Observations ON THE PATHOGENICITY AND TREATMENT OF FLAGELLATE DYSENTERY.

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For the past four years there has been a determined attempt on the part of the Ministry of Health to prevent or limit certain infectious diseases which have become a real and great danger to the community as a result of the demobilization of the services. The Public Health (Pneumonia, Malaria, Dysentery, etc.) Regulations, 1919, have made these and certain other diseases notifiable, and definite power to deal with such diseases has been given to medical officers of health.

It is with flagellate dysentery that these remarks are concerned. The definition of dysentery in Article I (1) F of the Regulations reads: "The expression 'dysentery' includes amoebic and bacillary dysentery." Other forms of dysentery such as flagellate, are not notifiable, and thus there is no attempt to safeguard the public against them.

A survey of the literature of the flagellate dysenteries leaves the mind of the reader in a turmoil as to their pathogenicity or otherwise. Few writers in the past have admitted that the presence of flagellates in the bowel is anything but a mere coincidence when found along with dysenteric symptoms. Other observers would credit only *Lambli* *intestinalis* with pathogenic effects on man and still leave *Trichomonas intestinalis* and *Chilomastix mesnili* in the "mere coincidence" group. The opinions of a few authorities on the pathogenicity of *Lambli* *intestinalis* may be quoted with advantage.

Hurst (1918)¹ states regarding flagellate diarrhoea: "Sometimes, however, recurrent attacks of abdominal discomfort and diarrhoea, with the passage of large quantities of yellowish mucus containing enormous numbers of active lamblia, occur; in such cases the organism is probably the cause of the symptoms. The diarrhoea, which may persist in cases of dysentery after treatment with emetine or antidiysenteric serum, is probably sometimes due to additional infection with lamblia, which is not cured by these means."

In the *Memoranda on Medical Diseases in the Tropical and Sub-tropical War Areas*, 1919,² the opinion of the vast majority of workers at that date reads: "The only one which is possibly pathogenic is *Lambli* (*Giardia*) *intestinalis*, whose habitat is the small intestine, and which is said sometimes to induce a persistent and troublesome diarrhoea."

Manson (1921)³ states: "Lambli infection is associated at times with a type of recurring diarrhoea accompanied with abdominal discomfort and the passage of bile-stained mucus. . . . Relapses of a periodic type tend to occur. . . . Symptoms are thought to be due to the mechanical action of the parasite. . . . Many kinds of treatment have been tried without success."

Wenyon remarks (1915)⁴: "In other cases there occur at intervals attacks of diarrhoea with the passage of mucus in which lamblia are to be found in enormous numbers, so much so that the whole microscopic field is packed with them. After recovery from such an attack the stools become normal again and only encysted forms are to be found. The occurrence of repeated attacks of this nature with a certain degree of abdominal uneasiness preceding the attacks and the passage of such extraordinary numbers of flagellates, especially in the mucus, leads one to suspect that sometimes, at any rate, *Lambli* *intestinalis* may produce sufficient irritation of the small intestine to justify us in regarding it as pathogenic. The invasion of the glands of the small intestine as seen in the rabbit is suggestive of such a pathogenic rôle."

Dobell and O'Connor (1921)⁵ sum up the evidence for and against the pathogenicity of the intestinal flagellates, thus: "There is as yet no good evidence to prove that any intestinal flagellate found in man is pathogenic, but that there is very considerable evidence to show that most and probably all of them are harmless."

Phillips (1915)⁶ observes that "the evidence brought forward that they [faecal flagellates] are pathogenic is not very conclusive, but in the case of *Lambli* *intestinalis* is more convincing." The same author quotes a large number of cases recorded by such observers as Darling, Mathis, Meyer, Fairise, and Jannin. These observers record cases of lambliasis leading to ulceration and even to perforation of the gut. One case ended fatally after perforation (Fairise and Jannin).

Except for this latter case, the general opinion, especially in the tropics, seems to be that *Lambli* *intestinalis* is a harmless parasite of the bowel, or of minor pathological significance.

