Original Articles.

ON THE DYSENTERIES OF INDIA.

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PERHAPS in no field of therapeutics in India to-day is treatment more random and less standardised 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 war and the post-war years have seen so many additions to our knowledge of the subject that it is time that such lessons were incorporated in the general body of medical practice in India. That such knowledge has not yet been properly appreciated in India is shewn 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.

DEFINITION.

The term *dysentery* is not the name of a disease, but of a symptom-complex in which there are frequent stools containing blood and mucus, whose passage is 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. Thus we have known cases of intestinal tuberculosis and even of internal hæmorrhoids treated with emetine by the clinician because there was blood in the stools, whilst such other conditions as fistula-in-ano and rectal syphilis and carcinoma may also lead to the appearance of blood in the stools. On the other hand, in many cases of true dysentery, whilst the presence of mucus is visible to the naked eye, that of blood it may only be possible to detect under the microscope.

Of the causative agents of dysentery in India, we can at once eliminate schistosomiasis, since *S. mansonii* is not indigenous in India. *Fasciolopsis buski* is said to be a cause of dysentery, but, although this parasite does occur in India,—(e.g. S. M. Lal, 1923),—it is sufficiently rare to constitute an exceptional curiosity. The position with regard to *Balantidium coli* is still obscure. Sinton (1923) has recently recorded symptomless infection with this parasite in a Pathan prisoner in Lahore jail; we have recently encountered *Balantidium* of the pig in the fæces of two out of four pigs examined in Calcutta; whilst Ramsay (1923) considers *B. coli* to be a common intestinal parasite of pigs and even of cattle in Assam, and that balantidial dysentery may be not uncommon in India. Although we have encountered *Balantidium* infection in Mesopotamia, yet during many years of work in India we have never encountered the infection in this country. In one instance referred to us, the ciliate protozoon present was not *Balantidium*, but a free-living *Chilodon* accidentally present in the stool from extraneous sources.

The dysenteries associated with malaria and with kala-azar we believe to be of either amœbic or of bacillary origin. During the past three years we have frequently examined the stools of such cases and have often identified either *E. histolytica* or dysentery bacilli as the causative agents, and we regard the dysenteries of malaria and of kala-azar as due to secondary infections with dysenteric organisms. With regard to the intestinal flagellate protozoa, Dobell and O'Connor (1921) shew clearly that all of them—(with the possible exception *of Giardia intestinalis*, which may possibly be an occasional cause of diarrhœa, but never of dysentery, and which is usually harmless),—are non-pathogenic. To all intents and purposes, the dysenteries of India are due to infection with either *Entamœba histolytica* or with the dysentery bacilli, or with both.

RELATIVE FREQUENCIES.

During the earlier years of the war, it was commonly believed that most of the dysentery in the Eastern theatres of war was of amœbic origin. The careful work of Dobell, Wenyon, O'Connor, Ledingham and several others, however, soon shewed that such a view was entirely erroneous. Throughout Mesopotamia and India, probably indeed throughout the East in general, bacillary dysentery is some five to six times as common as is amœbic dysentery. Thus Dobell and Harvey (1923) record that of a series of cases from different war fronts in hospital with clinical symptoms of acute dysentery, only 6.1 per cent. shewed motile *E. histolytica*, the remaining 93.9 per cent. being judged to be bacillary either by 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, 1915. J. 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. Our experience in Calcutta during the years 1920-1923 is that bacillary dysentery is at least five or six times as common as is amœbic dysentery.

Further, whilst we cannct definitely establish any seasonal variation in the types of dysentery commonly met with in Calcutta, yet there appears to be a definitely different geographical incidence in the two types. Thus amœbic dysentery is relatively frequent in wind-swept desert regions, where the infective cysts are swept on to foodstuffs by hot and arid winds, whilst bacillary dysentery is relatively more common in communal and city conditions, and especially where water supplies may come to be contaminated.

DIFFERENTIAL DIAGNOSIS.

The medical practitioner cannot treat a case of dysentery properly until he has correctly diagnosed the type of dysentery from which the patient is suffering. Hence the true diagnosis can only be established by laboratory examination, although a fairly accurate guess can often be given upon purely clinical grounds. It is therefore necessary for us to take in turn each element in the differential diagnosis of dysentery.

Clinical Symptoms. Bacillary dysentery, especially if due to Shiga's bacillus, is—as a rule—an acute and febrile disease, with fairly sudden onset. Further it is especially the dysentery of in-patients, since such patients are at once prostrated by toxæmia. As has been shewn by Acton, Chopra and Boyd (1923) the Shiga bacillus, when present in a substrate rich in proteids and proteoses such as results from mixed or meat diet, can manufacture poisonous pressor bases with a profound action on both the cardiac and respiratory mechanisms. Essentially bacillary dysentery, in the acute phase, is a febrile disease, which sends the patient to bed, unable to cope with the degree of toxæmia present.

On the other hand, amœbic dysentery is characteristically walking dysentery, or out-patient dysentery. It is only when secondary infections supervene, or when grave gangrenous lesions of the colon are present, that the amœbic dysentery patient is compelled to take to bed. Usually, he keeps at work, however incommoded. Admittedly subacute and chronic cases are less easy to diagnose; they are not infrequently amœbic, especially when associated with palpable thickening of the colon, sometimes, however, they are due to infections with Flexner's bacillus. These will be dealt with later.

In general it may be said that acute bacillary dysentery is a disease which at once sends the patient to bed with fever, prostration and symptoms of toxæmia; whereas typical amœbic dysentery is a disease of more gradual onset, and the patient is often able to carry on his daily work, although his colon may be ulcerated. A single instance of the latter condition may suffice to shew how the colon may be ulcerated and eroded, even in the absence of all clinical symptons of dysentery:—

During the war in Mesopotamia in 1917, 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 shewed two small ulcers in the cæcum, each about the size of a four-anna bit, with numerous *E. histolytica* present in the cæcal contents, and also in nests in the submucous tissue of the cæcum wall, as seen on section. A second shewed a small ulcer in the region of the splenic flexure, with cysts of *E. histolytica* in the gut contents and vegetative forms found in sections of the gut wall. Both these men were on the active list, had not been recently in hospital, and would have been classified as being in ordinary good general health.

Macroscopic Examination of the Stools. As shewn by Cunningham (1923), such examinations for the presence or absence of visible traces of mucus are of value, not only for the detection of cases of dysentery, but also of latent dysentery carriers. The bacillary dysentery stool may vary much in character, but—essentially—it is an inoffensive stool composed mainly of bright red blood and mucus, with few other elements. In amœbic dysentery the macroscopic characters of the stool may be very varied. 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 wth the fæcal matter than in the bacillary stool. Further, as a rule more fæcal matter is present than in the bacillary stool. Taken all round, however, an inoffensive stool consisting of only 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.

