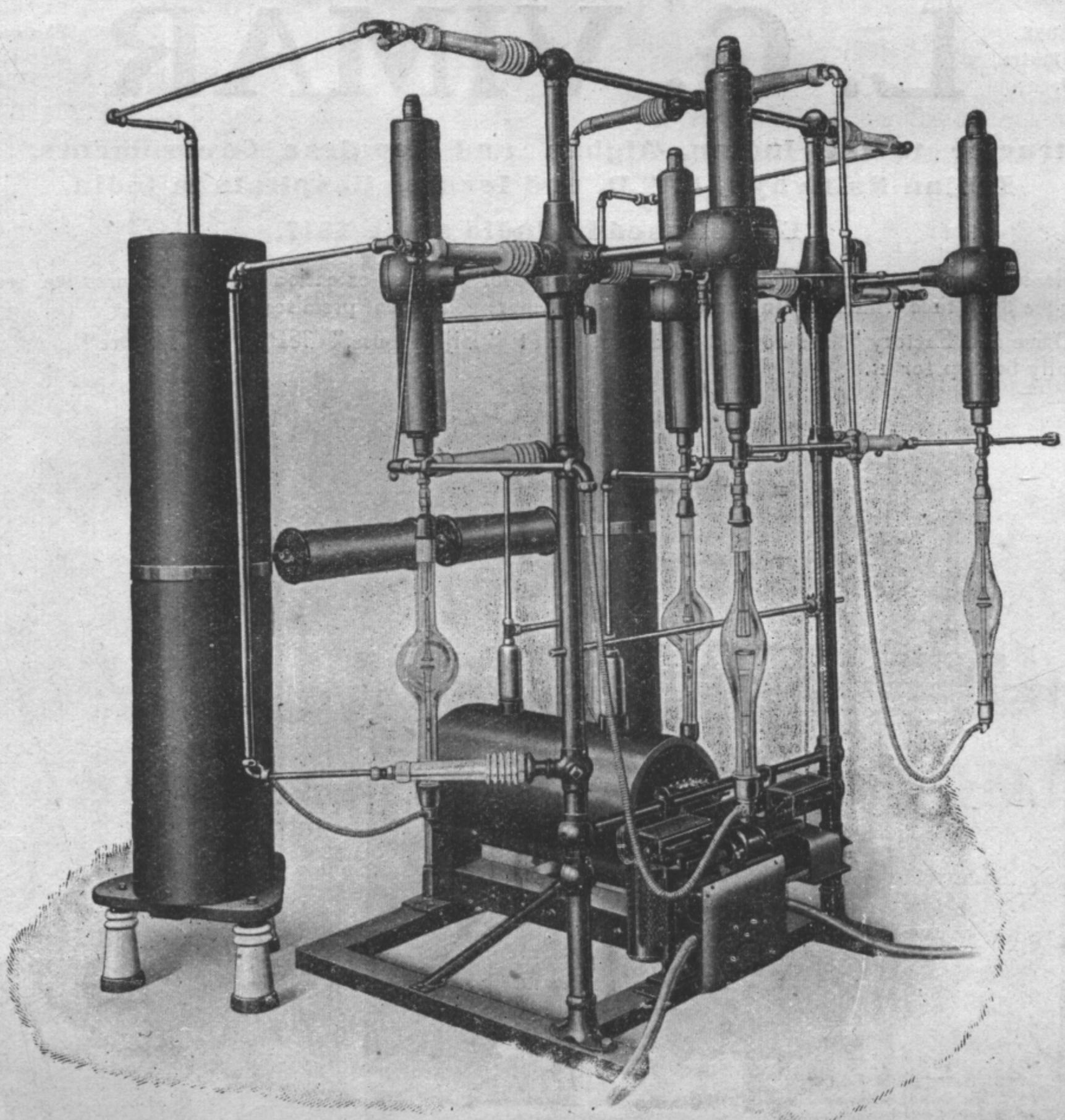
PACKED IN SERULES



READY FOR INJECTION

BEHRING INSTITUTE, MARBURG.

Representative : J. MAYR, 7, Pollock Street, CALCUTTA.



PANDOROS

Apparatus for intensive deep Therapy and Diagnosis.

We undertake to supply and erect

X-RAY APPARATUS

for all requirements and to supply

Complete Hospital Equipments

and

Electro-Medical Apparatus.

All the abovementioned instruments and equipments are manufactured by us specially for the tropics on medical advice, and the modern manufacturing process represents best workmanship and quality, thus ensuring highest reliability in running.

