A CASE OF TRYPANOSOMIASIS TREATED BY
INTRATHECAL SERUM.

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In view of our recent advocacy of the treatment of sleeping sickness by the injection of serum into the spinal canal, we wish to record the case of Mr. X. in fuller detail.

The first point of importance is the probable date of infection. As to this, Mr. X. lays stress on the fact that, to the best of his belief, he was bitten only once by a tsetse fly. This point is impressed on his memory, as he often remarked in jest that alcohol, if taken into the system systematically, would keep all insects away, and he would call attention to the fact that, owing to his un-failing regularity as regards his evening "peg," he had never been bitten by a tsetse fly. This period of immunity applies to the interval between April 8th and May 7th, 1920, when he was in the fly area. From the later date till about July 12th Mr. X. was not exposed to the risk of infection. He was again exposed between July 14th and 17th and bitten once, but he is convinced there was not more than one bite.

Taking this history as correct—and we have no reason whatever to doubt it—infection was caused by a single bite, and the incubation period was either approximately a fortnight or, alternatively, as long as eleven weeks.

On July 30th Mr. X. had an attack of what he believed to be malaria, which lasted till August 3rd, with a temperature of 102° to 103° F., but unaffected by quinine. Attacks of fever recurred on August 4th–5th, 10th–15th, and 24th–25th.

On August 24th his blood was examined by an Indian sub-assistant surgeon (there being no medical officer in the district), who sent the slide to headquarters, where the presence of trypanosomes was confirmed by three medical officers, including Dr. Duke, the Government Bacteriologist, who diagnosed *T. gambiense*.

Mr. X. was seen by one of us (C. H. M.) on September 24th, 1920. He was then suffering from malaise, distaste for food, vomiting, pains in the back, and a dull headache. His face was grey and drawn; his weight had decreased from his normal 13 st. odd to 11 st. 8 lb. He had no sleeplessness or sexual excitement, nor was any rash observed. He had one small gland at the base of the neck on the left side, but this was possibly septic in origin (from a carious tooth). The gland was too small to puncture, but the peripheral blood showed two or three trypanosomes in each field.

On September 24th 0.9 gram of neo-kharsivan was injected intravenously; half an hour later 20 c.cm. of blood were drawn off and allowed to stand in a sterile covered jar for twenty-four hours, by which time a solid clot had formed; 12 c.cm. clear blood serum were thus obtained.

On September 25th, after 15 c.cm. of cerebro-spinal fluid had been withdrawn by lumbar puncture, the 12 c.cm. of clear blood serum were injected into the spinal canal. From September 26th to 30th there was severe reaction with pyrexia (101° F.) and intense headache. Subsequently convalescence was rapid.

Mr. X. then proceeded to England, but on the journey was examined at Khartoum by Major W. E. Marshall, R.A.M.C. (November 2nd). No trypanosome was found microscopically in the blood, either fresh or stained; nevertheless animal inoculations yielded positive results, for Major Marshall's cable report, which awaited the patient on his arrival in England (December 12th), stated that the inoculation of 1 c.cm. citrated blood into a monkey and 1 c.cm. into each of two rats resulted in one rat showing trypanosomes in its blood on November 30th, 1920, and reinoculation from this rat into another was again positive.

In spite of this report it was decided, in consultation with Dr. W. T. Prout, Medical Adviser to the Colonial Office (December, 1920), to give Mr. X. no further treatment of any kind, as clinically he was perfectly well and his weight had increased to 13 st.

The results of subsequent microscopical examinations and subinoculations of the blood and cerebro-spinal fluid carried out in the bacteriological department of Guy's Hospital by one of us (J. W. H. E.) are recorded in the accompanying table. In view of the negative result of inoculation of Mr. X.'s blood into the monkey and the positive result obtained upon the rat by Major Marshall, it seemed fair to infer that the particular strain of trypanosome concerned was more virulent for the latter animal than the former, therefore all our inoculation experiments were performed upon small rodents.

To summarize this report the original infection must have occurred not less than thirteen months ago (at the time of writing), and the single injection of salvarsanized serum was given eleven months ago; there has been no other treatment of any kind whatsoever. Clinically Mr. X. is and has been perfectly well ever since.