During the past four years there has been exceptional opportunity of thoroughly overhauling men who have returned from overseas suffering from dysentery, diarrhoea, enteritis, general debility, and neurasthenia. The failure to

find any obvious reason for their unfitness led to a routine investigation of these cases. Eventually, in an endeavour to get to the bottom of all such cases, the following routine examination was adopted in the Central R.A.F. Laboratory, London:

1. Thorough clinical examination.
2. Blood culture and blood smears for parasites. Blood count and agglutination tests for indirect evidence of certain diseases, such as chronic protozoal infections, sepsis, tuberculosis, enterica, dysenterica, undulant fever, etc.
3. Wassermann reaction for syphilis.
4. Faeces examination for bacterial, protozoal, or helminthic infection.
5. Urine for albumin, blood, casts, and parasites.
6. Sputum, especially for tuberculosis.

The examination of blood films, faeces, and sputum was performed for ten consecutive days in all cases; if any part of the examination cast suspicion on the diagnosis further tests were carried out. It should be mentioned that the stools were examined as passed normally as well as after purgation with calomel and magnesium sulphate. The latter procedure ensured a good evacuation of the bowel and minimized the chance of missing parasites inhabiting the upper bowel. The whole stool was immediately sent to the laboratory, and special attention was paid to the toilet paper, because mucus was often found on this when not present in any other portion of the motion. In this manner 716 cases have been investigated, with the results shown in Table I.

TABLE I.

Organism.	Cases in which Present.	Per-centage.	Cases of Pure Infection.	Per-centage.
<i>Entamoeba histolytica</i> ...	68	10	32	5
<i>Entamoeba coli</i> ...	34	5	18	3
<i>Iodamoeba bütschlii</i> ...	30	4	12	2
<i>Endolimax nana</i> ...	6	1	2	0.3
<i>Lambli</i> (<i>Giardia</i>) <i>intestinalis</i> ..	57	8	22	3
<i>Trichomonas hominis</i> ...	8	1	4	0.5
<i>Chilomastix mesnili</i> ...	14	2	6	1
<i>Tricercomonas intestinalis</i> ...	8	1	3	0.4
Helminths ...	12	2	10	1
Bacillary infections ...	10	1	8	1
Total number of cases in which the above organisms were found in the faeces	183	26	—	—

Many of the cases showed a mixed infection of flagellates and other intestinal protozoa or helminths with other diseases, such as malaria, syphilis, and enterica. Out of 716 cases examined, one or more types of the above enumerated intestinal organisms were found in 183 instances (26 per cent.). In 117 of these only one type of organism was found. As is shown in Table I, no abnormality could be found in 35 of the cases beyond the presence of flagellates in the bowel. Thus a prolonged investigation regarding symptoms and treatment was made of 22 cases of pure lamblia infection, 4 of trichomonas, 6 of chilomastix, and 3 of tricercomonas.

PATHOGENICITY.

The pathogenicity of an organism is best studied by macroscopic and microscopic examination of the organs forming its habitat, and especially of any lesions produced. Short of this, the only method applicable is to prepare careful laboratory and clinical evidence. In "flagellosis" the opportunity of obtaining material at operation is small; the same holds good for *post-mortem* material. The writer has been forced to draw his conclusions from evidence obtained during the life of the patients.

Preparatory to discussing the symptoms of flagellosis it is well to note the chief intestinal flagellates and their habitats. They are as follows (the authority is given in parentheses):

1. *Lambli* or *Giardia* *intestinalis*. Duodenum or small intestines. (Lambl, 1860.⁷)
2. *Trichomonas hominis*. Large intestine and ileum. (Wenyon, 1920.⁸)
3. *Chilomastix* or *Tetramitus mesnili*. Large intestine (Wenyon, 1920⁸); small intestine (Boeck, 1921⁹).
4. *Tricercomonas* or *Enteromonas hominis*. Large intestine. (Da Fonseca, 1917.¹⁰)
5. *Embadomonas* or *Waskia intestinalis*. Large intestine to caecum. (Da Fonseca, 1917.¹⁰)

The symptoms to which attention is drawn in flagellosis are: recurrent attacks of diarrhoea and colic, passage of mucus and perhaps blood (ulceration), thickening and tenderness of certain areas of the bowel, a blood picture showing slight leucocytosis accompanied by a distinct relative increase of the large lymphocytes with at times an eosinophilia and neurasthenia.

Dobell and O'Connor (1921)⁶ state that "flagellates are found more often in persons with diarrhoea than in healthy persons for the simple reason that the stools of the healthy persons are seldom examined." A detailed examination over a period of several years of the faeces of healthy and unhealthy persons has convinced the writer that flagellates occur far more frequently in the bowel of the unhealthy than in the healthy; flagellates are not found in the faeces of more than 5 per cent. of apparently healthy persons. This means that flagellates are not normal inhabitants of the bowel.