A modern equipped Workshop is maintained by us, and the services of our X-Ray expert are always at the disposal of our clients.

SIEMENS (India), LIMITED.

CALCUTTA	BOMBAY	LAHORE	RANGOON
P. Box 2109.	P. Box 898.	P. Box 147.	P. Box 54.

BIJLI HOUSE,
38P. New Theatre
Road,

L. G. VIMAR

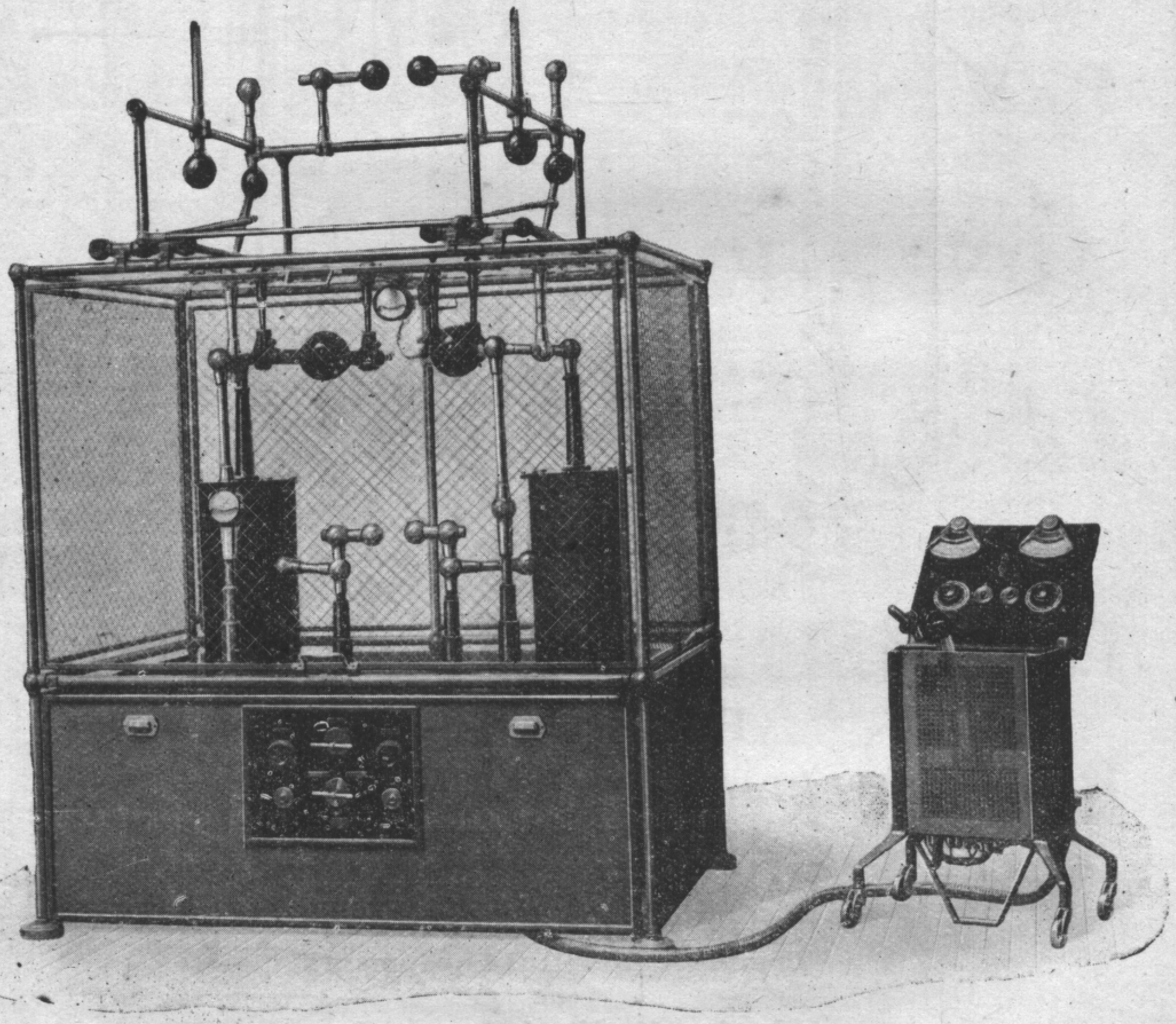
Phone ; Cal. 5749.
Cable :
"SKIAGRAM."

Contractor to the Indian, Afghan and Nepalese Governments, the Indian Railways, P.W.D. and leading Hospitals in India.

Established in India since 1917.

