

has hallucinations of smell; he also has visual hallucinations, he sees people in his room. In fact, the state is very nearly allied to a delirious condition.

Hallucinations of Smell.

And one has always felt it is interesting that the organ of smell, though a lower one, is still very highly organised, and it is very closely associated with our whole mental stability and mental growth; it is interesting that it should show disorder in devolution and in adolescence.

I have constantly met men who have complained bitterly about their houses. Take an example. A man told me it is perfectly useless, he cannot get on, and that his wife will not understand that they have a bad cook, and that there are always stinks about the house.

I will tell you of one of the most tragic instances I remember, though there was a comical side to it, too, as there often is. It was the case of an old doctor with a large practice in the neighbourhood of London, who had known me from childhood. His wife asked would I come up and dine with them, so that I could see her husband, who was causing her anxiety. I went. The first thing I noticed about him was that he was very restless. He said, "I am very sorry, you cannot have any dinner." "Why?" "I have discharged the cook." "Why?" "The whole place is stinking of stinking fish. And I cannot send you home." "Why?" "I have discharged the coachman, the stable stinks." It was a trying experience, to some extent. A week later I had a communication from the authorities asking what I thought of Dr. So and So. I asked why. They said, "He is medical officer of health, and he has given orders for the drains to be had up in several of the leading streets." Fortunately, for the sake of the ratepayers and other things, he had an apoplectic seizure and died.

Hallucinations of Sight.

Then I must mention hallucinations of sight, which also are very interesting. I think the best thing I can do, again, is to give one or two examples.

I had to go down to the West of England to see a wealthy old bachelor, who was a big coal owner. He had a kind nephew and a hard nephew. The former said, "Let the old fellow live in his own house under care." The other, the more businesslike of the two, said, "The old fellow is a fool; send him to an asylum." It was decided that I should go and see him, and give my view as to whether he should be treated at home or sent to an asylum. I found in the old man many signs of age. He was a charming personality, and, like so many merchants, a collector of pictures. He took me round and showed me his pictures, and told me where he had got them. Then suddenly he said, "That's a nuisance." I said, "What?" He said, "Don't you see that water running across the floor?" "No, there is no water there." "Do you mean you don't see it?" I said, "Put your finger down." He said, "That is all very well. I put blotting paper down and it does not get wet, but there it is." Looking out into his garden he said, "Well, do you see that old rabbit and her young?" I said, "There is no rabbit there." "Yes there is, running just into that laurel bush." I said, "No. Look here, if I get a gun, will you shoot it?" "No," he said.

The next night have been a very serious case. It was that of a lawyer with a very large city practice, and he had a lot of trust securities. One Christmas day some years ago he thought he would go and have a look at the securities by himself, with no clerks or anybody about the office. In he went and got out securities for many thousands of pounds and was looking at them. He turned round and thought he saw his son and said, "You put these securities away," and he went home. His son, fortunately, went early next morning of business and found these securities, which the old man had left on the table.

You see how difficulties might arise in that way. A man may have hallucinations of that kind and think burglars are about. I knew one who had that impression and fired a revolver. Fortunately, the "burglar" was a ghost, and no harm was done.

These hallucinations are in old people not infrequently most prominent at the waking moments. There was one old lawyer I saw some time ago who recognised that his ideas were wrong, but said they were so dominating that he could not control himself. I said to him, "What are your troubles?" He said, "To begin with, in the morning I

wake up and—I cannot help it—I spring out of bed because I see a dirty gipsy using my tooth-brush. Yet I know there is no gipsy there, and I go back to bed again, and reflect on what a fool I was." I said, "Does it occur at any other time?" "Yes, it is always after waking. I come home from the office, I sit down about 6, and have a nap before I dress for dinner, and when I wake up from the nap I see the same gipsy pulling up my favourite flowers."

These hallucinations are most marked. There may be other hallucinations, but usually they are not so marked.

It is interesting that, in these decadent cases, you get a reversion, to a certain extent, to the form of disorder which may occur in youth.

SOME POINTS EMERGING FROM STUDY OF CASES.

There are two or three things to learn from a study of these cases. One is, one's limitations. I often think of a time I was on the moors in Scotland, where there was an elderly Scotch lady. I had failed at something—shooting, golf, or something—and she said, "You are old enough to have learned your limitations." That is one of the things we have all got to learn; and not only our own limitations, but normal limitations. There are lots of people who, though old, are very useful; there are many people whose age need not interfere with their capacities.