Further, in bacillary dysentery the blood tends to be of a bright red and unaltered colour; in amœbic dysentery the blood tends to be of a darker and more brown colour, owing to the conversion of hæmoglobin to acid hæmatin.

Reaction. In amœbic dysentery the stool is usually acid to blue litmus paper; whereas in bacillary dysentery it is usually alkaline to red litmus paper. This easily applied and most useful test deserves further trial than it has hitherto secured. The point is of considerable importance, since—in the acid amœbic stool, the hæmoglobin of the red blood corpuscles is changed into acid hæmatin, which leads to the dark brown or tarry colour of the blood in the amœbic stool. In the alkaline bacillary dysentery stool the blood is bright red, and the hæmoglobin unchanged. As will be seen later the point is also important from the point of view of treatment and prognosis.

Correlated with this go the pH findings in the two classes of stools. It has been shewn previously by Knowles, Napier and Das Gupta (1923) that the pH of the amœbic stool is usually in the neighbourhood of 6.3; whilst that of the bacillary dysenteric stool is markedly alkaline. The following table gives our further findings on this matter, brought up to date. The 23 stools classed as bacillary shewed no *E. histolytica* on careful examinaton, and were classed as bacillary either from

Figure A.—The microscopical characters of the stool in acute amœbic dysentery. Drawn with a Zeiss 1|7th inch oil immersion lens and No. 2 Periplanat ocular.

Note the scanty cellular exudate.

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

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

(*c*). Flakes of mucus.

(*d*). Degenerated polymorphonuclear leucocytes, shewing "mouse-eaten" appearance.

(*e*). Lymphocyte.

(*f*). Coarsely granular eosinophile leucocytes.

(*g*). Pyknotic and nuclear residues.

(*h*). Yeasts.

(*i*). Chains of streptococci.

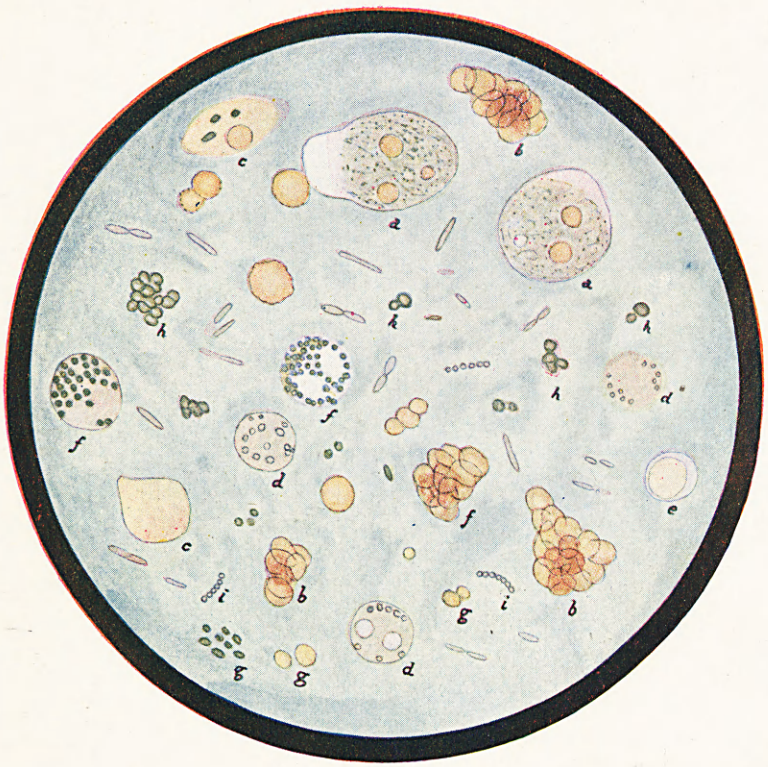

Figure A.

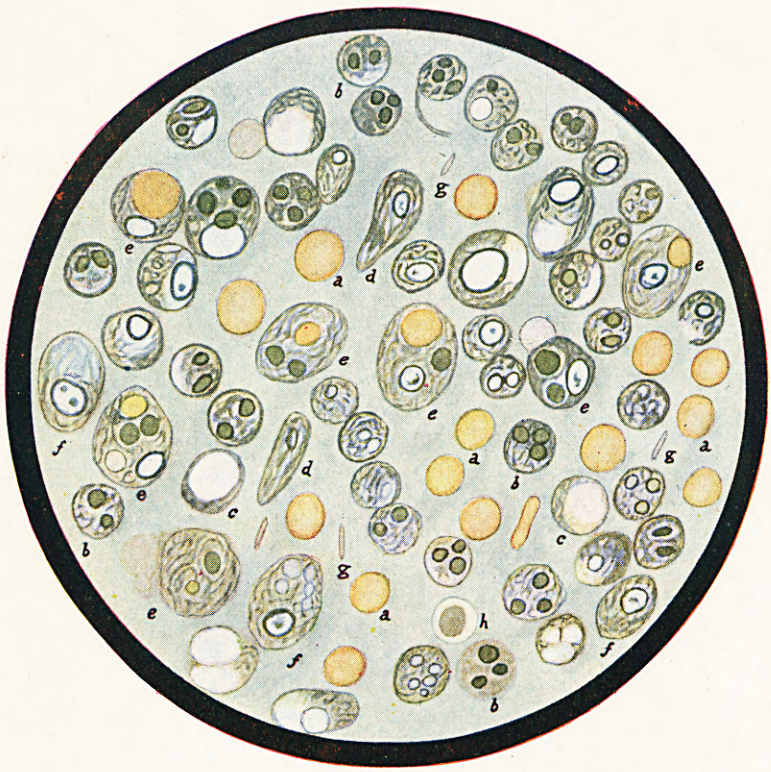

Figure B.

Figure B.—The microscopical characters of the stool in acute bacillary dysentery (Shiga infection). Drawn with a Zeiss 1|7th inch oil immersion lens and No. 4 Periplanat ocular.

Note the abundant cellular exudate.

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

(*b*). Polymorphonuclear leucocytes, shewing fatty degeneration and refractile dots.

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

(*d*). Degenerated epithelial cells.

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

(*f*). Endothelial cells, many degenerating.

(*g*). Scanty non-motile bacilli.

(*h*). Lymphocyte.

the typical character of the cell exudate or from the finding of dysentery bacilli on culture.

TABLE I.