We are pleased to inform our clientele that owing to the ever-growing extension of our business we are moving again for the third time within eleven years into new and more convenient premises.

" Head Office and Factory " are now grouped together at " Bijli House," 38P, New Theatre Road, which we had specially builtup for us.



Sole AgentsinIndia for Messrs. Gaiffe-Gallot et Pilon of Paris, we carry a stock of their latest types of Diathermy, Electro-Medical and X-Ray Apparatus including the Valve Rectifying sets now in general use but originally designed and put on the market by this firm so far back as 1904 (The D'Arsonval-Villard Transformer).

Our Workshops equipped with the latest machinery will enable us as in the past to carry out any sort of repairs including rewinding of Coils and Transformers and to alter or modernise any type of plant and also to give a real and efficient **SERVICE AFTER PURCHASE.**

We have lately secured the representation for India of Messrs. Drapier of Paris the well-known Surgical Instruments Makers and this new Department is under the supervision of Mr. L. Roy whom this firm has specially sent to India. We carry a large stock not only of rustless Knives, Forceps and most usual instruments but also of Operation Tables, Artificial Pneumothorax Outfits, CO_2 Freezing Cauteries, Hypodermo-oxygenators, Plethysmo-sphygmo-manometers, Apparatus for testing permeability of Fallopian Tubes, etc., etc.

X-RAY APPARATUS

An ideal equipment for the physician's office or small hospital. Victor "Wantz Jr." X-Ray Machine in combination with Victor Model 9 Table

INSTALLATIONS

Suited to the needs of the Private Laboratory, the Civil Hospital, the Mofussil Hospital or large General Hospital.

Write for descriptive matter and quotations.

TECHNICAL SERVICE ALWAYS AVAILABLE

INTERNATIONAL

GENERAL ELECTRIC

SCHENECTADY NEW YORK U.S.A.

COMPANY INCORPORATED

120 BROADWAY NEW YORK. U.S.A

ELECTRICAL ENGINEERS AND MANUFACTURERS.

Victor London Office and Showrooms:—Morley House, Regent Street, London W. 1.

BALLARD ESTATE, BOMBAY.

STEPHEN HOUSE. CALCUTTA.

KRISHNA BUILDINGS BANGALORE CITY.

"I. G." Pharma "Bayer-Meister Lucius."

Leverkusen. ***Hoechst am Main.***

Offers the following preparations for the treatment of Tropical Diseases :

(i). PLASMOQUINE

(alkyl-amino-6-methoxy-quinoline)

The first synthetic antimalarial remedy. It is the only compound which shows a specific action upon the gametocytes. Can safely be given in Blackwater-fever and Quinine-Idiosyncrasy.

(ii). NEOSTIBOSAN (693 b.)

(p-aminophenylstibinic-acid-diethylamin)

The safest and most reliable pentavalent Antimony-Compound. 90% cure-rate in Kala-Azar.

Also indicated in Bilharzia and Venereal granuloma.

(iii). SALVARSAN COMPOUNDS.

(Novarsenobenzols).

Since their discovery through Ehrlich they have made their headway over the world.

Indications: Syphilis in all states, febris recurrens, Yaws, Benign-Tertian Malaria.

(iv). SPIROCID.

(4 oxy-3 acetyl-amino-phenyl-arsinate)

A compound closely allied to Salvarsan for peroral administration.

Chief Indications: Amœbic dysentery, other protozoic intestinal infections, Yaws, relapsing fever.

(v). "BAYER 205."

(for human use: GERMANIN
for veterinary use: NAGANOL).

Indicated for all diseases caused by Trypanosomes.

(vi). M.L.B. SERA AND VACCINES.

Known by their standard of efficiency and purity.

Sole Importers for India, Burma and Ceylon.

HAVERO TRADING CO., LTD., CALCUTTA.

Pharmaceutical Department, "Bayer-Meister Lucius."