The reasons that led us to employ intrathecal medication in the treatment of sleeping sickness were based upon clinical observation upon the disease which suggested the theory¹ that definite antibodies—trypanolysins—are formed during the course of treatment. This assumption might be correlated with the statement of some observers that cases of the disease undergo spontaneous cure, and of others that either the natural resistance of the native is increasing, or that the virulence of the strain of trypanosome is undergoing progressive diminution. (Our own observations do not, however, lend support to either of these views.) Dr. Vasello, of the Uganda Medical Service, further considers that the formation of trypanolysin is a natural phenomenon and is cyclic in periodicity. Data bearing on these points are being collected, but much experimental work is needed before evidence necessary to support these contentions can be presented for criticism.

We would recall that much of Ehrlich's preliminary work on chemotherapy was concerned with the employment of arsenic compounds in experimental trypanosome infections, and the first great principle aimed at throughout his search for an effective agent against protozoal diseases was the complete sterilization of the tissues by a single

Examination of Patient. Date.	Material.	Microscopical Examination.	Result.	Experimental Animals Inoculated.	Method of Inoculation.	Killed.	Post-mortem Examination.
21.12.20	Blood	(a) Fresh (b) Stained	No trypanosomes detected (?) One degenerated trypanosome in eight slides	Guinea-pig	1 c.c. intraperitoneally	17.2.21	No evidence of trypanosome infection.
20.1.21	Cerebro-spinal fluid, centrifugalized	(a) Fresh (b) Stained	No leucocytes observed No trypanosomes detected	Rat 1 Rat 2	1 c.c. intraperitoneally 1 c.c. intraperitoneally	17.2.21	No evidence of trypanosome infection.
7.4.21	Blood	(a) Fresh (b) Stained	No trypanosomes detected	Rat 3 Rat 4 Mouse 1 Mouse 2 Mouse 3 Mouse 4 Mouse 5 Mouse 6	2 c.c. intraperitoneally 1 c.c. subcutaneously 0.5 c.c. subcutaneously 0.5 c.c. subcutaneously 0.5 c.c. subcutaneously 0.5 c.c. intraperitoneally 0.5 c.c. intraperitoneally 1 c.c. intraperitoneally	29.4.21	No evidence of trypanosome infection.
2.5.21	Cerebro-spinal fluid, centrifugalized	(a) Fresh (b) Stained	No leucocytes observed No trypanosomes detected	Rat 5 Rat 6 Rat 7 Mouse 7 Mouse 8	1 c.c. subcutaneously 1 c.c. intraperitoneally 1 c.c. intraperitoneally 0.5 c.c. intraperitoneally 0.5 c.c. intraperitoneally	18.7.21	No evidence of trypanosome infection.
7.7.21	Blood	(a) Fresh (b) Stained	No trypanosomes detected	Rat 8 Rat 9	2 c.c. intraperitoneally 2 c.c. intraperitoneally	9.7.21	No evidence of trypanosome infection.

massive injection. Practical clinical experience has shown that this result is, however, very rarely achieved; and in connexion with the commonest of protozoal infections—namely, syphilis—multiple doses and alternation of drugs has now become the accepted method of treatment.

Syphilis and trypanosomiasis present many points of similarity, particularly as regards treatment when the infection has involved the central nervous system, so that we are justified in applying the accumulated experience of the past eleven years in the treatment of syphilis to the problem of the treatment of sleeping sickness.

It is now a matter of common knowledge that the arsenic introduced into the circulation by the intravenous injection of salvarsan or neo-salvarsan is at its maximum concentration during the injection, and can only be detected, as such, in the blood for a few hours afterwards, and does not appear at all in the cerebro-spinal fluid. Given an otherwise healthy patient, arsenic derived from 914 is rapidly excreted, chiefly by the intestines and kidneys, and usually at the end of forty-eight hours is no longer to be detected by chemical analysis.