	No. of Observations.	pH findings: mean and standard deviation.
E. histolytica, actively motile.	25	6·35±0·2988
E. histolytica, dead or dying, vegetative.	22	7·00±1·1118
E. histolytica, cysts ..	51	7·24±0·2535
Charcot Leyden crystals present.	54	6·96±0·2909
Bacillary dysentery stools.	23	8·11±0·1679

Microscopical Examination of the Stool. Even in the absence of *E. histolytica*, and prior to plating for dysentery bacilli, it is often possible to give a diagnosis of the type of dysentery present from a study of the character of the cellular exudate in the stool. For this purpose at least two films should be made: (*a*) a thin and well ground up emulsion of suspicious portions of the stool in normal saline; and (*b*) a similar thin emulsion in a solution consisting of iodine 1 gm., potass iodide 2 gms., and saline 100 c.c. (This latter solution tends to decolourise after a few days, and the stock bottle should be kept in the dark, or more iodine added to it if it weakens in colour). In preparing the emulsions the most meticulous attention should be paid to technique; the slides and cover slips used must be scrupulously clean, and free from grease (which can be removed by flaming if present); the emulsion must be so thin that print can easily be read through it, and the examination of three or four thin films from different suspicious portions of the stool is worth far more than is the attempt to examine an impossibly thick film in which nothing can be made out clearly. All excess of fluid should be blotted off; the slide being tilted and excess of fluid removed from the edges of the cover slip with bits of filter paper. Finally, if examination is likely to be prolonged, the preparation should be ringed with vaseline. In very cold weather, if amœbic dysentery be suspected, both stool and saline should be kept in the warm incubator, as this will often prevent the entamœbæ from becoming motionless for some time. Examination should ordinarily be made with a fairly high ocular, e.g., No. 6 and the 1|6th inch dry objective; but if a good preparation has been made and a thin and clean cover slip used, the oil-immersion lens can often be substituted and will shew more detail. A combination which we have found almost invaluable for such work is a stereoscopic binocular eye-piece (× 12.5 magnification) with a 1|7th inch oil-immersion objective (Zeiss). This gives good illumination, clear definition, a magnification equal to that given with a 1|12th-inch immersion lens and low ocular, but with a greater working distance, and the great advantage of stereoscopic vision.

The appearances seen in the acute amœbic and acute bacillary dysenteric stools are illustrated in the accompanying coloured plate.

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 (*loc. cit.*), 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 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 shew 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 organims 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. We may here give a striking instance of this degeneration. In November 1923 our 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 shewed the nature of the artefact present. The stool was full of spirochætes with regular, even curvature,—presumably *S. eugyrata*. 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 shews 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 shewing a very small proportion of polymorphonuclear leucocytes,—7½ 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 shew 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 shew 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, a detached endothelial cell from the capillaries more usually, or sometimes a wandering plasma cell. They shew 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 shew 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 shew 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 shew a very scanty bacterial content. In the early and acucte 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 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 shew 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, 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. These are of four types; (*a*) thin, sharply pointed, whetstone-shaped crystals, varying from 5 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 shew up with a green, clear, refractile look, and stain an intense jet black with iron-hæmatoxylin staining. In iodine preparations they shew up badly. Chemically Charcot-Leyden crystals appear to consist of ethyl-imine; and to be a product of tissue digestion by *E. histolytica.* As shewn 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 dysenteric stool*, as the acute symptoms subside, the secondary intestinal protozoal parasites become prominent. Motile, vegetative *Endolimax nana* and *Iodamœba butschlii* are frequently seen at this stage, whilst such stools often shew 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.

Identification of the Specific Organisms Concerned.—In the acute amœbic dysenteric stool, the laboratory worker will concentrate his attention upon trying to find the motile vegetative forms of *E. histolytica.* These have been so well described by Dobell (1919), and by Dobell and O'Connor (1921), that any further description would be superfluous. As these authors well remark, the true characters of this parasite can only be made out by a study of preparations of perfectly fresh material, properly fixed and well stained,—preferably by Haidenheim's method. Here in general, we have to consider three possibilities, as follows:—

(*a*) The stool may be perfectly fresh, not admixed with urine, and with no preliminary saline purgative administered. Under such circumstances motile *E. histolytica* presents an unmistakable picture. It moves

across the microscope field "like a slug moving at express speed." One-third of the parasite consists of perfectly clear, green, translucent ectoplasm, which is being constantly thrust forward into advancing pseudopodia. The direction of movement may be repeatedly altered, and, whilst one pseudopodium is at any one instant the most prominent, one, other new ones may be forming laterally. The endoplasm is finely granular, translucent, greenish, and the nucleus invisible. It shews scarcely any vacuoles, but may contain ingested red blood corpuscles, which lie, either partially digested and much reduced in size in the endoplasm singly, or—quite frequently—a prominent digestive vacuole is present containing from two to eight red blood corpuscles. As many as 48 have been counted within a single motile *E. histolytica*, and Wenyon and O'Connor's remark (1917, p. 46), that any entamœba in the stool which shews included red blood corpuscles is, *ipso facto*, *E. histolytica*, is the surest guide for the laboratory worker. On the whole, the laboratory worker will be safe if he refuses to diagnose a suspected form as the motile phase of *E. histolytica* unless he sees it in active motility or containing ingested erythrocytes.

(*b*) If the stool be from two to four hours' old, however, vegetative *E. histolytica* *now presents an entirely different appearance*, and the only accurate description of this degenerative phase is that given by Dobell and O'Connor (1921, pp. 22 and 26). By degrees the movements become slower and slower, until the parasite finally ceases to move. The pseudopodia,—which are thin, long and finger or ribbon-like in the active amœba,—now become large, spherical and dome-shaped, but still consist of ectoplasm only; whilst it is still clear that one-third of the parasite consists of ectoplasm only,—a most useful point in differential diagnosis. From two to three large, dome-like pseudopodia of clear ectoplasm may be thrown out simultaneously, the parasite itself being nearly motionless at the time. The nucleus, previously invisible, commences to degenerate, and how becomes visible, as a distorted ring, of greenish, refractile colour, shewing one or more granules of bright, refractile chromatin within it.

(*c*) A little later bacteria and yeasts commence to invade the dying entamœba. In the fresh, pristine state *E. histolytica* feeds only upon ingested erythrocytes and the digested tissue fluid pabulum prepared for it by its secreted and powerful proteolytic ferment. When it dies, however, it is preyed upon and invaded by the bacteria and yeasts of the stool. Pseudopodia formation ceases, the organism rounds up into a refractile greenish ball of protoplasm, the protoplasm becomes more and more vacuolated,—the vacuoles, however, at first being spherical, as is typical of *E. histolytica;* but later coalescing to form a large but still spherical vacuole. The final degenerative picture of dead, vegetative *E. histolytica* is a spherical mass of greenish protoplasm, full of spherical vacuoles and stuffed with invading bacteria; or else reduced to a mere greenish rim of protoplasm surrounding a large vacuole, and somewhat simulating a much degenerated *Blastocystis hominis*.

