Gram-positive diplococcus in one. In every instance the diagnosis of infective endocarditis was made without the aid of the bacteriological report. It was based upon signs of gross valvular disease—*aortic regurgitation* or *mitral stenosis* associated with *pallor*, *enlargement of the spleen*, *petechiae*, and in many *clubbing of the finger-tips*. There may have been no fever at the time of the examination, *petechiae* may not have been found, and the bacteriological examination of the blood was often negative. The diagnosis was correct, as the *post-mortem* findings proved in 22 cases.

Of the 55 cases, 44 are known to have died with an average duration of symptoms of fourteen months; no information could be obtained from 8 after discharge from hospital; three of these had no signs of venous stasis and one was a doubtful case. The cause of death in 26 was gradually increasing heart failure, acute heart failure in 5, the sudden onset of auricular fibrillation and death in a few hours in one; 3 died following a hemiplegia, one from pulmonary embolism, and one from a streptococcus pneumonia.

The pathological changes revealed at autopsy were typical in every instance of subacute infective endocarditis. There were recent vegetations, and these were usually engrafted on an old valvular lesion with extension in many with mitral disease on to the posterior wall of the left auricle, and on to the septal wall of the left ventricle in those with aortic disease. Sometimes myocardial degeneration was easily recognized. The spleen was enlarged in all, with old or recent infarcts in many. In others they were absent, and the organ was congested and swollen as in typhoid fever. Nephritis was always noted when sections of the kidney were made; usually of the parenchymatous type, but in all the glomeruli were more or less replaced by fibrous tissue. Infarcts were found in the kidneys of many. The other pathological changes were those found after death from cardiac failure.

Conclusions.

Subacute infective endocarditis is not a rare disease. It is seen in 8 per cent. of patients with signs of gross valvular disease attending a special heart clinic.

The signs are easy to recognize. In the diagnosis chief reliance should be placed on the following signs: Gross valvular disease, pallor, enlarged spleen, and clubbing of the finger-tips.

Aortic regurgitation is the type of valvular disease usually seen in this disease; it is rare to find the mitral valve alone involved.

The course of the disease from the onset of symptoms is usually less than fourteen months; death may occur within two months of the onset of symptoms.

A bacteriological examination of the blood is useful in confirming the diagnosis. Without such an examination the diagnosis may be made with certainty.

The disease is always fatal.

REFERENCES.

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ON THE ACTION OF TARTRATE OF ANTIMONY IN INTRAVENOUS INJECTIONS:

THE "PERMEABILITY" OF BILHARZIA OVA AND
SOME PROTOZOAL ORGANISMS.

BY

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THERE is a fact to be borne in mind regarding intravenous injections of antimony tartrate—namely, that the drug appears in the blood stream as antimony tartrate and not as a complex derivative of antimony, produced by contact with gastric and other secretions and elaborated by digestive glands, as is possibly the case when tartar emetic is given by the mouth.

Whether antimony tartrate remains as such as it circulates in the blood or whether it combines with a constituent in the blood stream we do not know, but it would not be unreasonable to think that a stable and simple

compound such as antimony, potassium (or sodium) tartrate remains in solution in the blood until it is dealt with by the kidneys, liver, bowels, and skin for the purpose of storing or of eliminating it.

It does not seem to be necessary, therefore, on the face of it, in order to explain the action of antimony tartrate in bilharzia disease, to introduce the complicated picture of antibodies and indirect action on the parasite. For living bilharzia ova are certainly porous and permeable, pervious and foraminous, whether they be imbedded in the tissues or free in urine. The miracidium living inside the chitinous shell is aware of what is taking place in the atmosphere around the shell.

In the specimen glass, and we may assume, I think, in the bladder also, the concentrated urine would be as deadly to the miracidium without the protection of the shell as it is to other forms of animal life. The miracidium inside the shell, it is true, may, and often does, turn right round in its shell in the undiluted urine (the preliminary step to hatching),* but it does not often hatch. But if bilharzia urine be diluted ten or eleven times with water, and the temperature maintained at about 130° F. (which is not hotter than water exposed to the sun in Egypt), hatching takes place in four or five minutes.

The miracidium inside the shell, in other words, is in touch with the world outside the shell, and is ready to respond to favourable local conditions; this communication can only be explained by supposing the shell to be permeable and porous.

There are several other facts which prove the permeability of the bilharzia ovum. In hunting for helminths or ova in faeces at Khartoum Civil Hospital we are in the habit of using an ounce of 40 per cent. formalin to the specimen. This acts as a deodorant and facilitates the examination in various ways. Now we (Mr. Newlove and myself) found that this formalin sterilized the bilharzia ova when present, but that it left ankylostoma ova unharmed. This fact suggests that the ovum of bilharzia is permeable and allows the formalin to penetrate it and kill the miracidium inside; it also indicates that all ova are not permeable, and as an example of an impermeable shell we have the ankylostoma; there are biological reasons for permeability or otherwise, but we are only concerned in the fact at present.

