Remarks

ON

A CASE OF TRYPANOSOMIASIS.

BY

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PROFESSORS BOYCE, ROSS, AND SHERRINGTON have described so recently and so fully the history of the discovery of trypanosomes in man that it is unnecessary to revert to this aspect of the subject of this communication. Suffice it to say, that having had the privilege last August of a demonstration by Dr. Dutton of Mr. Forde's patient,¹ we were led from the clinical features of the case we are about to describe to a provisional diagnosis of trypanosomiasis. The patient was sent to one of us on October 3rd, 1902, by Dr. Habershon for an opinion, Dr. Habershon having been struck by its anomalous characters—so unlike in many respects those of malarial cachexia, the disease for which she had been and was being treated. Subsequently the patient entered the wards connected with the London School of Tropical Medicine at the Seamen's Hospital, Royal Albert Docks, where she became the subject of close and prolonged observation, extending over a period of five months. At first the blood examinations, made with a view of establishing our diagnosis of trypanosomiasis, were negative, but knowing how scarce the parasites sometimes are in this class of disease arrangements were made to test our suspicions by means of injections of the blood into certain of the lower animals. Meanwhile, as the leucocyte count was peculiar, microscopic examination of the blood was persevered in, with the result that trypanosomes were found in it on October 27th and many times subsequently.

History.—Mrs. S., married, aged 40, with a good personal and family medical history, went to the Congo Free State in July, 1900. She resided at Monsembe, a mission station on the Upper Congo, for fifteen months, from August, 1900, to November, 1901. She had one short attack of malarial fever in November, 1900; a second, lasting only a few hours, about four months later; and a third, lasting for a few days, in June, 1901. These attacks promptly yielded to moderate doses of quinine. Her present illness may be said to date from the end of August, 1901. About a fortnight before its commencement—that is, about August 14th, she was bitten on the left leg by some insect or other animal. The bitten part became red, swollen, and very painful, so much so that suppuration was apprehended: under treatment, however, the inflammation subsided in a few days. She states that the bite may have been inflicted by a species of fly about which her husband writes: "The only biting insect I have noticed the natives making a fuss about are what we call 'the blood-sucking flies.' We almost never see them on shore, but are pestered with them so soon as ever we get into a boat or canoe, especially if it has a

shelter or awning." On August 28th she commenced to have fever. It set in suddenly like a malarial attack, but without rigor. The associated general aching, and especially the vertical pain and sense of fullness in the head were more intense than in the malarial attacks previously experienced. In addition, she had severe abdominal pains, possibly corrected with her period which occurred about this time. The temperature during the first eight days did not exceed 102° F.; it was usually a little lower, but not normal, in the morning. Quinine up to 40 gr. was given daily. On the eighth day the temperature fell to normal and remained so for thirty-six hours. She got up, but on the afternoon of the ninth day she felt chilly, and the fever returned accompanied with much vomiting. This attack proved more severe than the first, so much so that hyperpyrexia threatening, the large doses of quinine—up to 90 gr. a day—which she had been taking were abandoned and she was treated with cold baths. About the eighth day of the relapse the temperature began to fall, and on the tenth day was again normal. Unfortunately no accurate record of the temperature during the initial fever was preserved, but Chart 1 is a faithful record of the temperatures during this, the second, attack. There was now an apyretic spell of about ten days, which was succeeded once more by a febrile recurrence of about fourteen days' duration. This was milder in character than the two previous attacks, the thermometer rising only to 100° F. or 101° F. Her health not improving she left the Congo on November 21st. On the voyage home she had fever about once a week, the temperature sometimes rising to 103° F. On what were assumed to be apyretic days her temperature was not taken. During the passage she had 10 gr. of quinine daily, a larger dose being administered when fever was pronounced. The attacks at this time were preceded by rigor and followed by profuse diaphoresis. Mrs. S. arrived in England on December 11th, 1901. She kept well for the first week and was able to get about a little, but ever since that time she has suffered from irregular pyrexia of an intermittent, undulant type. Possibly she had feverless weeks, but this cannot be asserted with confidence as her temperatures were not taken regularly. In May, 1902, she had an attack of phlebitis in the left leg, which became swollen as high up as the knee. Swelling partly subsided in a week, but pain persisted for three months, and both legs gradually became more or less persistently swollen.