It has also been shown clinically that the serum from a salvarsanized patient possesses curative effects when injected into another case of syphilis, even when the blood is collected after a lapse of time that apparently ensures its freedom from arsenic,² although Ellis and Swift make it clear that *in vitro* the spirochaeticidal activity of the serum is in direct proportion to the intensity of the Abelin reaction.³

The hypothesis to be adduced from the foregoing observations is that a phenomenon analogous to that which takes place in bacterial infection occurs in protozoal diseases also; that is to say, definitely lytic antibodies are formed in the serum in consequence of the stimulus afforded by the dead spirochaetal protoplasm—a theory originally put forward by Ehrlich himself.⁴ The acceptance of this hypothesis, together with the admitted impossibility of forcing arsenic into the spinal canal by way of the blood stream and the danger of introducing it directly into the subdural space, were probably the factors that decided Swift and Ellis⁵ to resort to intrathecal injections of so-called "salvarsanized serum" in cases of tabes and other syphilitic infections of the central nervous system. This procedure was followed in a considerable number of cases by a definite measure of success,⁶ depending, it is true, to a certain extent on the duration of the nerve lesions, although we personally have had some striking successes in distinctly late cases.

As invasion of the central nervous system is the rule in infection with the trypanosome, and as the date of this invasion in point of time from the original inoculation by the insect host is a variable and unpredictable quantity, we hold that it is essential to apply curative measures to this area, when infected, simultaneously with the attempt to sterilize the more immediately accessible tissues; and to apply identical measures with prophylactic intent, if happily infection of the central nervous system has not yet taken place, in order to prepare an antagonistic medium to await the advent of the trypanosome.

Communication of the details of this method to the Society of Tropical Medicine and Hygiene, although sympathetically received by those present, naturally evoked some criticism, and we fear that disregard of these comments may retard the progress of attempts to place the treatment of the disease on a sounder footing. The criticisms fall under two distinct headings, some being levelled against the particular case of Mr. X., others against the general principle involved. Under the first heading the suggestions made are:

1. That Mr. X. never had the disease. The positive finding of the trypanosomes on several occasions by five different observers, two of whom are expert protozoologists—namely, Dr. H. L. Duke and Major W. E. Marshall, R.A.M.C.—the successful inoculation of a rat with the trypanosome by the latter observer, and the re-inoculation of a second rat from the first, renders comment under this heading unnecessary.

2. That the trypanosome which has caused the disease in Mr. X. (and also in the native cases we have recorded) is a strain of low virulence, and the resulting infection is one which requires little or no treatment. If this suggestion is maintained there appears no reason why the trypanosomes of different districts and villages, or even

individuals, should not also be differentiated into strains of high virulence and low virulence, until in all cases that recover after treatment the infecting trypanosomes are described as practically non-virulent. In controverting this thesis we would quote one case treated as a control.⁷ This was a native who received an intravenous injection of neo-kharsivan on August 3rd, 1920, but did not have intrathecal serum; he made no improvement, and living trypanosomes were found in his cerebro-spinal fluid at the end of October, when clinically he was rapidly going downhill. Further, several natives in whom trypanosomes were found to be present died during the course of the few weeks they were waiting for treatment. Again, in untreated cases numerous deaths are reported, and the number of deaths, compared with the percentage of infected cases found on examination of large numbers of the population, affords no indication that cases of sleeping sickness recover by natural means or that the trypanosome is of low virulence.

3. That the disease was cured simply by the anti-parasitic action of the original intravenous dose of neo-kharsivan, without any trypanolysin formation. This is rendered unlikely by the fact that subinoculation was positive six weeks after the original injection of neo-kharsivan.

4. That the case is not cured and the disease is dormant. Time alone can confirm or confute this argument, but so far the clinical history is an excellent one; Mr. X., who was very ill, is in the best of health now, and so compares favourably with other cases treated by routine methods of intravenous injections only or various arsenic and antimony compounds.

5. That another case now in London treated by the intrathecal serum method has not improved. We are informed, however, that this patient had been previously treated with repeated doses of atoxyl and antimony tartrate, so that—assuming always that the technique was identical with ours—we are quite justified in suggesting that the previous drug treatment may have resulted in the formation of "fast" strains, or, alternatively, have prevented or affected the formation of trypanolysin, which may well be the curative factor.

Criticism under the second heading is more destructive and uncompromising, as it definitely states that the treatment is unsound and unjustifiable.