There is, therefore, no *a priori* reason why the bilharzia shell should be impermeable—in fact, certain biological facts can only be explained on the supposition that it is permeable. By direct experiment *in vitro* we are able to show that bilharzia ova are permeable to antimony tartrate which kills the miracidium within the shell. Mr. Newlove and I found at Khartoum that, if $\frac{1}{10}$ c.cm. of urine laden with ova was diluted with 6 c.cm. of tap water at 130° F., ova hatched out in four or five minutes, and most of the ova in the specimen were hatched out within one hour. If one grain of antimony tartrate were added, before the hatching, only about half the ova would hatch, a good many were found dead, half in and half out of the shell, or, in other words, they appeared to have survived the hatching process only a short time as they were seen lying dead by the side of the evacuated shell, like corpse and coffin. The more resisting miracidia which survived and which were swimming about, did not swim nearly so long as miracidia hatched in plain water. The addition of about 2 grains of antimony tartrate to the 6 c.cm. just about stopped the hatching process altogether.

Now if to a solution of about 6 c.cm. wherein were hatched miracidia swimming about, $\frac{1}{2}$ grain of antimony tartrate be added the movements of the miracidia were markedly changed. Normally they dart about with a pulsating movement, the sharp non-ciliated end forwards, revolving all the time on their own axis. This characteristic movement no doubt assists in the process of penetrating the snail, though it is not the engine of penetration. On the addition of the antimony the miracidia slow down, they wriggle, they writhe: they have, seemingly, convulsions, and, assuming a thicker and shorter form, they

* A bilharzia miracidium is as a general rule found with its head end in the blunt end of the ovum—that is, away from the spike, normally in fresh urine. Before the hatching takes place it turns right round in the shell; it escapes eventually by smashing a way through the shoulder, the broadest and weakest part of the shell. It is a curious fact that sometimes bilharzia patients, in order to "flush out the kidneys," drink a glass or two of beer or two or three cups of tea. This dilutes the urine and sometimes causes some of the ova to hatch, inside or outside the bladder, without further dilution of the urine.

die. Some appear to escape, but the period of activity is considerably diminished by the antimony in every case.

In making these observations with bilharzia the variation in resisting power of the different individual ova or embryos or miracidia was striking. Some ova hatched very much sooner than others under normal conditions, and some miracidia appeared to be more active than others, and some appeared to have a longer life, this quite apart from any accidental external circumstance such as becoming entangled in a wisp of mucus.

Therefore, judging from direct experiments *in vitro* with antimony tartrate, and from clinical results, one arrives at the conclusion that antimony tartrate has a profound and direct specific effect on bilharzia in all its stages. It kills the parent worm *in situ* in the portal tributaries. It penetrates the ova as they lie deposited in the tissue wall and kills the enclosed embryo. It has also the power of killing the free miracidium.

As no experiments have been made *in vitro* on the action of the antimony tartrate on the adult worms the matter cannot be considered settled. I have not had the opportunity of making them myself, but it would not be difficult to do the tests, obtaining the worms from animals experimentally infected.

We (Mr. Newlove and J. B. C.) concluded (speaking under correction and from clinical evidence only regarding the parent worms) that:

1. The parent worms are the most readily affected by antimony.
2. The ova next.
3. The miracidia are the most resisting of the three to antimony tartrate.

There are, therefore, ample grounds for believing that the action of the antimony tartrate introduced into the veins is a direct one on the ova, and probably on the adult worms also.

Continuing the doctrine of "permeability" and "direct action" further, it would appear likely that it also applied to the action of antimony tartrate on certain protozoal diseases; for instance, we know that it has a specific action on the Leishman-Donovan body in all its clinical manifestations, and that it has a decided curative effect in trypanosomiasis, though that disease is more resisting to antimony tartrate than either leishmaniasis or bilharzia. I am inclined to think that the enclosing membrane of the Leishman-Donovan body is also "permeable" (more permeable and less resisting than the enclosing membrane of trypanosome). If, in taking a specimen of splenic blood from a kala azar patient for the purpose of diagnosis, there be water in the syringe the bodies will not be found; they are hygroscopic. They take up water and disintegrate. The logical way of explaining this fact is, I think, that the shell or limiting membrane of the body is "permeable."

Permeability of the confining membrane may also be the explanation of the fact that in kala-azar it is extremely difficult to find the bodies in the peripheral blood. It may be that it is so delicate and sensitive to external conditions owing to the porosity of the "shell" that when it arrives in the peripheral blood exchange takes place between inside and outside "shell," and the body disintegrates. This is conjecture, but it is a fact which requires explanation that occasionally, though not often, the Leishman-Donovan body is found in the peripheral circulation. "Permeability" may also explain the difficulty in finding the body in tissues *post mortem*; so responsive is it inside its "shell" to external influences that it disintegrates and disappears as soon as the patient dies.