Turning to the bacillary dysentery stool, the first essential here is to obtain a fresh specimen, as, in the hot weather, a couple of hours is sufficient for the other bacteria present to overgrow the *Bacillus dysentericæ*. In the cold weather, the bacilli can be recovered from the stools after a longer interval, e.g., two to four hours after they have been passed. The next important point is that the bacilli are recovered more easily during the first 24 to 48 hours of the disease, when the stools consist almost entirely of pus and mucus, admixed with a little blood, than later in the disease.

A small piece of mucus is picked up on the platinum needle, and well washed in sterile normal saline in order to remove the extraneous bacteria on the surface of the mucus. The flake of mucus is next placed on a Petri dish of Conradi-Drigalski or MacConkey medium and smeared in turn over the four sectors of the plate. During the war,—owing to the shortage of Petri dishes and of the materials for making media,—it was customary to divide each plate by grease pencil lines into four sectors. The plates are incubated for 24 hours, and the likely-looking non-lactose fermentors are then fished up on a platinum loop, colony by colony. One-half of each colony is next inseminated on an agar slope, and the other half into lactose broth, and the cultures incubated for 24 hours. The lactose broth test is important in order to confirm the non-lactose-fermenting character of the organism, as some late lactose-fermenting organisms may simulate the dysentery bacilli. In a fluid medium such late lactose-fermentors produce acid or acid and gas, whereas the change of colour on a MacConkey plate may be delayed for a couple of days or more; the dysentery bacilli do not alter the medium.

If the colony selected is a true non-lactose-fermentor, the agar culture is then smelt in order to see if indol has been produced. If the smell is offensive it is pretty certain that it does not belong to the dysentery group, as these organisms produce a peculiar seminal-like odour in agar cultures.

The agar growth is next tested against dilutions of standard polyvalent antidysenteric serum. Here it is better practice to use the *polyvalent* serum than different monovalent sera, as any agglutination to a high titre identifies the organism as belonging to the dysentery group. Finally, if agglutination occurs, cultures are put up in sugar media,—especially mannite, since mannite is *the* one sugar which differentiates the Flexner-Strong group from the Shiga-Kruse group. Finally the organism may be tested against its own specified high-titre serum, and against the patient's own serum.

By carrying out the technique in the above order one can rapidly eliminate the various organisms which simulate the dysentery bacilli. The secondary invading micro-organisms found along with the dysentery bacilli,—especially in cases of chronic infection,—are the staphylococcus, the *B. proteus*, and the *B. pyocyaneus*.

MIXED DYSENTERY.

If such a condition as "mixed dysentery" truly exists, we believe that it merits most careful definition. During the last two years we have had several instances of patients who have passed through an attack of amœbic dysentery, have been treated and apparently cured, but who have returned to hospital from 6 to 12 weeks later suffering from an attack of bacillary dysentery. On the other hand, amœbic dysentery appears to be a less common sequel of bacillary dysentery. If the figures given in Table I be considered, it is obvious that conditions where the pH is on the acid side are suitable for amœbic infections, and conditons where the pH is on the alkaline side are suitable for bacillary infections. It is not likely that at any given intermediate pH conditions in the colon mucosa would favour the pathogenic action of *both E. histolytica* and the dysentery bacilli.

Bacillary dysentery not infrequently occurs in an *E. histolytica* carrier. Such a case was encountered in 1923, in an adult European female patient, where the characters of the cellular exudate were constantly of the bacillary type, the pH of the stool was constantly between 7.8 and 8.3, and where a single vegetative form of *E. histolytica* was encountered upon only one of six daily examinations. Such findings indicate—not mixed

dysentery—but bacillary dysentery setting in in a *histolytica* carrier, and in this instance the bacillus of Shiga was finally isolated in culture. If "mixed dysentery" really exists, the term should be reserved for cases where *both E. histolytica* and the dysentery bacilli are present in considerable numbers and in a *pathogenic* phase.

We believe such a condition to be relatively uncommon. What is common, on the other hand, is a transitional phase associated with a rapidly changing pH,—bacillary dysentery setting in in a convalescent amœbic case, and the stool becoming more and more alkaline; or amœbic dysentery setting in in a convalescent bacillary case, and the stool becoming more and more acid.

It cannot be too sufficiently emphasised that *every dysenteric stool should be examined both microscopically and by cultural methods,* and that any less examination is inadequate. The finding of vegetative *E. histolytica* does not exclude infection with dysentery bacilli, whilst an amœbic infection may easily be missed upon a single examination.

In many instances the specific organism or organisms concerned cannot be identified, whilst the cellular exudate picture is uncertain. This is especially the case where the stool is not examined until some hours after it has been passed. *To all intents and purposes, the examination of a stool more than two hours after it has been passed, is useless.* In such cases the only possible line of procedure is repeated daily examinations of the fresh stool.

Before leaving the subject of diagnosis, it should be noted that a diagnosis of acute dysentery can often be made by a distant laboratory. Two perfectly clean glass slides are taken, and a portion of the blood-stained mucus of the stool squeezed between them. The slides are now drawn apart so as to leave a thin film of the mucus upon each. They are then dropped into a jar containing either rectified spirit, or—better—Schaudinn's fixative (one part of absolute alcohol to two parts of saline saturated with corrosive sublimate, and with 5 per cent. of glacial acetic acid added),—and despatched by post to the laboratory. On receipt of such material, the films are stained by Haidenheim's iron-hæmatoxylin method and examined for vegetative *E. histolytica.*

TREATMENT.

A diagnosis—either proved or reasonably probable—of the type of dysentery present having been made, treatment should be appropriate and not random.

The *first* and most important indication is to send the patient to bed. No surgeon would think of permitting a patient with a severe ulcer of the leg to walk about, and in acute dysentery the gut is severely ulcerated. To permit even a mild case of dysentery to walk about is to invite disaster, to convert the acute into chronic dysentery,—a condition which is one of the most difficult to deal with in tropical medicine. The patient must be kept in bed for ten days, no matter how trivial the symptoms, and no matter what are his wishes. Further, a bedpan should be used, and the patient should not be allowed to get up to visit the latrine.

In both types of dysentery the value of the stock "dysentery mixture" of aperient sulphates is considerable. In both they flush the colon, whilst in the amœbic case they tend to increase the alkalinity of the colon mucosa,—a condition inimical to *E. histolytica.* On the other hand, in amœbic dysentery, since such saline aperients render the passed stool more alkaline, the *E. histolytica* in them tend to become sluggish and non-motile, and microscopical diagnosis is thereby rendered more difficult.