Another thing to bear in mind is that a person who has had energy enough to live to 80 has probably a reserve energy which can be called up when required. I used to say, and still say, that as far as mental disorders are concerned I would much sooner consider a patient hopefully who broke down for the first time at 60 years of age than I would one who broke down mentally at 16, because, unless there is some special cause, in the first case we have a person who has lived long without accident, and may therefore be assumed to have some reserve, which may be used towards recovery.

And we must also remember that a lot of the brightest, best, and most intellectual people die "at the top."

BILHARZIASIS: SOME RECENT ADVANCES IN OUR KNOWLEDGE.

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I. Historical Account of Recent Work.

Up to the year 1912 the exact conveyance of bilharzia disease from one man to another was still a matter of conjecture. Looss,¹ who had worked for many years on the subject, was of opinion that the life-history of bilharzia differed materially from that of the other trematodes in that the *Miracidia*, or ciliated embryos, emanating from the ova passed directly through the skin, while Manson,² arguing on biological analogy, stipulated that an invertebrate intermediary host must exist. Looss³ also denied the existence of two species of bilharzia worms in Egypt. Manson⁴ and Sambon,⁴ on the contrary, on geographical and morphological grounds, considered that there were two species of bilharzia, the one giving rise to a lateral-spined egg, and occurring commonly as an intestinal infection, and that the latter worm occurred in parts of the world (West Africa, South America, and the West Indies) where the terminal-spined egg is not found.

As regards *Bilharzia japonica*, the general morphology of the worm and its pathology were at that time understood and its specificity established. For the earliest work on the transmission of *B. japonica*, and, in fact, bilharzia worms in general, we are indebted to Japanese workers. The earlier efforts of Cobbold⁵ in 1870, Sonsino,⁶ in 1884, Lortet and Vialleton⁷ in 1894, to trace the development of Egyptian bilharzia in molluscs and arthropods, as well as numerous

* In adopting the generic term *Bilharzia* in preference to *Schistosomum* I have followed Leiper's latest dictum, 1918, R.A.M.C. Journal, xxx., No. 3, 235-60. Bilharz discovered the worm in 1851, which he named *Distomum hæmatobium*, but which was renamed *Bilharzia* in honour of its discoverer by Cobbold. In 1858 Weiland had created the genus *Schistosoma* for the worm *Distomum hæmatobium* of Bilharz and von Siebold. One must agree with Leiper that the generic name bilharzia which conformed to the generally accepted views on nomenclature of those days should stand as a perpetuation of the name of its discoverer. The specific name thus becomes feminine, i.e., *B. hæmatobia*.

attempts to transmit the disease directly to man by the agency of miracidia, failed.

In 1908 Fujinama⁸ and Nakamura first found domestic animals infected with *B. japonica*, and that if non-infected cattle, dogs, and cats were immersed in streams, popularly reputed to be dangerous, an intense infection resulted. In 1910 they repeated these experiments with animals, such as mice, which are not found naturally infected, and found young parasites in the portal vein three days after immersion. In addition, the infection of man by these means was proved by Matsuura,⁹ who placed his legs in infected water and some time after passed ova in his stools. In 1911 Miyagawa¹⁰ repeated these experiments and described the invasion forms.

In 1913 Miyairi and Suzuki¹¹ indicated that a freshwater mollusc acted as the intermediary host, and early in 1914 Ogata¹² accurately described the bifid-tailed cercariæ (or larva) of the worm. In that year Leiper and Atkinson¹³ were on an expedition to Yangtze Valley and Japan to investigate the matter and amplified these observations, and demonstrated the life-history of the parasite in the freshwater mollusc now known as *Katayama nosophora*, a new species; furthermore, they completed the story by infecting mice with the characteristic cercariæ through the skin and later by demonstrating the adult worms of both sexes in the portal system.

Our knowledge of the life-history of *Bilharzia japonica* was thus complete at the outbreak of the world war. Realising that the high endemic index of bilharziasis in the Nile Valley (61 per cent. of fellaheen (Ferguson¹⁴) with a death-rate of 10 per cent. (Madden¹⁵)) and the consequent danger of infection to a large number of British troops, the War Office decided to dispatch a special mission, consisting of Leiper, J. G. Thomson, and Cockin, to reinvestigate Egyptian bilharziasis.