It is agreed that the finding of an abnormal organism in the bowel of a neurasthenic person in no way proves its pathogenicity, but it is folly to explain away any abnormal symptoms that may develop in that person as nervous in origin; should an attack of diarrhoea supervene it is labelled as nervous and no attempt is made to discover the cause of the neurasthenia. As is well known, chronic infections are apt to cause a series of symptoms termed neurasthenia; should this occur a vicious circle may be set up.

No one can say that recurrent diarrhoea is a normal condition in man, nor are such flagellates as *Lambliia intestinalis*, *Tricomonas hominis*, and *Chilomastix mesnili* normal inhabitants of the bowel. When a case of recurrent diarrhoea is subjected, as detailed above, to a careful examination for a possible cause of the malady and none is found, except the presence of some flagellate, there is at least a strong suspicion of its pathogenicity.

Most of the cases of flagellate infection recorded here had a history of recurrent diarrhoea. The stools passed by patients with a lamblia infection were often distinctive. The motions were pultaceous, pale, and had a peculiar mousy odour—quite unlike the diarrhoeic stool usually met with in Great Britain. During the past two summers, while investigating patients suffering from phlebotomus fever in Malta, some cases were noted where the premonitory symptoms of that fever were diarrhoea and colic. In practically all of these cases some intestinal protozoon was found in the faeces, while in those which did not show these symptoms such a finding was exceptional. *Lambliia intestinalis* was the protozoon most frequently found, then *Entamoeba histolytica*, and lastly *Trichomonas hominis* and *Tetramitus mesnili*. Of the total number of cases of phlebotomus fever roughly 20 per cent. showed these symptoms, associated with the presence of a protozoon in the gut. This percentage of cases of diarrhoea and colic closely coincides with that observed in phlebotomus fever by other workers^{18, 19}.

This contention as to the pathogenicity of some flagellates is further strengthened by the frequent passage of mucus containing large numbers of flagellates. In some instances microscopic examination of this mucus showed the presence of large masses of epithelial cells amongst which were entangled numerous lamblia or other flagellates. At times some of the lamblia were seen attached by their sucking discs to these intestinal epithelial cells. Thus certain flagellates appear to exert a physical or chemical action on the intestinal mucosa. The effect may be simply an increased stimulation of the mucous glands, or a more intense action leading to epithelial desquamation or even actual ulceration of the mucosa, as is evidenced by the passage of blood mixed with the mucus. The latter condition was particularly noticed in two cases of trichomonas infection when the bloody mucus passed per rectum contained large numbers of these organisms; on palpation of the abdomen a distinct thickening of the bowel was felt in the region of the splenic flexure in both cases, and also in the sigmoid flexure of one.

Attempts have been made to ascertain the tissue invasion power of intestinal flagellates. Wenyon (1915⁴ and 1920⁸) and others, have made histological sections showing these flagellates filling the gland acini and invading the mucosa of the bowel. In one case at least this invasion seems to have occurred *ante mortem*. This power of invading the tissues is proved in the case of animals by the culture of a trichomonas from the blood stream of a gecko suffering from a trichomonas lesion of the intestine (Chatton, 1920).¹¹

Wenyon (1920)⁸ has reported the invasion of the mucosa of the whole extent of the large bowel and the lower portion of the small intestine by *Trichomonas intestinalis*. In the

present series of cases the occurrence of jaundice in a patient suffering from a pure trichomonas infection points to the possibility of a higher habitat in the intestine. No other cause for the jaundice could be found. The trichomonas disappeared under the routine treatment described below. After five weeks the case relapsed; the jaundice and trichomonas returned together. The condition disappeared after a further course of treatment, and up till now, three years since treatment, there has not been any return of the jaundice, nor on periodic examination have parasites been detected.

Many of the cases of pure intestinal flagellosis investigated showed a distinct relative and absolute increase of the large lymphocytes in the peripheral blood stream. The objection so often made to the fallacy of blood counts was checked as far as possible by the fact that the blood counts of all the cases of disease and the controls were collected by a constant method, with the same instruments and between 9 and 10 a.m. daily. A point of interest was the occurrence of a varying degree of eosinophilia (5 to 8 per cent.) in some of the cases most troubled with flagellates. The percentage of eosinophiles returned to normal with the disappearance of the flagellates from the stool. Careful examination of the patients for several weeks before, during, and after treatment failed to reveal the presence of any other cause for the eosinophilia. According to Gulland and Goodall (1914)¹² intestinal irritation produces an eosinophilia. The occurrence of eosinophilia in flagellate dysentery further supports the theory of intestinal irritation in that condition.