Emetine is of no value in bacillary dysentery: in fact its action here is only to increase peristalsis, and that often in an irregular manner, thus leading to increased colic.

TREATMENT. (A) ACUTE AMŒBIC DYSENTERY.

The mode of action of emetine upon *E. histolytica* remains to this day a mystery. Dale and Dobell (1917) have shewn that it is without direct action upon the parasite, and attribute its action to some effect upon the host. Allen (1921) found that in no instance did emetine affect the appearance or motility of *E. histolytica* in the stools in dilutions weaker than 1: 2,000 in the space of one or two hours, whilst often dilutions as strong as 1: 150 failed to kill the entamœbæ in the allotted time. The same worker (Allen 1922) further found that the blood and serum of man and cats, withdrawn after the administration of therapeutic doses of emetine, or when admixed with emetine in vitro, also failed to arrest the activity of *E. histolytica.* Sellards and Leiva (1923) consider that emetine has a weak amœbicidal action, and that this, plus the powers of resistance of the patient, afford the clue to the success of emetine therapy in amœbic infections. Whatever be the true nature of the action, there can be little doubt of the very considerable—though far from invariable—value of the drug in amœbiasis.

Whilst emetine is a most valuable drug in the treatment of amœbic dysentery, yet its administration must be most carefully controlled. As shewn 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 more*, but such cumulative doses have been known to prove fatal, whilst, even when they do

* In a case recently seen, the patient had been given 23 grains of emetine in 11 weeks, the drug being administered twice a week. Dysentery was still present and the stool shewed actively motile *E. histolytica.*

not, emetine diarrhœa may ensue, the practitioner may consider that this is due to insufficient dosage, and may 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 to all his dysentery cases per diem, on the supposition that if this cured the dysentery it must have been of amœbic origin, whereas if it did not, it must have been of bacillary origin. How many patients he killed, we do not know; but one of the saddest of the innumerable war cases which we know of personally is that of a military medical officer, whose cardiac machanism has been permanently damaged by over-administration of emetine during the war, but who still suffers to-day from periodic relapses of amœbic dysentery, and who is wondering how to keep the infection under control.

When given orally, the action of emetine is most uncertain, and for this reason we have abandoned oral administrtaion. We have not yet had an opportunity of testing the newly-introduced emetine periodide, but it seems to us that if the true ætiology of amœbic dysentery be considered, with the pathogenic entamœbæ lying deeply buried in the submucous tissue of the colon, it is futile to expect that emetine, when administered orally, can ever affect them. Sellards and Leiva (1923) strongly advocate the use 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 desired in actual large scale practice in India is some ready, reliable and efficient mode of administration by the mouth or hypodermically. (If given intravenously, emetine is too toxic to be tolerated in any but absolutely minimal doses.)

The whole rationale of emetine treatment to-day demands very careful investigation. Sellards and Leiva (1923) shew that to sterilise an infection with *E. histolytica* in man a course of some 17 to 28 grains is necessary for an adult of average weight; yet such a dose is on the toxic side, and might easily do irreparable injury. In kittens infected experimentally with amœbic dysentery, and in whom this disease runs a hyper-acute and usually fatal result within a few days of inoculation, two kittens were saved by the rectal administration of large amounts of emetine; yet here the margin between the effective dose and the toxic dose is almost negligible. Further we have to remember the true pathology of amœbic dysentery, that the pathogenic amœbæ are deep down in the submucous tissues of the colon wall, and will not be reached by any drug which is merely present in the fluid contents of the colon. It is clear that the whole problem demands the most careful exploration, both in experimental animals and in man. And as a preliminary step towards such exploration, a reliable method of cultivating *E. histolytica* on artificial culture media would constitute a big step forward.

Our present method of treating cases of amœbic dysentery is of necessity, under such circumstances, a compromise between what we consider to be desirable, and what we believe to be safe. It is as follows:—

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

(2) The diagnosis of amœbic dysentery having been confirmed in the laboratory, the patient is placed upon a milk diet, and is treated as follows for the first six days:—

(*a*) In the early morning, a full dose of saline aperient, to clear the colon.

(*b*) Deeks' bismuth treatment. As far as we can ascertain, 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 into alkalinity; and we have found experimentally in 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 four hours. It is best administered suspended in half a glassful of water, or preferably soda water.

(*c*) Two and a half hours after the first dose of bismuth for the day, one grain of emetine hydrochloride is given subcutaneously. It is very difficult to know whether such injections should be given subcutaneously or intramuscularly. If given intramuscularly, the immediate pain and reaction are less, but subsequent induration is more, and often leads to localised, painful, small lumps: if given strictly subcutaneously the immediate pain is more, but the reaction less, whilst absorption is probably more rapid. We prefer the latter route accordingly. Cawston (1922) recommends dissolving the tabloid of emetine in one per cent. carbolic acid, which, he states, renders the injection quite painless and does not interfere with its efficacy.

The timing of this injection is important. The senior writer has found that, as with quinine, so with emetine, the alkaloid exerts its maximal activity when the environment 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 those which are causing tissue-destruction and ulceration. Hence we desire to throw emetine into the portal circulation and the colon submucosa, if possible, at the moment when the blood stream here is in its most alkaline tide.

(3) After six days of this treatment, all treatment, except the administration of a morning saline aperient, is suspended for three days.

Treatment (2) is then repeated for a further three (or six) days. During this period, examination of the stools is useless, since few if any *E. histolytica* are to be found whilst the patient is under full emetine treatment.

(4) The patient has now received nine (or twelve) grains of emetine hypodermically, or nearly as much as he can safely stand. The emetine is accordingly discontinued. The early morning aperient and the bismuth treatment may be continued, the latter if there is still any looseness of the bowels. We prefer, at this stage however, to administer *Yatren* or other intestinal antiseptic.

Yatren, No. 105 Behring Werke, is iodo-oxyquinolin-sulphonic acid, and is a fairly stable compound. For an adult male of average weight one of the 7½ grain pills may be given three times on the first day; two of them three times on the second day; and two or three of them three times on the third and subsequent days. Clinically, we have found that this compound is of value; and its value is presumably due to liberation of quinoline in the colon. The drug has a tendency to cause diarrhœa if pushed to large doses, and its administration should be supervised. On the other hand, it appears to be of definite value in amœbic cases; and its administration tends to check the secondary bacterial infections to which such patients are liable.

(5) At this stage daily examinations of the patient's stools for *E. histolytica*, in either its vegetative or encysted phases, are commenced. With the examination for cysts of *E. histolytica* we hope to deal in a subsequent paper.