This mission was a complete success. Within six weeks of commencing work in February, 1915, the non-eyed, bifid-tailed cercariæ (characteristic of the genus) were found in two different genera of snails. During the following year Leiper followed up his observations by completely vindicating the existence of two separate species of bilharzia worms in man. The one now known as *Bilharzia hæmatobia* presented distinctive morphological features, laid a terminal-spined egg, and developed in a sinistral and spiralled freshwater snail (*Bullinus* sp. *contortus* and *dybowskii*). The second is now known as *Bilharzia mansonii*. It gives rise to a lateral-spined egg and develops in a flat freshwater snail, *Planorbis boissyi*. In addition to this he experimentally infected animals both via the unbroken skin and via the alimentary tract.

II. Life Cycle of the Bilharzia Worms.

The ova are voided either in the urine or fæces, or in both. On coming into contact with water (that is, a fluid of lower osmotic pressure) the chitinous envelope of the egg becomes distended and ruptures, thus freeing the active, ciliated miracidium which it contains. This ciliated embryo swims about rapidly in search of the intermediary host for a period of 24–36 hours, to which it is attracted by chemio-tactic influence. It then enters the snail by piercing the pulmonary chamber by means of its piercing papilla and makes its way to the digestive gland (or liver), situated in the central whorl.

In this situation the germinal cells of the embryo multiply rapidly and become hollowed out into mother and daughter cysts, which are now known as sporocysts, and which radiate throughout the glandular substance. No redial stage as in other digenetic trematodes exists. Inside the sporocysts cercariæ are produced by a process of internal budding. After a period of from four to six weeks, fully developed, active cercariæ are discharged by rupture of the sporocysts, and make their way through the body cavity of the intermediate host into the water. In this medium they can remain alive for 36 to 48 hours, and in this limited time must meet their definitive host or else perish.

The cercaria† itself consists of: (a) a body with two suckers, anterior and ventral, and a number of secretory cells called "poison cells." (b) A tail with terminal fork.

† One must emphasise that there may exist other furcocercous cercariæ in the snails which act as intermediary hosts for human bilharzia. These have distinct morphological characters, and probably represent the larval stage of some bilharzia-like parasite of small mammals or birds. Two of these species have been found by Leiper and Bahr in Egyptian snails.

The bilharzia cercariæ belong to the furcocercous group of the distome trematodes, and are further distinguished by absence of a muscular pharynx and absence of eye-spots.

There are minor features which differentiate the cercariæ of the three species of bilharzia. On the whole those of *B. hæmatobia* are slightly larger (0.472 mm.) than those of *B. mansonii*, while those of *B. japonica* are about half this length. A point by which the cercaria of *B. mansonii* can be distinguished from *B. hæmatobia* is the prominence on lateral view of the ventral sucker in the former (Fairley and Bahr: Report to Australian Government, 1918). Furthermore, in this report it was shown as a result of 10,000 dissections of freshwater snails in Egypt (*Planorbis* and *Bullinus*), that the period of maximum infectivity for both species of parasite occurred, contrary to general expectation, during the winter months (54 per cent. of *P. boissyi* and 11 per cent. of *Bullinus contortus* dissected near Cairo).

Infected snails may be distinguished on macroscopic examination by the great friability of the shell and by the change in colour it undergoes. On placing such a snail in water, after a few minutes, cercariæ can be seen emerging with the naked eye or low-power lens.

On entering the skin of the host these cercariæ cast their tails and bore their way through the tissue by means of papillæ on the oral sucker and possibly assisted by a chemical ferment. Not infrequently in man, as in experimentally infected monkeys, cercarial invasion is accompanied by intense skin irritation. The larvæ reach the portal system via the veins and possibly via the lymphatics as well, and there develop in a period of from five weeks into adults of two sexes.

III. Morphological Distinctions between Adult Worms.

I propose to deal with the chief morphological distinctions of the two Egyptian species of bilharzia, as *B. japonica*, having no tuberculated coat and laying a small rounded and lateral knobbed egg, is easily separated.

The following are the main points:—

Males.—The male of *B. mansonii* is generally smaller in size and more grossly tuberculated than *B. hæmatobia*. The testes are smaller, and eight or nine in number, whereas in the latter there are four or five larger ones.

Females.—The female of *B. mansonii* is smaller than that of *B. hæmatobia*, which measures 2 cm. The ovary is situated in the anterior half, in front of the union of the intestinal cæca and the uterus, and contains generally only one lateral-spined egg at a time; occasionally, however, I have seen two or even three lateral-spined ova in the same female worm. In *B. hæmatobia* the ovary bears the same relationship to the intestinal cæca, but is situated in the posterior third of the worm, and the uterus contains large numbers of terminal-spined ova.