Condition on Admission.—She is a fair-skinned woman, having a somewhat plump and fictitiously healthy appearance, the result of a patchy erythematous flushing and oedematous fullness of the face and body generally. Her pulse is quick (108) and feeble. Her tongue has a rough and raw appearance, which, she states, is associated with a feeling of soreness and dryness. Her appetite is capricious; her bowels are confined, and she frequently suffers from vertical headache, though less so than formerly. The spleen is very much enlarged, extending to the umbilicus and crest of the left ileum. The area of liver dullness is probably somewhat larger than normal. Ophthalmoscopic examination reveals a peculiar condition of the choroid, to be presently described. The temperature on admission was 102.8° F. during the following night she had profuse sweating, and next morning the temperature had fallen to 96.6° F. There is marked muscular feebleness and a tendency to palpitation on exertion. Lungs, heart, and urine appear to be normal.

Progress.—During her stay in hospital she seemed at times to be gaining ground; at other times her condition was almost critical, owing to the general weakness and prostration accompanied by palpitation and nervous depression, especially so during and after an attack of mild diarrhoea at the end of November and beginning of December. About this time she suffered much from pain in the left thumb, accompanied by

Chart i.

slight swelling of the part and a tenderness of the upper and outer surface of the corresponding forearm, with slight local discoloration as if from a slight bruise. The pain in the thumb continued for weeks. Part of January and February, 1903, she spent at Eastbourne with benefit to her general health. She returned to hospital on February 24th, and left again for her home in Bristol on March 27th, much in the same condition as when admitted in the preceding October. During the second stay in hospital she had another and more alarming attack of depression, apparently supervening on the course of injections of horse serum, as will be detailed later on. When she left her spleen was much smaller than when admitted, but fever, sweats, palpitation, rapid pulse, and prostration, as well as the skin symptoms and the presence of the parasite in the blood, were practically unaltered.

She was seen again by one of us on May 5th, when the following note was made: Her general condition is much improved. There is now no flushing or puffiness of the face, but there is still distinct patchy erythema of the trunk with slight oedema; there is no oedema of the feet and legs. She walks about freely, but is short of breath on going upstairs or on unusual exertion. If she fatigues herself the evening temperature may rise to 101° F., but there are now no night sweats. The spleen is smaller and softer. In the course of a short microscopic examination of the blood several trypanosomes were discovered. Slides of blood taken from time to time since she left hospital sometimes contained trypanosomes, sometimes they did not. Her left arm and thumb are no longer painful, but they are weak, somewhat smaller than the other side, cold, and blue; the radial pulsation is easily made out.

Details of Special Symptoms.

Temperature.—This as a rule, while in hospital, ranged from about 97° F. in the morning to 100° F. in the evening. It was never absolutely normal for 24 hours on end. Occasionally for a few days it would rise to 101° F. or 102° F. in the evening; these rises were generally succeeded by profuse night sweats and a fall to 96° F. or 96.5° F. the following morning. Only once was there anything like smart fever— 103° F.; this was associated with the horse serum injections alluded to.

The pulse was always rapid and feeble. During exacerbations of temperature it mounted to 140 or even 150, and then palpitation and sometimes headache were complained of.

The erythema, which was so remarkable a feature in the case, was first observed during the primary fever on the Congo. At that time she suffered much from prickly heat; it is therefore possible that the erythema may have been present though unobserved before the onset of the severe symptoms. The skin of the limbs, trunk, and face were all involved, more especially the back of the trunk and the face. The eruption was said to have been more marked during the initial pyrexial period than subsequently. While she was in hospital it showed itself on many occasions only as an obscure patchy mottling; at other times the cutaneous congestion was very pronounced. The individual patches, which were of a very evanescent character, varied in size and form from an inch to many inches across, from distinct rings, or segments of rings, to ill-defined irregular blotches shading insensibly into healthy-looking skin. One or both sides of the face and forehead often presented a flushed appearance as if from wine. There was no pruritus or urticaria.