(6) If six consecutive daily examinations of the stool have failed to shew *E. histolytica*, the patient is by this time usually ready for discharge from hospital. But it by no means follows that he is absolutely cured, or that the *E. histolytica* infection is eradicated. Much more probably the infection has merely been so reduced that all clinical symptoms of dysentery have cleared. The infection is still latent, and relapses may—and very often do—occur. On the other hand such "relapses" are not infrequently instances of reinfection. We would like to particularly emphasise this point. If a medical officer in charge of a regimental mess or hostel, etc., gets a number of consecutive cases of amœbic dysentery and of relapses, examination of the mess or hostel servants will almost always shew that one or more of them are histolytica carriers; and attention to this matter will save many cases of infection.

The patient is usually discharged from hospital at this date. He is told to take three times daily for three weeks a dose of two drachms of *Extract Kurchi Liquidi*, or the corresponding dose of the Burroughs, Wellcome and Co.'s tabloid of the same drug. *Kurchi* is an indigenous Indian drug with some value in dysentery. It is not a cure for either amœbic or bacillary dysentery, as the incidence of relapse cases in our series assures us; but it will usually keep the clinical symptoms of dysentery under control, whilst it is harmless and non-irritant.

The patient is further instructed to send one stool every week to the laboratory for examination; for at least six, but preferably for eight weeks. The stools are examined for cysts of *E. histolytica*. (The question of relapses will be dealt with later however.)

Whilst such a line of treatment may not sterilise the majority of cases of *E. histolytica* infection, yet we claim that it is safe and free from dangers of overdosage, that it will cure the vast majority of cases as far as clinical symptoms go, and that it is well tolerated. Also, it is applicable in any dispensary. If Yatren be not available, the patient can be put directly on to treatment with *Kurchi*, after the nine or twelve doses of emetine have been given. If infection still persists on re-examination, the entire course of treatment should be repeated after an 8 to 10 day interval to allow of elimination of all emetine from the system.

TREATMENT. (B) ACUTE BACILLARY DYSENTERY.

Here everything depends upon whether the infecting organism present belongs to the Shiga or to the Flexner group. In either case, the first essential is ten days' complete rest in bed in order to allow the ulcers an opportunity to heal. This should be an invariable rule in all cases of dysentery, of whatever character, and whether acute or chronic.

(2) As regards diet, everything depends upon the nature of the infecting organism present. The Shiga and Flexner bacilli both produce endotoxins. But, as shewn by Acton, Chopra and Boyd (1922), the Shiga bacillus, if grown in a medium rich in proteoses, such as results from a meat diet, also produces an exo-toxin of the nature of a pressor base, which induces a condition of profound shock in the patient. Hence, whether an infection with the bacillus of Shiga may result in a fulminant and fatal attack of dysentery, or merely in a mild diarrhœa, may depend very largely upon the richness of the substrate, i.e. of the contents of the colon in proteoses or otherwise. In a Shiga infection animal proteids should be absolutely eliminated from the diet and carbohydrates administered instead. The diet should in general consist of arrowroot, barley water, Mellins' food, glucose feeds, tea and coffee with very little milk, and possibly light biscuits.

In a Flexner infection, on the other hand, proteids may be given freely; and meat extracts, chicken broth, citrated milk, gelatine and jellies may be given. These cases often shew intolerance to carbohydrates, and carbohydrates should accordingly be eliminated.

(3). *Specific Treatment.* In Shiga infections the specific anti-serum should be given immediately, and is only of value during the first 48 hours of the attack. It should be given intravenously and in doses of from 40 to 100 c.c., depending upon the severity of the attack. If so used, it acts like a charm. The number of stools is immediately reduced; the symptoms of toxæmia

disappear; the temperature comes down, and the patient passes from a critical condition into one of relative comfort. It is a curious fact that India to-day is entirely dependent upon other countries for this much needed and valuable remedy. Further, the transit of such serum through the Red Sea during the hot weather months may perhaps lead to a lowering of its potency. There seems no valid reason why all the antidysenteric serum required in India should not be manufactured in this country.

(4) *The state of the bowels.* If the case be seen early, the best purgative to give is castor oil with a little tinct. opii. added to it, as it acts upon the small intestine, clearing out the contents, which are rich in amino-acids and sugars, the products of proteid and carbohydrate digestion. As soon as the oil has acted, a change should be made to saline purgatives, and magnesium or sodium sulphate given in one drachm doses every two hours. Although such saline aperients are often regarded as specifics, they act by mechanical removal of bacilli and their toxins, and may also so alter the pH of the contents of the colon as to interfere with toxin production.

As soon as the pain and tenesmus have passed off, the sulphates should be given only every four hours. When the stools have become fæcal and are free from pus, the bowels should be kept open daily by a morning dose of saline or an evening dose of liquid paraffin. The latter aperient is perhaps the best of all for repeated use after dysentery, as it is entirely non-irritant. After-constipation must be avoided for at least three weeks. A daily dose of *bæl*-sherbet is a pleasant way of accomplishing this.

(5) *Sedatives.* As soon as the stools become fæcal in character, it is time to omit salines (except for the daily morning single dose), and to turn to sedatives. Here the best line of treatment is repeated doses of bismuth salicylate and pulv. ipecac. co., until the stools are black and becoming formed and a good prognosis assured, when the dose may be reduced or the bismuth discontinued. *Iysufgul* or *bael*-sherbet may next be given and act as demulcents.

Stimulants are rarely necessary except in very acute cases, whilst with severe collapse, hypertonic salines on the lines used for cholera may be necessary.

With regard to *relapses* in both amœbic and bacillary dysentery, they must be treated along the lines given for the primary attack in either case; and with even more care and thoroughness than in the primary attack, since the infection is here more established and more difficult to eradicate.

CHRONIC DYSENTERY.

Were all cases of dysentery seen and properly diagnosed and treated at an early stage, an endless amount of suffering would be saved to patients in India. With ten days of complete rest in bed and proper treatment, based upon full and accurate clinical and laboratory diagnosis, such a condition as chronic dysentery should never be seen. On the other hand, it is one of the most common complaints in India among patients of all races and both sexes. The patient who refuses to go to bed when suffering from acute dysentery or who gets up before the ulcers have had time to heal, or the patient who is inadequately and improperly treated is the typical victim of such a condition; a condition which is one of the most difficult to deal with in the practice of medicine in the tropics. The middle-aged European female patient suffering from this complaint finally tends to drift into the "chronic abdominal type" so amusingly described by Hutchison (1923), the subject of the surgeon, the homœpath and the quack; presenting at last a confirmed neurasthenic picture with a history of gastro-enterostomy, plication of the stomach wall for distension, unrecognised endocrine deficiency, introspective, morbid, a nuisance to all around her, and a misfortune for her medical attendant.