IV. Some Recent Points in the Clinical Appearances of Early Bilharziasis in Man.

From a clinical point of view bilharziasis, at least as it has manifested itself amongst soldiers, can be divided into two stages: (a) the toxæmic stage, occurring four to ten weeks after infection; (b) a much later stage of localised disease characterised in the case of *B. hæmatobia* by vesical and in *B. mansonii* by intestinal symptoms.

(a) The Toxæmic Stage.

The earliest symptoms associated with bilharziasis were first accurately described in *B. japonica* infections. Excellent descriptions of this disease have been given by Edgar¹⁷ (1911), Bassett-Smith¹⁸ (1912), Miyagawa¹⁹ (1913), and Laning²⁰ (1914). Archibald²¹ in 1914 described febrile symptoms in *B. mansonii* without eosinophilia, and suggested it was due to a secondary infection. Previous to this Flu²² in Surinam called attention to the appearance of febrile symptoms resembling katayama disease in cases with lateral-spined ova in their fæces.

In 1916 Lawton²³ described an outbreak of bilharziasis amongst Australian troops in Egypt. His cases presented some or all of the following symptoms: "Abdominal pain, enlargement and tenderness of the liver and spleen, pyrexia, bronchitis, urticaria, and diarrhoea." Eosinophilia was always present and the fæces contained the lateral-spined ova of *B. mansonii*. The onset was often insidious and the incubation period averaged four to eight weeks. The temperature lasted from ten days to eight weeks. Emaciation was marked.

The analogy between this and *B. japonica* infections—the “katayama disease” of Japan—was thus complete. In a series of 75 cases amongst Australian troops I have abundantly confirmed and amplified Lawton's original observations. That these toxæmic symptoms, however, are not necessarily dependent upon an infection with one species of bilharzia alone is evident from the fact that I have noted identical symptoms in pure *hæmatobia* infections from Serapeum† as well as in double infections. In fact, 34 out of 35 cases of the present series from Tel-el-Kebir belonged to the latter category, that is to say, that terminal- as well as lateral-spined ova were present in the urine and fæces. In addition to this, 10 out of 13 of Lawton's original cases who have since developed vesical symptoms in Australia were found to be similarly affected.

The present series of cases may be classified, according to the presence of outstanding clinical phenomena, as follows: (1) those presenting symptoms of urticaria and prolonged pyrexia; (2) those with urticaria and pyrexia of less than ten days' duration; (3) cases with urticaria alone.

It is unnecessary in the present paper to amplify the clinical details, except to say that the urticaria is of the most intense type, causing a general œlema of face and often of penis and scrotum as well, with the formation of wheals on the trunk and limbs. It is sudden in appearance, remarkably transient, and lasts on and off from one to ten days.

After disappearance of this stage a latent period supervenes, which may last anything from six weeks to two and a half years before obvious symptoms of localised bilharziasis are noted, though ova are being passed in the dejecta during the whole of that period.

(b) Localised Disease: (1) Vesical Bilharziasis.

The localised symptoms can be classified according to the site of the lesion and the species of the parasite.

This description of early vesical bilharziasis is compiled from 45 cases of pure *B. hæmatobia* infection.

The onset is most commonly ushered in by a burning and scalding urethral pain, in others the pain may be deep-seated, perineal, or referred to the penis; this is followed by a terminal hæmaturia, the most characteristic feature of vesical bilharziasis. This hæmaturia may be a constant feature or may be of a most irregular nature. I wish to emphasise that pain is not a dominant feature of the disease. When it occurs it may be referred to the perineum, the urethra, the suprapubic region, or to the loins or small of the back. Suprapubic pain is especially marked during distension of the bladder, and the suprapubic region is the most common site of discomfort.

Frequency of micturition is generally met with at some stage of the disease, but is usually an early and transient symptom lasting four or five weeks. Urgency is a common complaint.

In these pure *hæmatobia* infections it is quite common to elicit a history of passage of blood and mucus per rectum, though they do not actually amount to dysenteric attack. On rectal examination localised tenderness above the prostate gland and in the region of the vesiculæ seminales is noted.

Cystoscopic examination shows congestion of the mucosa and frequently the presence of white submucous nodules. The urine may show macroscopic evidence of mucus and blood, and a small amount of albumin may be present. The ova can best be demonstrated in the centrifuged deposit of the urinary residuum, and are associated with pus and red cells. A point of considerable importance is that these ova may be passed in a most vagarious manner, and that therefore a single negative examination of the dejecta does not exclude the disease.