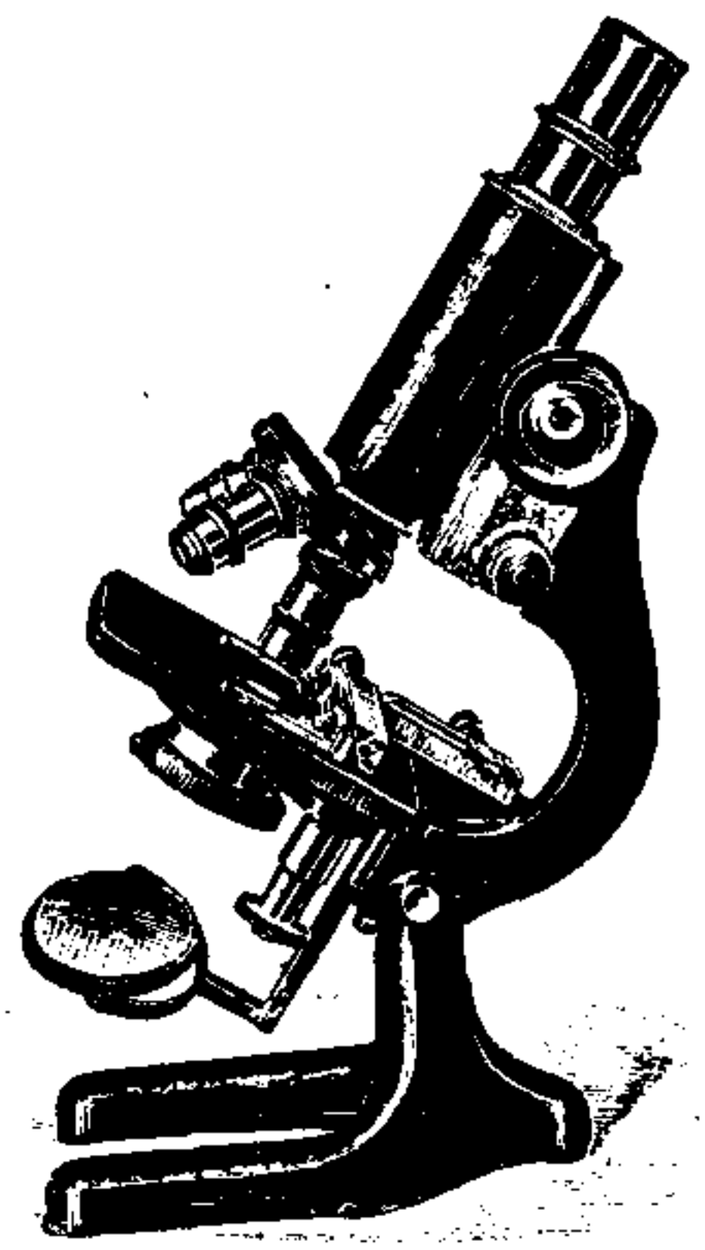
P. O. Box 2122.

15, Clive Street, CALCUTTA.

THE EMPIRE

BRITISH MADE

MICROSCOPE



The **EMPIRE** Microscope is the Ideal Microscope for students. It is so designed that it may be purchased by the student in the first instance in the most simple form and as his tuition advances additional parts may be added until eventually the instrument is converted into a complete Research Microscope.

The stand itself is of full size so that even after all accessories are added complete rigidity and stability are assured. All **EMPIRE** parts are interchangeable and are standardised.

The **EMPIRE** Microscope is made throughout of British material by British labour and with proper care can be guaranteed to give life-long service.

Write for booklet giving full details and prices.

Sole distributors :—

STEPHENS & CO., LTD.,

(INCORPORATED IN ENGLAND).

275, Bow Bazar Street, CALCUTTA.

EPHEDRINE HYDROCHLORIDE

EPHEDRINE is the Pure Alkaloid obtained from roots of *Ephedra Vulgaris.* It has been thoroughly tested both Chemically and Biologically.

EPHEDRINE when administered perorally acts in the same way as Adrenaline which is only effective when injected. EPHEDRINE is less toxic and exerts a more prolonged action than Adrenaline.

EPHEDRINE produces remarkable effect in Bronchial Asthma, Hypotonia, Chronic Bronchitis, etc.

Put up in bottles of 25 tablets each ½ grm. and Boxes of 6 Ampoules ½ gr. in 1 c. c.

Literature sent on Request.

STIBURAMIN

(Carbamide Derivative of Para-Amino Phenyl Stibinic Acid.)

FOR THE TREATMENT OF

KALA-AZAR

Prepared in our laboratory under the supervision of highly trained experts and thoroughly tested both Chemically and Pharmacologically.