Finally, chronic irritation of the intestinal mucosa is liable to lead to neurasthenia. This irritation may be either of a physical or chemical nature, and akin to the action of intestinal nematodes. Consider for a moment the structure and function of the intestine and its relations to the central nervous system. There is a certain store of nervous energy which is more or less the common property of the whole nervous system. This store may be drawn upon by any of the spinal, cerebellar, or cerebral arcs. Stimuli and their appropriate responses passing along these arcs gradually use up the available nervous energy. In health, sleep comes to restore this lost energy. Normally a person should start the day with 100 per cent. of nerve energy. Imagine the physical irritation set up by millions of flagellates whipping away in the gut, and, in the case of *Lambliia intestinalis*, often attached to the epithelial cells lining it, or the chemical irritation produced by the effete substances thrown off by these flagellates. By one or both of these means unconscious messages are sent along the sympathetic nerve tracts, and all night long there is a leakage of the nerve energy which should be reserved for the coming day. Depending on the degree of the physical or chemical stimuli set up, the patient may awake with only 75 or 50 per cent., or less, of the normal amount of nervous energy required for the work of the day. There is no feeling of refreshment. Work is started, and when only three-quarters or a half is done, definite signs are seen of loss of nervous energy and tone.

There is irritability and want of concentration, and any extra pressure of work causes confusion. The term "flat spin" is very appropriate whether the work is that of flying or otherwise. How often do the subjects of chronic dysentery or malaria show irritability, want of concentration, and a long train of so-called minor and unimportant symptoms. In fact the condition is glibly termed "neurasthenia." Much time is often wasted in trying to restore the nervous equilibrium, but nothing is done to cure the disease which has produced these symptoms. Work is gradually decreased in amount and quality. The whole nervous system loses tone. Vasomotor symptoms such as lassitude, flushings, syncopal attacks, giddiness, and irritability are marked.

Symptoms such as the above are serious enough on terra firma where any mental errors may be corrected by others, but their importance is increased considerably in the case of the air pilot. A little delay in the reaction time may mean a serious crash. The sooner the condition is diagnosed the more likelihood there is of a cure. The earliest manifestations of neurasthenia are readily made apparent by the elaborate modern physiological tests to which air pilots are subjected from time to time (Flack, 1920¹³). The diagnosis does not end here—the cause must be investigated, for unless efficient treatment is given a proper cure will never be attained. Enough has been said to show that any chronic disease is a great danger to health, and that the so-called non-pathogenic infection, flagellate dysentery, is really pathogenic.

TREATMENT.

Many of the cases under treatment harboured more than one type of parasite in their bowel. The habitat of these various parasites has been shown to differ, therefore an attempt was made to devise some form of treatment that would suit all or most cases of chronic protozoal or helminthic infection of the gut. With this end in view the contents of the alimentary tract were reduced to a minimum by putting the patient in bed for three days and placing him on as light a diet as possible. Thus it was hoped that more or less complete absorption of the food given would occur. At the same time sodium bicarbonate was given thrice daily in 15-grain doses. This treatment was repeated for three days, the idea being to clear away any mucus coating the internal surface of the gut, for the flagellates have been proved to be frequently embedded in the gland acini of the intestine. The clearing of mucus from around the head of any helminths present was also attained in this manner. In order to clear the intestines further of their contents and thus allow the specific drugs to exercise their maximum effect on the parasites lodged in the wall of the gut, a 3-grain dose of calomel was given at bedtime on the third day, and 2 drachms of magnesium sulphate administered at 8 o'clock the following morning. When the bowels had moved thymol was given in three 30-grain doses. This was given in cachets (15 grains in each cachet was found to be a convenient amount to swallow), two cachets hourly for three consecutive hours—usually at 9, 10, and 11 a.m. At 12 noon a further dose of magnesium sulphate was given to clear the bowel of the excess of thymol and diminish the risk of thymol poisoning. No food or drink was allowed from bedtime the previous evening until the thymol treatment had been completed. When the bowels had operated actively after the second dose of salts, a cup of tea without milk and a piece of dry toast was given. At tea-time an ordinary plain tea was allowed and chicken diet for dinner. At bedtime that evening emetine bismuthous iodide powder (E.B.I.), 1 grain in a gelatin capsule, was given, the following evening E.B.I. 2 grains, and thereafter for ten consecutive days the dose was increased to 3 grains. Thus a total of 33 grains of E.B.I. was administered.