Contrary to what is stated in most text-books terminal-spined ova have been found in the fæces of most of these cases.

† As a notable confirmation of Lieper's work the following points are remarkable. In the first instance the patients, who were stationed at those posts in 1916, were admitted to hospital with symptoms of bilharziasis; the nature of their infection being determined by the usual methods. Cases from Serapeum showed only *B. hæmatobia*, while cases from Tel-el-Kebir showed double infections. Following on this discovery the snail fauna of both these localities was investigated by Captain Bahr and myself with the result that in the former the presence of bullinus only could be substantiated, while at Tel-el-Kebir infected snails of both species were demonstrated. As a further proof it may be cited that monkeys were infected with bilharziasis, with cercariæ derived from infected snails obtained from these localities. The chain of evidence was thus complete.

The examination of the blood shows certain constant changes. There is a moderate *leucocytosis*. In 35 cases the average count was 10,030; the lowest 4700; the highest 22,000. The differential count in these cases demonstrates an average eosinophilia of 13.5 per cent., with a relative decrease in the polymorphs. The tendency is for eosinophilia to be most marked in the toxæmic stage (Lawton 50 per cent.), and gradually to decrease during the subsequent two years to an average of 11 per cent. The red cells and hæmoglobin show nothing of interest, except a slight secondary anæmia.

The ravages of late urinary bilharziasis, resulting from the repeated infections, to which the Egyptian fellaheen are constantly exposed, have not been observed in European troops during the war. In the Egyptian such complications as septic cystitis, hydro- and pyonephrosis, interstitial nephritis, urinary calculi, vesical carcinoma, urethral and perineal fistulæ are commonly observed. The comparatively high death-rate (10 per cent.) amongst these unfortunate people is occasioned by three factors: mechanical obstruction by bilharzial granulation tissue, secondary septic infection, and malignant supervention.

As Day²⁴ first pointed out in these late cases the blood picture differs in certain respects. There is a relative and absolute increase in the polymorph neutrophiles, with a corresponding decrease in the eosinophile elements and the establishment of a severe secondary anæmia.

(2) Intestinal Bilharziasis.

This description of early intestinal bilharziasis is compiled from a study of 38 cases of *B. mansoni* infection. Most of these were complicated by concomitant *B. hæmatobia* infections. In the latter the vesical symptoms were identical with those already described. Thirty out of 38 cases first reported sick on account of bladder trouble, not associated with any intestinal disturbance. Eleven of these on cross-examination denied all history of any intestinal trouble, although they were at the same time passing lateral-spined ova.

Even when present, intestinal symptoms were generally slight. These manifested themselves by a sense of rectal uneasiness, occasional attacks of diarrhœa with blood and mucus in the stool, but rarely accompanied with tenesmus.

The dysenteric attacks lasted from two days to three weeks or more, and were sometimes accompanied by emaciation. In the intervals between individual attacks the condition of the patient steadily improved, the only abnormality noted being the passage of solid stools with abundant yellow mucus.

Microscopic examination of the mucus revealed the presence of lateral-spined ova, and in four cases lateral-spined ova were present in the urine as well. The results of a systematically conducted blood examination in no way differed from that already described for *B. hæmatobia*.

The late symptoms of the disease, as in the case of *B. hæmatobia*, were not observed in British troops at this comparatively early stage. In the Egyptian fellaheen massive pedunculated submucous tumours and subperitoneal infiltrations form in the colon; the former by sloughing may give rise to extensive intestinal ulceration. A coarse “pipe-stem” periportal cirrhosis, first described by Symmers, is not very commonly observed at autopsy, but I believe that further investigation will prove that a finer grade of cirrhosis must exist in a large proportion of all *B. mansoni* infections.

It is hardly necessary here to point out that all these late pathological changes correspond with what is known to occur in *B. japonica* infections.

V. Researches on the Pathological Basis of these Clinical Symptoms.

For a correct appreciation of the differences of the clinical picture of these two diseases a careful study of the morphology and habits of the two species of trematodes is essential, as well as the morbid changes in the tissues of artificially infected monkeys.

Habitat.—The different distribution of the paired worms in the two species of infections is of considerable importance, as it explains the different anatomical situation of the pathological lesions. In *B. mansoni* the habitat in infected monkeys was the inferior and superior mesenteric veins and the portal system of the liver; in *B. hæmatobia* infection, while paired worms were found in the portal, inferior, and

mesenteric veins, they were present in the largest numbers in the pelvic plexuses of veins, the vesical and the uterine. From here worms may wander into the inferior vena cava and be actually filtered out in the lungs.