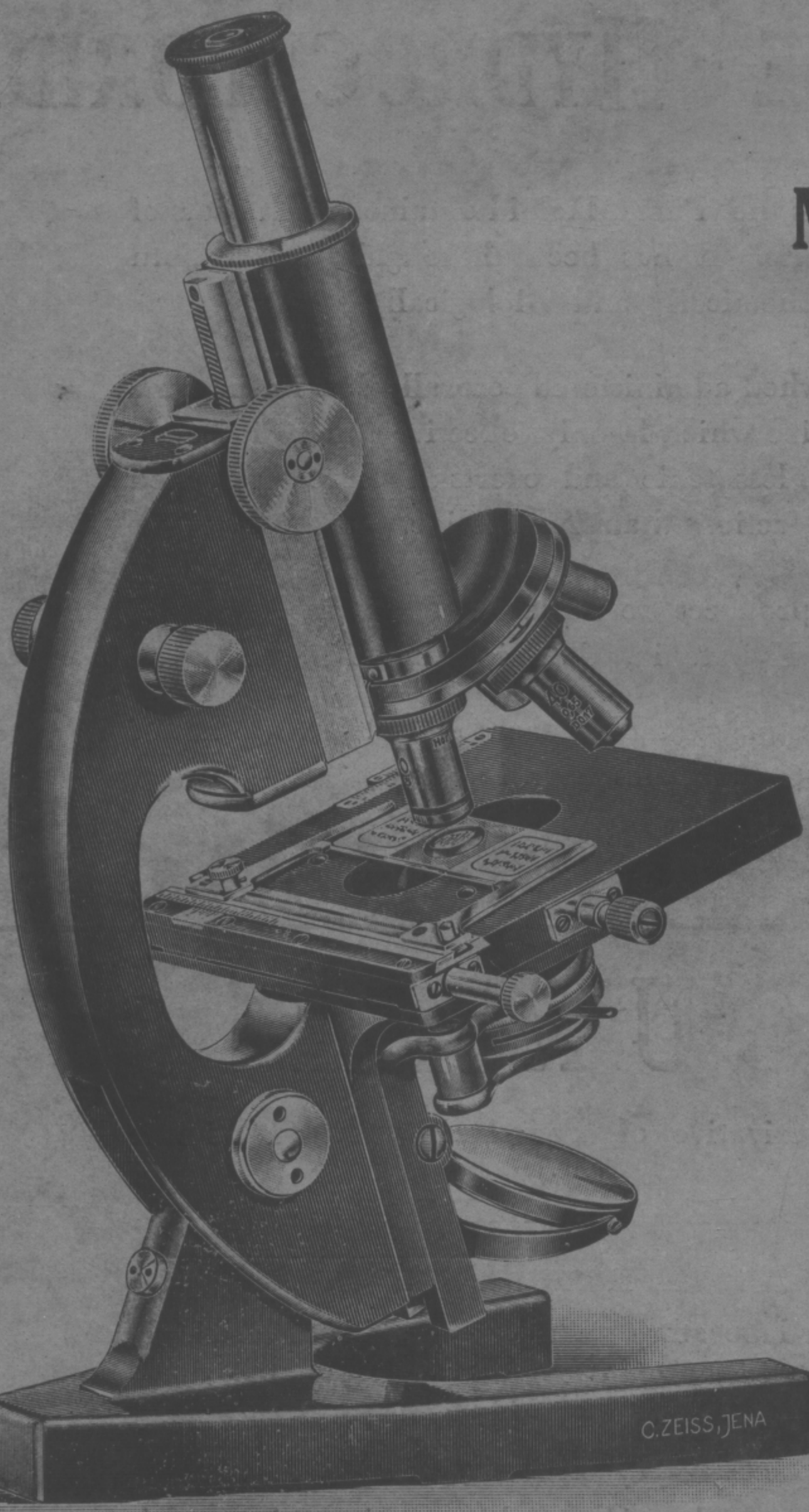
STIBURAMIN

produces prompt and uniform therapeutic action and is decidedly less toxic than similar other preparations.

Literature and Prices sent on application.

BENGAL CHEMICAL AND PHARMACEUTICAL WORKS, LTD.

CALCUTTA.



CARL ZEISS
JENA

MICROSCOPES

NEW MODEL STAND ESG

Sets a new standard in design and utility

As used at the School of Tropical Medicine, Calcutta

Prince of Wales Medical College Patna

Lady Hardinge Medical College Delhi

Medical College Calcutta

and by a large number of Civil Surgeons and Medical Officers of Health.

Full details upon request, post free, from the Sole Distributors in British India:

Adair Dutt & Co Ltd

INCORPORATED IN ENGLAND.

HEAD OFFICE
47, VICTORIA ST. LONDON.

Stephen House
5, Dalhousie Sq.
CALCUTTA.

Exchange Building
Ballard Estate.
BOMBAY.

And at KALEELI MANSIONS, MOUNT ROAD, MADRAS.

Dealers in Biological, Medical and Surgical Instruments.