The Oedema.—This, like the erythema, was most pronounced on the back and face; especially, in the case of the former, towards the flanks and sacral region. The legs were also distinctly implicated, the arms less so. The oedema evidently involved the cutis as well as the subcutaneous tissue, for by pressing firmly with the finger a distinct imprint of the papillary ridges of the finger-pad, as if impressed on a piece of putty, would persist for some time. Although distinct enough, the oedema was nowhere, nor at any time, very great—it was just sufficient to give the appearance of comfortable *embonpoint*. Like the erythema, it fluctuated in degree from time to time, and had perhaps a similar tendency to patchiness in its distribution.

The Spleen.—We were informed that there was no manifest splenic enlargement after the three malarial attacks occurring during the earlier part of the patient's stay on the Congo; but when she arrived in England, in December, 1901, the enlargement was very marked. On admission the organ extended forwards to the umbilicus and downwards to the crest of the left ileum. Subsequently, whether as the result of treatment or spontaneously, it diminished considerably, so that when she was discharged from hospital the edge had retreated about a handbreadth from the umbilicus. There was never any complaint of pain in the splenic region.

Eyes.—We are indebted to Mr. Treacher Collins for the following note on the condition of the patient's eyes on October 31st, 1902:

Vision: R, $\frac{3}{6}$, partly Jaeger 1; L, $\frac{3}{6}$, Jaeger 1.

Field, tested with hand, normal. Colour vision normal. Pupils active & light and accommodation. Media clear.

Ophthalmoscopic appearances: In the macular region of each eye there is an area of superficial choroidal atrophy with some pigmentary disturbance. In the right eye this area is irregularly star-shaped. In the left eye the pigment disturbance is more marked and forms denser spots than in the right.

Outside the patch of atrophy in the macular region in the right are some small, regularly circular, discrete, whitish dots, situated at a deeper level than the retinal vessels.

In the periphery of the fundus in each eye there are several disseminated small patches of a light colour, apparently due to choroidal atrophy. Some of these are without any, and some have a slight amount of pigmentary disturbance about them.

The optic disc and retinal vessels are normal; there are no hæmorrhages to be seen.

The Parasite (Fig. 1).—For observations on the parasite, as

Fig. 1.

well as for long series of blood counts, we are indebted to Dr. Duncan Whyte and Dr. George Low, both of whom devoted much time and conscientious work to the elucidation of these features of the case.

Frequent examinations of the blood were made during the first three days following admission, but, as already mentioned, no trypanosomes were found till October 27th. They must have been present, however, before this date, for when the films prepared by Dr. Duncan Whyte during this period were subsequently re-examined, parasites—though few in number—were found in them. From the date mentioned trypanosomes were almost always found on prolonged examination, and on some days fairly readily.

Fig. 2.

The number of trypanosomes present at any time was so small that an estimate based on a count of them in a measured volume of blood was considered unreliable. Accordingly, the number met with in the course of counting 500 leucocytes was taken as a basis for a rough estimate. But as the thin films employed gave only one leucocyte to 800 to 1,500 red blood corpuscles, whereas from estimates made in the usual way it was ascertained that the true proportion of white to red blood corpuscles was 1 to 560, it follows that the actual proportion of parasites to leucocytes, and therefore their number per c.mm. of blood was considerably different from that indicated by the findings in the films.

The accompanying chart (2) prepared by Dr. Whyte gives some idea of the number of trypanosomes per slide and their variations in this respect from time to time. It was noted

Chart 2.—Showing fluctuation in the numbers of trypanosomes to 500 leucocytes.

that there was no manifest alteration in the condition of the patient corresponding to the fluctuations in the numbers of the parasites present in finger blood.