Though the adults of *B. mansoni* were never found in the latter situation, its lateral-spined ova were. On a priori grounds one would therefore expect the liver to be involved in monkeys, by both species of bilharzia, but pulmonary lesions to be mainly limited to *hæmatobia* infections. This actually is what one finds at autopsy in experimentally infected monkeys.

The mode of deposition of ova in the tissues. §—When the time for oviposition arrives the paired worms travel against the direction of the blood stream to the furthest possible point. Here the female leaves the male partner, and being of a much narrower calibre migrates until unable to progress owing to actual mechanical obstruction. The ova are then ejected, with their spines directed posteriorly through the vaginal opening, which is situated immediately behind the ventral sucker, into venules of a diameter approximating to the diameter of their own. As the female withdraws her head the blood current tends to assume its normal course and thus forces the ovum onward, engaging its spine in the vessel wall. The blood now forces the ovum through the wall into the perivascular tissue. Hereafter its progression through the tissues is independent of the spine and is brought about by an active ulcerative process.

The capacity of the two species for producing ova.—*B. hæmatobia* has a much greater capacity for ovum-production than has *B. mansoni*. This is probably due to their anatomical characters, for *B. hæmatobia* has, on account of the situation of the ovary, a much greater uterine capacity than has *B. mansoni*. I have actually counted as many as 50 terminal-spined ova in the uterus of one female worm, while in the female of *B. mansoni* as a rule, only one ovum is found at a time. Occasionally, however, I have observed two or three ova in the same female worm. This latter fact may explain the greater severity of the localising symptoms of *B. hæmatobia* infections, as compared with those of *B. mansoni*.

Some explanation is obviously required, for in Egypt there exists a greater chance of infection by cercariæ of the latter species, which are much more frequently discovered in systematic snail dissection than are those of *B. hæmatobia*; in fact, on an average they are 18 times more common, and, moreover, *Bullinus* snails are much scarcer than are *Planorbis*.

The Investigation of 25 Experimentally Infected Monkeys.

Those animals hyperinfected with bilharziasis may die from two to five weeks from the date of infection, and prior to the deposition of ova in the tissues. Death in these instances was due to toxins elaborated by the maturing worms and was accompanied by complete suppression of the cellulo-humoral response (such as leucopenia, absence of eosinophilia, and complement-fixation reaction). The effects of these toxins on the tissues are shown by the cloudy swelling of the parenchyma of the glandular organs, such as the liver, spleen, and kidney, and by a round-celled periportal infiltration.

In less severely infected monkeys emaciation and general malaise may be observed as above, but they survive and localising symptoms appear. Furthermore, in these animals the cellulo-humoral response is marked. A high eosinophilia and a marked leucocytosis are present. The eosinophile myelocytes in the bone marrow are increased, and a positive complement-fixation is obtained in 90 per cent. of cases. It is interesting to note that localising symptoms in the vesical form appear at least two weeks later than do dysenteric symptoms in monkeys experimentally infected with *B. mansoni*; in fact, terminal-spined ova may be found in the faeces of monkeys before they make their appearance in the urine.

Blood cultures from monkeys in the first two months are always sterile, thus disproving the suggestion of Archibald that febrile symptoms are due to secondary infection.

§ This theory was based on certain direct observations. The habits of the worms were studied in the mesenteric veins of infected and anaesthetised monkeys on which laparotomy was performed. Fresh pieces of bowel were examined microscopically by fixing between glass slides apposed by rubber bands. In this fashion the deposition of ova in the vessels in the various stages, as well as the actual mode of egress, were observed.

|| To be described in detail later on.

The Morbid Anatomy of Infected Monkeys about the Twelfth Week.

(a) *B. hæmatobia* infections.—On opening the abdomen the liver is found enlarged and congested and studded with whitish tubercles, 0.5–2 mm. in diameter, which are in reality minute abscesses composed of eosinophile cells. The spleen may be enlarged and congested. The colon is frequently thickened and subperitoneal and submucous nodules of 1–3 mm. in diameter have been noted. The omentum may form vascular adhesions to the outer surface of the colon and may tear on separation. The bladder may show massive papillomatous formations of from 5–8 mm. in height; the mucosa is dark red and engorged. On section the uterus in the female may present the same whitish nodes or nodules in the submucous zone. The lungs are often found to be affected with a condition resembling miliary tubercle.