Clinical experience demonstrates the value of local treatment in dealing with infections of the central nervous system as conclusively as it proves the impossibility of influencing them by intravenous medication; anatomy and physiology supply the logical explanation, rendered even more obvious by a study of the morbid anatomy of trypanosomiasis cases; and we would again take the opportunity of declaring our conviction that, whilst intrathecal medication is essential in cases where the infection has reached the cerebro-spinal fluid, we are also satisfied that it should form an integral part of the routine treatment of early, and indeed of all, cases. From a recent German publication,⁸ it appears that this line of treatment was adopted in the Cameroons in the treatment of sleeping sickness, though its exponent has relied upon the effect of direct medication by arsenic compounds, injecting intrathecally 0.04 gram of neo-salvarsan mixed with salvarsanized blood serum, a procedure which we regard as inadvisable on account of its inherent dangers, a point which Reichenow himself admits.

We venture to think that the result of our serum treatment in the case of Mr. X. detailed above, supported as it is by the eight cases of natives who remain well more than eighteen months after treatment by a single dose of serum (two of these after over two and a half years) establishes a case for immediate investigation of an extended character in those countries where the disease occurs, simultaneously with careful laboratory experiment and control both at home and in Africa. If further support of our attitude is needed it is provided by the fact that among a total of nearly eighty cases that we have treated, some have died of intercurrent disease, two have disappeared, and two advanced cases did not respond to treatment, but no case to our knowledge has relapsed. The cases have been followed up and examined at regular intervals, both clinically and by microscopical methods.

Such an investigation as we have in mind involves a clinical study and experimental research by a team unhampered by any routine or official duties, but devoting all its

energies to the elucidation of this problem. Moreover, as the mentality of the native precludes the possibility of accumulating the necessary material at a permanent base, the team would be essentially a roving body, well equipped in every way and furnished with a really efficient travelling laboratory; whilst its activities, including periodical examination of treated cases and the collection of statistics, would extend over a period of about three years.

The personnel would include probably two clinicians and two or three trained protozoologists, assisted by an adequate staff of assistants, and also one or more veterinary surgeons—since it is obvious that, if the method we have put forward fulfils our anticipations, it opens up the possibility that the treatment of the future will resolve itself into the simultaneous intravenous administration of arsenical compounds and the intrathecal injection of salvarsanized serum derived from the horse, ox, or other large animal already experimentally infected and treated.

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GLYCOSURIA OF MALARIAL ORIGIN.

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MALARIA may simulate very many internal diseases, but we are not aware of cases of malarial glycosuria and malarial diabetes having been placed on record; the following two cases may therefore be of some interest.

CASE I.

J. F. S., a demobilized soldier aged 32, was admitted to the Tropical Section of Orpington Hospital on April 13th, 1921, as a case of malaria. He had his first attack in August, 1916, when malignant tertian parasites were found; since then he had had numerous relapses. On admission the temperature was 98.8°, and the pulse 120; the patient was pale and tremulous; he stated that he had lost flesh and complained of great weakness. Physical examination of the chest revealed nothing worthy of note. The spleen was not palpable. No malarial parasites were present in the blood. Differential count: Polymorphonuclears 63, large mononuclears 9, lymphocytes 33, eosinophiles 1. In the faeces no cysts were found. The chemical analysis, kindly carried out by Dr. Lynch at the Central Chemical Laboratory, Ministry of Pensions, Chelsea, gave the following results:

Total solids, 22.1 per cent.				
Fat	...	...	...	8.6 per cent.
Fatty acid	...	...	...	2.8 "
Soaps (as fatty acid)	...	...	...	2.8 "
Total	...	...	...	14.2 per cent.

The urine, specific gravity 1031, was slightly acid, the amount passed during twenty-four hours was only very slightly increased. It contained sugar 8.5 grams per litre, but no albumin. Acetone and diacetic acid were absent.

On April 14th the patient was placed on a fairly intensive quinine treatment (10 grains three times daily). The sugar present in the urine decreased rapidly after twelve days' treatment, but there was still a quantity sufficient to reduce Fehling's solution and to give phenyl-glucosazone crystals, though not enough to estimate. The patient was then given, in addition, a course of six injections of quinine hydrochloride intramuscularly of 15 grains each. On May 10th the quinine hydrochloride injections were discontinued, and quinidine was given in their place (30 grains daily).