During the fortnight following the thymol treatment high lavage of the colon was performed on alternate mornings with a solution of quinine sulphate in water (10 to 20 grains of quinine to the pint). For this purpose a rubber catheter was inserted into the rectum for a distance of ten to twelve inches and the quinine solution (1½ to 2 pints) run in gently by gravitation. The patient lay on the left side during the administration, and on withdrawal of the catheter was requested to lie flat on his back for five minutes, thereafter on the right side for another five minutes. In this manner a good lavage of the colon was obtained. This lavage was found most valuable in clearing away lumps of mucus containing large numbers of free forms of trichomonas and chilomastix. (Such lumps of mucus are often held up by the folds of the large intestine.) The rapid removal of large numbers of free flagellates must materially aid their final eradication by reducing the number of proliferating organisms.

After this course of emetine bismuthous iodide the stools were examined daily for at least three weeks, a purge being given at least once a week, and if the findings were negative during that period the patient was encouraged to lead a normal life, alcohol not being forbidden. If there was no return of the intestinal parasites during the next three days the patient was discharged from hospital and put on a tonic pill containing iron, arsenic, strychnine, and cascara. Monthly examinations of the stool were done for three or four months after discharge from hospital.

In the case of relapses an interval of seven to ten days was allowed after the first course of E.B.I. before a second course of thymol and E.B.I. was administered. During the interval salol, 10 grains, was given thrice daily to act as an intestinal antiseptic. In a few cases of lamblia infection salol had a distinctly beneficial action.

Only in a few cases was a third course of treatment given, as it was found that those cases which did not respond to the above treatment were practically incurable. These cases were put on salol, 10 grains thrice daily for a fortnight every month, and given colon lavage twice weekly. This treatment was continued for three months, the patient meanwhile doing light duty.

The results of the above treatment have been very satisfactory. At least 50 per cent. of lamblia infections have been cleared up according to the standards laid down, all the trichomonas cases except one have recovered, and two of the chilomastix cases have relapsed. (See also Barlow, 1916.¹⁴) This strenuous treatment has given results very comparable to those of E.B.I. in *Entamoeba histolytica* infections. In this latter infection, under the systematic lines of treatment laid down by Dale,¹⁵ Low,¹⁷ and Dobell,⁵ quite a number of chronic cystic carriers fail to clear up; the percentage of cures is certainly less than 75. Dobell and O'Connor (1921)⁶ criticize the treatment of flagellate dysentery thus: "The appearance of flagellates or their cysts in the stools of infected persons is frequently very irregular. We have numerous records showing that the stools of infected persons may be 'negative,' on microscopic examination, for considerable periods of time; and this is true of persons undergoing no treatment whatsoever." This statement is admitted, but it applies with equal force to infection with *Entamoeba histolytica*.

During 1918, in conjunction with Major O. H. Gotch, late R.A.F. Medical Service, twelve cases of protozoal infection of the gut (*Entamoeba histolytica*, trichomonas, and lamblia) were treated with novarsenobillon ("914"). The drug was administered intravenously, and a series of four to six injections given in each case. The first dose was 0.45 gram, the second 0.6 gram, and the remaining doses 0.75 gram. In no case was there any improvement of the intestinal condition.

CONCLUSIONS.

The object of this paper is to emphasize the following points:

1. Flagellate dysentery is a *pathogenic condition* which, if allowed to persist, will eventually undermine the health of the patient and cause neurasthenia.
2. Certain cases are simply "carriers," as are some cases of *Entamoeba histolytica* infection. This in no way proves their non-pathogenicity. Such "carriers" are a great source of danger, inasmuch as they may infect others, especially in a military service where they are likely to be drafted overseas.
3. Contrary to what is usually stated, flagellate dysentery may be *cured* in at least 50 per cent. of cases. Stress is laid upon the advisability of the combined treatment by purgation, thymol, emetine bismuthous iodide, and lavage of the colon.
4. All cases of recurrent diarrhoea or neurasthenia for which no cause can be found, and in whom flagellates can be detected in the stools, should have a course of treatment as outlined above.

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