Examination of the venous system shows paired worms in quantity in the liver, portal vein, mesenteric, and very especially the pelvic veins as well as in the inferior vena cava and pulmonary veins.

By using a modification of Ferguson's method of digestion with 3 per cent. caustic soda, the distribution of ova in the tissues was as follows: They occur in the greatest numbers in the bladder, the uterus, liver, lung, the small and large intestines, but they also occur in the lymphatic glands, spleen, and kidney.

(b) *B. mansoni* infections.—On opening the abdomen, again, the characteristic appearance is the large congested liver with similar whitish nodules. In heavily infected monkeys constant changes occur in the colon; in some cases the subperitoneal coat may be studded with minute nodules, in others various grades of inflammation of the intestinal submucosa may be manifested by congestion, increased mucoid secretion, minute ulceration, and scattered bilharzial tubercles. Actual papilloma formation was never observed. The lungs and bladder rarely show macroscopic evidence of the disease in this species of infection.

Ova are most commonly found in the liver, colon, and small intestine, and may also be demonstrated in the stomach, the duodenum, spleen, lymphatic glands, pancreas, lungs, and kidneys.

Microscopical pathology of the lesions of both species.—Microscopically, the characteristic features consist of an infiltration of eosinophile and round mononuclear cells. Actual softening may form in the centre of these whitish nodes (these are analogous to the eosinophile abscesses in trichiniasis). Giant-cell systems are commonly present in the vicinity of ova, and may actually form a plasmodial mass completely enveloping them. This type of cell reaction is to be regarded as a response to the mechanical irritation produced by a foreign body.

The distribution of the microscopic lesions in the body corresponds to the blood-supply; for example, in the liver it is the periportal zone, in the hollow viscera the subperitoneal and submucous coats. Ova in the tissues, as well as the adult worms in the veins, exert their influence by virtue rather of a toxic secretion than by any actual mechanical action. The cytological response to bilharzia toxins is the eosinophile cell. From these lesions ultimately granulation tissue is produced, and this is later replaced by fibrous tissue. The local tissue reaction and systemic response may be responsible for the death of ova as well as of adult worms in situ. Not infrequently such results are noted in microscopic section.

VI. *Resume.*

As a result of these pathological and clinical studies it is obvious that bilharzia worms and probably also their ova exert their deleterious influence on the tissues mainly by toxic action. Such a view is inevitable when one considers:—

1. The nature of the early clinical manifestations both in man and in experimentally infected monkeys (obviously toxic in origin).

2. The nature of the pathological lesions demonstrable in monkeys dying two to four weeks after immersion and before ova are deposited in the tissues.

3. The type of cellulo-humoral response. Antibody can be demonstrated in the peripheral blood of infected monkeys and man by means of a specific complement-fixation test about to be described. The eosinophilia in bilharziasis and the excess of eosinophile myelocytes in the bone marrow can only result from chemiotactic or specific toxic action.

VII. *The Complement-fixation Reaction in Bilharziasis.*

The frequency with which urticaria, fever, and other symptoms were observed in the early stages of bilharziasis first suggested to me the presence of some circulating toxin, the product of maturing or adult parasites. To demonstrate the presence of immune body against such a toxin I manufactured an antigen from the livers of snails (*Planorbis boissyi*) infected with *B. mansoni*, and utilised the method of complement-fixation first described by Bordet and Gengou.²⁵ In June, 1917, I was able to report to the military authorities the discovery of a positive complement-fixation test for bilharziasis.

Technique employed.—The most satisfactory antigen is prepared by macerating a number of infected livers in a quantity of absolute alcohol and thoroughly shaking on an electric shaker. This mixture is then stored for 24 hours at 37° C. and filtered. The filtrate is evaporated at 45° C. by means of a Sprengel's exhaust pump. The residue is dried, weighed, and made up into solution with 0.85 per cent. saline + 0.5 per cent. phenol (0.05 g. of residue to 20 c.cm. solution). The anticomplementary dose is then estimated and one-third this amount used in the test. Lately, as an alternative, I have adopted the simple procedure of diluting the concentrated alcoholic extract with saline and not evaporating to dryness. The results so far have been most satisfactory. Besides estimating the anticomplementary dose the antigen is always tested for hæmolytic tendency, as similar extracts of the livers of normal snails and also of those infected with allied cercariæ yield negative results; the antigen must be regarded as absolutely specific.