The treatment of chronic dysentery should be not less thorough than that of the acute attack. As before, the patient should be sent to bed for ten days, and every effort made to establish the diagnosis. Repeated and daily examinations of the stools are called for. Here it is far harder to establish the correct diagnosis by laboratory methods than with the acute case; yet accurate diagnosis is even more essential. The patient should be given a placebo or a tonic until such diagnosis is confirmed. The stools should be examined by both microscopical and cultural methods, and in addition to a positive diagnosis of the specific organism concerned, all secondary factors present should be considered.

(A) CHRONIC AMŒBIC DYSENTERY.

The chronic amœbic case is especially characterised by thickening of the walls of the colonic flexures, palpable in the pelvic colon, at the splenic and more frequently at the hepatic flexure. The entamœbæ are often found in sections to lie deeply in nests in the submucosa with fibrotic tissue over them replacing the columnar epithelium, and they are less amenable to treatment than in the acute case. We have no belief in the so-called "emetine-fast" strains of *E. histolytica*: the "emetine fastness" is explained by the morbid histological picture present, tissue-destroying parasites present in areas difficult of access to any drug, walled in by fibrosis.

In the stools of such cases on repeated examinations almost every phase of *E. histolytica* will be found; quite frequently the stool is a non-dysenteric, pasty one with motile, pre-cystic and encysted forms of *E. histolytica* present simultaneously.

Further, here the secondry bacterial flora is of considerable importance. If the stools of both acute and of chronic amœbic dysentery be plated on MacConkey's medium a most characteristic bacterial flora is shewn. There are scattered and scanty colonies of *B. coli*, together with scattered

fine dew-drop-like colonies in between, and little else. If these dew-drop colonies be subcultured and examined it will be found that there are two organisms present; (*a*) a hæmolytic streptococcus; and (*b*) a yeast. The former is a late lactose-fermentor, and the fine colonies later turn red.

Now subacute and chronic cases of amœbic dysentery are not infrequently febrile. If a careful four-hourly chart be kept, it will be found that there are occasional and irregular rises to 99, 99.5 or 100°F. These may arouse suspicion of early amœbic hepatitis, but they are usually due to invasion of the blood stream with streptococci from the bases of the amœbic ulcers in the gut. And with such "streptococcal showers" often go puzzling and but little understood symptoms, transient rashes, attacks of asthma due to invasion of the blood stream by pressor bases from the gut contents, joint pains, etc.

Hence the treatment of such a case must resolve itself into a careful consideration of *all* the factors present. The patient having been put to bed, the first indication is the twelve-day treatment outlined above, consisting of the morning saline purgative, bismuth in large doses, and the nine doses of emetine hypodermically, with the subsequent weekly examinations of the stool for *E. histolytica* cysts or pre-cysts. If, in addition however, a mildly febrile state persists and hæmolytic strains of streptococci have been isolated, the treatment should be supplemented later by a course of autogenous streptococcal vaccine. Here, as in all vaccine therapy, it is important to note that all recent work has shewn that it is a mistake to attempt to immunise a patient by giving rapidly increasing doses at weekly intervals. Small and frequently repeated doses, given not so much subcutaneouly as intradermally, give a better immunising response. With such a vaccine the dosage should be approximately 10 millions.

(B) CHRONIC BACILLARY DYSENTERY.

As before, here again, the indications for treatment can only be ascertained by a thorough and full laboratory diagnosis. The type of organism present must be worked out and identified. It is in this class of cases that vaccine therapy is particularly useful. The vaccines used may be either autogenous or a stock strain. With a Flexner vaccine the dosage should begin with 100 million. With a Shiga vaccine the greatest caution is necessary, since such vaccines often arouse violent reactions. An initial dose of five to ten million organisms is sufficient, and even this may cause a marked focal reaction: in one instance, a case of chronic Shiga bacillus infection, the patient who had been passing two stools a day received such a dose, and reacted so violently that there were 24 stools within the next 24 hours.

In all states of chronic septic ulceration to which chronic dysentery is no exception, there tends to go with the chronic ulceration, a diminished iodine content of the tissues, and of the thyroid secretion. Hence vaccine therapy may often be usefully combined with the simultaneous administration of potassium iodide orally.

The chronic bacillary dysenteries are especially apt to be misdiagnosed. Numerous cases in the tropics of "sprue," of "hill diarrhœa," of "chronic indigestion with flatulence" and of "chronic diarrhœa" will be found, if carefully examined, to be instances of infection with Flexner's bacillus.

THE POST-DYSENTERIC ABDOMEN.

Chronic dysentery being a condition which is far less amenable to treatment than is acute dysentery, many cases of the former pass on, in spite of all treatment, to a condition in which the true ætiology is often obscure unless careful and full clinical and bacteriological examination be made. The factors which are chiefly concerned in producing the "chronic abdomen" which so often supervenes upon chronic dysentery in the tropics are as follows:—

(*a*) *Mechanical obstruction.* In both types of chronic dysentery, adhesions may have formed, especially at the flexures of the colon and around the cæcum. Especially is this the case in patients who have been "treated" whilst still walking about, or who have refused to go to bed. In addition to this there is often severe loss of muscular tone. The result is *visceroptosis;* and there is probably no one ætiological factor of more importance in the tropics in producing this condition than chronic and neglected dysentery.

Such patients shew a well marked syndrome of alternating constipation and diarrhœa; so much so indeed that constipation is here almost evidence of previous dysentery. There tends to be constipation for two or three days, during which the relaxed colon is filling with fæcal contents which become more and more formed. On the third or fourth day a sharp attack of diarrhœa sets in and clears the overloaded colon, only to be again followed by two or three days of constipation, and so on.

Microscopical and bacteriological examination of the stools of such cases often shews little or nothing. The original specific dysentery organisms may indeed have disappeared, leaving behind mechanical after-results and secondary infections of the gut wall and tissues. *X*-ray examination after a bismuth meal usually shews a very characteristic picture; the cæcum is overloaded and water-logged. Together with the appendix it may have dropped right down into the true pelvis. The transverse colon sags down (with the patient *x*-rayed in the vertical posture), until it also may partly lie within the true pelvis. The hepatic and splenic flexures shew acute kinks. Adhesions tend to be present especially at the flexures and around the cæcum.

(*b*) Together with such mechanical obstruction and muscular defect goes a steady toxæmia from absorption of intestinal toxins from the overloaded and usually constipated colon. *Digestive function* tends to be lowered or almost entirely

lost, with considerable wasting. Hyperchlorhydria, indigestion for carbohydrates, gastric symptoms and flatulence set in and render the clinical picture still more obscure.