The four typical periodical rises of temperature in a twenty-four-hour kala-azar chart may possibly be associated with the periodical destruction in the peripheral

blood stream of the Leishman-Donovan bodies as they escape from the tissues where they have their habitat (liver, spleen, bone marrow, etc.).

There is a clinical fact also both in kala-azar and in trypanosomiasis which suggests direct action, and the breaking-up of the Leishman-Donovan bodies and trypanosomes with the introduction of the cell contents thereby liberated into the blood stream. If antimony tartrate is given to a patient with kala-azar or sleeping sickness the initial effect of the first dose or two is great aggravation of constitutional symptoms, shown by a sudden rise of temperature, etc. This is possibly due to the direct action of the drug entering and breaking up the organism, thereby liberating the toxins, etc.

Advancing this argument of "permeability" a step further, we find that parasites of "so many and so varied a nature" (Low) respond to antimony tartrate. It might be thought: It is a specific for bilharzia; why not, therefore, for other flukes and parasites, such as filaria, guinea-worm, and intestinal worms? It is a specific for leishmaniasis and trypanosomiasis, therefore why not for the plasmodium of malaria and the amoeba of dysentery? The answer to this may be found in the issue as to the direct action of drugs on the organism, and the question whether or no the organism is "protected" by a covering or membrane which is "permeable" to the antimony.

The following is a short statement made by Mr. N. H. Johnson of the Tropical Diseases Clinical Laboratory, from observations made independently by him on ova obtained from patients attending the Ministry of Pensions Clinic for treatment:

In the course of my experience during the past six months, examining the specimens of urine of bilharzia patients under treatment, I have discovered that antimony tartrate not only kills the miracidium but completely disorganizes the ova, which become shrivelled, blackened, and granular; I have repeatedly tried to hatch the treated ova, but without success. I have found that by adding 1 grain of antimony tartrate to 20 c.cm. of diluted urine at 37° C., with abundant ova, after twelve hours' incubation the ova appeared to be alive, but only a sluggish movement was noticeable. On adding 2 grains of antimony tartrate to 20 c.cm. of diluted urine at 37° C., on twelve hours' incubation the ova were completely sterilized, blackened, and granular, and I found it absolutely impossible to hatch these out. Not only do the ova appear to be blackened, but the surrounding debris and crystals are blackened; this, however, does not affect the blood corpuscles. Each of the above experiments has, of course, been worked with controls. In hatching out the untreated ova the miracidium revolves inside the shell prior to hatching until it finds a weak part—generally the centre of the lateral part of the shell—which it ruptures and escapes.—N. H. J.

In conclusion, I have to thank Dr. Broughton-Alcock, who has kindly given me the necessary facilities for carrying out observations at the Laboratory of the Tropical Diseases Clinic, Ministry of Pensions, London.

ANTIMONY IN LEPROSY.

BY

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IN view of the remarkable improvement that was shown in some leper patients whilst undergoing a series of intramuscular injections with Oppenheimer's colloidal preparation of antimony (oscol stibium) in March of this year, I decided to give the treatment a further trial.

A report of the treatment appeared in the BRITISH MEDICAL JOURNAL for July 17th, 1920, page 76, where it was stated that the course was brought to an untimely end because the Union Government was unprepared for these leper patients to remain under observation in Natal. Six months after treatment was discontinued a letter was received from Madras to say that one of the lepers, David, was enjoying the best of health, carrying on his ordinary occupation in India, and was complaining of no symptoms requiring medical attention.

Two more lepers were admitted to the dépôt hospital of the Indian Immigration Board on August 23rd.

Sital stated that he had suffered from the condition for four years, during which time he had lived at Weenen, in Natal. The fingers were stiff and the extremities covered with a blood-stained discharge. All the fingers and both thumbs were discharging, and he had lost the nail of one finger of the right and two fingers of the left hand. All the toes were discharging,

* In the only case verified by *post-mortem* examination, made on a man who before was heavily infected with bilharzia, and who died of influenza and pneumonia a short time after his injections had been completed (gr. 33), the man was apparently cured of his bilharzia, for no parent worms were found in the portal vein.—*Journ. of Trop. Med. and Hyg.*, April 1st, 1919 (Archibald and James).

† The miracidium needs more formidable protecting paraphernalia to enable it to survive the varied conditions of life it will experience in the Egyptian puddle where it should be hatched.

‡ Oriental sore, naso-oral leishmaniasis, kala-azar.

§ The spleen is, practically speaking, a large blood swamp; openly connected with the arteries and veins, it is impossible to think that the Leishman-Donovan body does not get very frequently into the general circulation, and it needs explanation why it is so seldom found there.—J. B. C.