The general technique I now adopt is similar to that utilised for the Wassermann reaction and need not be described in detail. Racks with four rows of tubes are utilised, the first, second, and third rows containing 3, 5, and 7 M.H.D. of complement respectively besides antigen, saline, and diluted serum. The back row contains 3 M.H.D. of complement, but no antigen, and acts as a serum control. Antigen controls and sure positive and negative sera are always included in the system. The first stage of the reaction is conducted for one hour at 37° C. and then sensitised corpuscles are added, final readings being made at the end of another hour.

Results are recorded as P+, P++, or P+++ according to the number of tubes in which hæmolysis is completely inhibited. On an average, pooled positive sera collected from early cases of bilharziasis fix 7 M.H.D. of complement over and above that fixed by pooled negative sera in the presence of specific antigen. In more chronic cases this excess fixation amounts to about 4 M.H.D. of complement.

Analysis of results.—In 322 consecutive cases investigated by this test the following results were obtained:—

1. In a group of 36 cases whose bilharziasis was under two years' duration 32, or 89 per cent., yielded positive reactions.
2. In a group of 97 more chronic cases 72, or 74 per cent., yielded positive reactions.
3. In 44 cases of syphilis yielding positive Wassermann reactions negative results were always registered. In one case a P+ reaction was obtained, but here there was anticomplementary tendency shown in the serum control tube.
4. In 150 other cases, which included protozoal, metazoal, and bacterial infections, negative results were uniformly obtained. In only one case was a positive result registered where ova were not found in the dejecta, but as only one examination was made, and as intestinal symptoms were present, bilharzia could not be here excluded. Probably the case was one of latent infection.

It is interesting to note that, as a general rule in bilharzial infections, the higher the eosinophilia the greater the amount of complement fixed. There are, however, many exceptions, and a proportion of cases without eosinophilia yield positive reactions.

The Practical Value of this Test is Twofold.

1. It affords a means of diagnosis, not only in latent bilharziasis, but also in very early stages of the disease prior to the onset of vesical or rectal symptoms. Thus in monkeys the reaction is generally well established by the seventh week (P+++ reactions).
2. It affords a therapeutic index to the effect of a given drug on bilharzial worms. In this respect the test should stand in the same relationship to bilharziasis as does the Wassermann reaction to syphilis.

VIII. *Prognosis.*

The experience of Smith²³ and Cottell,²⁷ based on bilharziasis contracted in the South African war, would suggest that the prognosis regarding life, in the milder grades of infection, is most favourable. As the majority of our soldiers who contracted the disease in this campaign were only occasionally exposed to infection those fell complications of the disease—malignancy and septic infections—are not so likely to ensue.

IX. *Reflections on Treatment.*

In the past it has been customary to estimate the therapeutic value of any drug in bilharziasis according to the following criteria: (1) the temporary disappearance of vesical or intestinal symptoms; (2) the diminution or cessation of the passage of ova in the dejecta. Such data, however, act as an index to the temporary amelioration of local conditions, but not to the cure of the disease. This information tells little concerning the fate of the true causal agents concerned—viz., the worms.

The recent advances in our knowledge of bilharziasis, however, now afford a scientific as opposed to an empirical basis for ultimate cure. Thus (1) the lethal action of various drugs in worms and cercariæ can be investigated in vitro; (2) monkeys can be readily infected and the effect of the intravenous injection of any drug which has been found to exert a selective lethal action in vitro tested; (3) the complement-fixation test (controlled perhaps by post-mortem examinations) can be used to determine the effect of the drug on the parasites, either in man, or in experimentally infected monkeys.

In 1917 I treated 4 cases with repeated intravenous injections of eusol with negative results, as indicated by the facts that the complement-fixation reaction and the eosinophilia were unchanged. On a priori grounds this result was to be expected, as, contrary to the findings of certain observers, I find that available chlorine possesses no special lethal effects on cercariæ.

Christopherson²⁸ has recently reported favourably on the treatment of bilharziasis with tartar emetic administered by the intravenous route. Further confirmatory evidence of cure, as controlled by the complement-fixation reaction and the demonstration of a specific or selective action of tartar emetic in high dilutions on the adult bilharzia and cercariæ in vitro, would be of the utmost value.

Benzene and thymol have been recommended by Robertson per os, but in the limited number of cases in which I have noted the effect of these drugs the results have been disappointing. Urotropin is indicated in certain secondary infections of the genito-urinary system, but, per se, it naturally can have no influence on the adult parasites since it does not liberate formaldehyde in the circulating blood. There is no unanimity of opinion regarding the results obtained by the subcutaneous injection of emetine hydrochloride in bilharziasis.

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