The urine was examined again on May 13th, 16th, 17th, and 18th, and did not give any reduction of Fehling's solution, nor did it give phenyl-glucosazone crystals.

At no time was the patient put on antidiabetic diet, and there was no restriction of his carbohydrate intake. There can be little doubt, therefore, that the disappearance of the sugar was due to the administration of quinine.

When the patient was admitted to hospital he was feeling very weak, and complained of having lost a great deal of flesh. There was, however, no polyuria, no boulimia, no thirst. On

May 20th, 1921, the general appearance of the patient had much improved, and he expressed himself as feeling better than he had done for years.

CASE II.

Mr. E. N., aged 44, married, with no family history of diabetes, consulted one of us in March this year. During the war he served in one of the allied armies, and in 1916 he contracted, while in the Balkans, a severe malarial infection; he had several relapses, the last being on December 19th, 1920. In January, 1921, he noticed that he was feeling more hungry and thirsty than usual, was passing much more urine than normal, and was losing flesh. He consulted a medical man, who found a fairly large amount of glucose in the urine (2 per cent.), and placed him on a very strict diet, which induced only a slight decrease in the amount of sugar present in the urine. When the patient consulted one of us in February the urine contained 1.5 per cent. of glucose; it was acid, specific gravity 1032, no albumin, and acetone and diacetic acid were absent. The amount of urine passed during the twenty-four hours averaged 6 pints.

The patient looked rather emaciated and very anaemic; the skin was of a pale, earthy colour, with patches of hyperpigmentation resembling chloasma, so often seen in cases of chronic malaria. His spleen was very slightly palpable and very hard. The examination of the blood did not show any malarial parasites, but there could not be any doubt clinically that he had chronic malaria, and the diagnosis was made of "diabetes in a malarial subject." He was advised to continue the strict diet he had been having for the glycosuria, and in addition to take 10 grains of quinine three times daily for his malaria. He came back three weeks later feeling much better; the enlargement of the spleen had disappeared, and—a most interesting feature—the amount of sugar had decreased enormously, being less than 0.1 per cent. We came to the conclusion that it might be a diabetes syndrome of malarial origin, and suggested to the patient that he should go back to ordinary diet but continue the quinine. He came to see us regularly once a week and the sugar did not increase; only a trace was present. During March the patient went to the South of Europe on business, and during all the time he was away (four weeks) did not take any quinine. He came back to this country in April, and three days after arrival, after playing golf in the rain, had a shivering fit, followed by very high fever, which ended in profuse sweating. The spleen again became palpable and hard, and examination of the blood showed the presence of a few rings of malignant tertian. The urine was examined after the temperature had come down to normal; it contained 1.2 per cent. of sugar. The patient was placed on an intensive quinine treatment by the mouth and intramuscular injections for six weeks without any dieting; not only did the symptoms of the chronic malarial infection disappear, but the urine became completely free from glucose, when examined by the usual methods of analysis (Fehling's, Nylander, phenyl-hydrazine, fermentation test).

CONCLUSION.

Our observations tend to show that there is a form of glycosuria of malarial origin, and that this condition may at times (Case No. 2) become so severe as to simulate true diabetes, the patient losing flesh, becoming very weak, complaining of thirst and hunger, and passing a large amount of saccharine urine. The glycosuria in our two cases was cured by the administration of quinine in full doses without any dietetic treatment.

SLOUGHING OF THE LOWER UTERINE
SEGMENT FOLLOWING PLACENTA PRAEVIA:
LAPAROTOMY: RECOVERY.

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A MARRIED woman, aged 27, was admitted to Addenbrooke's Hospital on January 22nd, 1921. She had been delivered, on January 1st, of her second living child, but not without complications. Twenty-four hours previous to delivery she had a sudden severe haemorrhage and had called in her doctor, who, although he was unable definitely to diagnose placenta praevia, had strongly suspected it. He immediately ordered her to bed with instructions to remain there. She failed to carry out these orders, but remained up and did her work for the twenty-four hours previous to the birth of the child, suffering from no further haemorrhage. The delivery of the child was uncomplicated and occurred rapidly after two or three pains and before the arrival of her doctor. The placenta however was retained, and was removed digitally and without anaesthesia one hour later. It was found to be very adherent to the uterine wall.