(*c*) Together with this, as in all chronic septic states, goes *endocrine deficiency,* especially in adult female patients, and in European women in particular. The ovarian and thyroid mechanisms are those especially affected. Such patients suffer from sensations of heat and cold, from flushing alternating with sweating. They are either apathetic in their home life, or else vivacious and irritable. The skin is harsh, the hair dull and lifeless. In such cases often hyper-thyroidism co-exists with hypo-thyroidism.

By degrees such a patient passes into the "confirmed abdominal neurasthenic," as described by Hutchison. To the physician such a patient is a source neither of interest, pleasure nor profit. The detailing of his (or more usually her) symptoms takes up hours of valuable time, whilst she will follow no set rules, and usually visits every consultant in the locality in turn.

What happens to such a patient depends entirely upon whose hands she may fall into. If she visits a surgeon she will have "exploratory" laparotomies carried out, short-circuiting operations, plication operations, kidney fixation operations and the like. If she visits a gynæcologist she may suffer a hysterectomy, or a ventro-fixation or even a panhysterectomy, after which she usually at least puts on flesh. She will "suffer many things at the hands of many physicians": whilst, if her income will afford it, she will probably ultimately become the habituée of spas and of European continental health resorts.

In such a case, even more than in cases of both acute and chronic dysentery, is full and accurate diagnosis essential. Again, every possible endeavour should be made to isolate the specific dysenteric organism or organisms concerned. This, one must confess, usually fails; but it must not be neglected.

A well fitting, broad abdominal belt is the first indication. It must fit snugly, take its support from below the iliac crests, and must press the viscera upwards. Above all it must not be so constructed that it is liable to slip upwards and compress the viscera downwards.

The second indication is glandular therapy. In women small doses of 1|6th to 1|4th of a grain of dried thyroid extract with 2 grains of dried ovarian extract may be given three or four times a day, whilst in both sexes polyglandular therapy may be tried. A study of the parathyroid functions and of the calcium metabolism in such cases might yield results of interest. We do not desire in this paper to dwell upon the ætiology of sprue, but whilst this most interesting disease appears to be a clinical entity, we are beginning to wonder whether such a single clinical entity may not be the end-phase of several different infections, e.g., with the Flexner bacillus, or after chronic amœbic dysentery, associated with pancreatic and parathyroid deficiency.

In general it may be said that the treatment of such cases is very difficult. These patients are the type which the harassed practitioner usually tries to hand on to somebody else.

To the reader it may appear as if much of this article is couched in a pessimistic strain. Yet such is not the case. Acute dysentery, whether of amœbic or bacillary origin, is one of the diseases most readily amenable to treatment. Yet if treatment is to be in any way efficacious, it *must* depend upon full, accurate and proved diagnosis, upon identification of the specific and causative micro-organism at work. The treatment of amœbic dysentery is entirely different from that of bacillary dysentery; whilst, in connection with the latter, there are marked differences with regard to a Shiga or a Flexner bacillus infection. The layman who chances to open a text-book on general medicine, is often surprised to see how large a space is devoted to primary and differential diagnosis, and how little to treatment. The reason is that the correct and efficient treatment cannot be applied until the full and accurate diagnosis has been both made and confirmed. The medical officer in charge of a *mofussil* dispensary may often have to diagnose "dysentery" and to prescribe the stock "dysentery mixture" of aperient sulphates. At least we have the knowledge that he is not thereby doing any harm; but we look forward to the day when a few relatively simple microscopical tests will enable him to at least give a more or less accurate guess and to apply the correct treatment. From the type of consultant who prescribes so toxic a drug as emetine in all cases of dysentery whether amœbic or not, who "boasts that he is independent of laboratories," and who tries to treat tropical diseases, some seven-tenths of which depend upon accurate laboratory examination for their diagnosis, without laboratory plus clinical diagnosis,—and who is like the captain of a ship who would put to sea without a compass,—we have less to expect.

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THE VARIABILITY IN RABBITS USED FOR THE ASSAY OF INSULIN.

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THE question whether insulin deteriorates in the tropics, owing to the heat to which it is subjected to when passing through the Red Sea or during the hot weather, was first brought forward by Major E. C. Taylor, I.M.S., in 1923. More recently, in a letter in the *Indian Medical Gazette,* it was suggested that this apparent deterioration may have something to do with the difference in breed of rabbits used in these assays. The more experience one gains in these pharmacological assays, the more one realizes the importance of the variations in the different individuals under test, or even in excised tissues taken from the same species.

Dale in 1923 first pointed out that the excised uteri of guinea-pigs varied considerably in their reactions to the different test drugs; thus the pregnant uterus is the most sensitive and most unreliable, then the multiparous, and the virgin uterus is the least sensitive and most reliable. The most consistent results are given by the virgin uterus of a guinea-pig weighing about 250 grms., whilst the long thin and fibrous type of virgin uterus responded very feebly to these stimuli.

Recently Acton and Chopra (1924) have shown that the various endocrine glands that stimulate the sympathetic nervous system play a large part in these individual variations. In 1911 and 1912 Acton and Knowles noticed that, during the course of immunising goats against cobra venom, the lighter the colour of the animal the more were they susceptible to cobra and Russell's viper venoms. Most of the white goats succumbed during the attempt at immunisation by gradually increasing doses of venom. The brown goats gave a good yield of serum, whilst the black goats, although they tolerated the venom well, gave a poor yield of antivenene and the blood was often hæmolysed. The best animals for producing these anti-sera are horses of middle age, grey, or chestnut in colour, with good bone. The white Arabs are sensitive to these poisons, so that immunisation has to be carried out more carefully, but the animal eventually yields a good serum.

McLeod and Banting (1924) pointed out that adrenalin produces hyperglycæmia when injected into a rabbit in 1 c.c. doses. Acton and Chopra (1924) showed that an excess of adrenalin tends to inhibit the action of many of these bases.

We were requested from Simla to test the different brands of insulin to see whether any deterioration had taken place in India. The first point that was necessary to study was to see how far these individual variations in the blood sugar by insulin depended on individual variations in these animals, before we could attempt any assay methods. We therefore determined to test (1) the effects of the colour variations of these animals, and (2) the antagonism exerted by adrenalin towards insulin. The results of our experiments on these two factors are as follows:—

The effects of colour variations in the rabbits tested by insulin.—Three types of rabbits were used, the albino Himalayan, the piebald Himalayan, and the grey Belgian hare rabbit. As we were unable to obtain rabbits of the standard weight of two kilograms, we kept our doses of insulin fixed at three units per kilo body weight, and varied the amount according to the weight of the rabbit. The results of these tests are shown in Table I.