As regards structure and habits Dr. Dutton's description of the trypanosomes in Mr. Forde's case applies to the parasites found in our patient. Dr. Whyte measured twelve examples (fixed and stained); the longest was 22 microns, the shortest 15 microns; average length 18 microns. Only two dividing forms were found; these occurred two days before a sudden and very marked increase of the number of parasites in the blood. One parasite (Fig. 2) furnished with two flagella at one end was found by Dr. Whyte; in other respects this example appears, judging from the stained preparation, to be normal and shows no indication, such as division of nucleus or of centrosome, of being in process of fission.

The Blood.—The red corpuscles were diminished in number but, except for a short time during treatment with horse serum, not to any very great extent. The highest count was 3,880,000. With the exception mentioned, the lowest count was 2,825,000. The haemoglobin was reduced in about the same proportion as the red corpuscles—36 per cent. was the lowest estimate. The red corpuscles were fairly uniform in size; there was no poikilocytosis. Including all the blood examinations only four nucleated red cells were found.

The leucocytes were slightly below the normal number in most counts. The lowest count was 4,200, the highest 8,600; the average of the counts made by Dr. Whyte and one of us was 6,520. The differential leucocyte count showed excess of the mononuclear elements, the excess being due to a marked increase of the large mononuclear cells, not of the lymphocytes. The polymorphonuclear and eosinophile leucocytes were fewer than normal.

	Dr. Duncan Whyte.* 20,000 Cells Counted.	Dr. Daniels.* 6,620 Cells Counted.	Dr. Low.†
Polymorphonuclears ...	51.5	55.2	53.7
Large mononuclears ...	29.75	22.7	19.65
Lymphocytes ...	16.0	18.4	24.0
Eosinophiles ...	1.0	1.8	2.5
Mast cells... ..	0.25	0.48	0.15
Abnormal mononuclears	1.5	1.3	—

* November to December, 1902. † February to March, 1903.

These figures show a marked increase in the large mononuclear elements and a diminution in the polymorphonuclears and eosinophiles, even without allowing for the circumstance that most of the counts showed a diminution in the total number of leucocytes. The lymphocytes were not affected beyond the normal range of variation, and there was a diurnal variation as usual. The large mononuclear elements were increased so as to be in two or three times their normal proportion. Mast cells were in larger numbers than are found in normal blood. The abnormal cells mentioned were mononuclear. They varied in size, had large round nuclei and protoplasm which stained deeply with Leishman's stain. They were quite different in appearance from either the lymphocytes or the large mononuclear leucocytes. It may be remarked that this type of cell is not peculiar to this disease; they are found in small numbers in spleno-

medullary leucocythaemia, and occasionally in other morbid conditions. The differences in the various counts were not greater than is usual in counts of blood taken at different times and made by different observers.

Inoculation Experiments.—Professor Hewlett carried out a series of experiments with the view of infecting with the trypanosome certain of the lower animals. The blood used was taken from the patient at such times as the parasites were specially numerous. It was immediately diluted with 8 per cent. of a 5 per cent. solution of sodium citrate, and injected as soon as circumstances would permit. Although in the blood so diluted the parasites were hard to find, yet when found, and though kept under observation for periods ranging from two to five hours, their movements continued to be quite active; the citration of the blood, therefore, so far as could be observed, impaired in no way their vitality. The animals injected were as follows: 4 rats, 2 mice, 2 guinea-pigs, 1 rabbit, 1 dog (two inoculations), 2 monkeys, 1 pony, 1 pig. Although these animals were kept under observation for a considerable time—some of them for several months—after inoculation, none of them showed any evidence, either clinical or microscopical, that the inoculation had succeeded. We are therefore justified in concluding that this trypanosoma of man is specifically distinct from those of the rat, of surra, of nagana, of *mal de caderas*, and of dourine.

Treatment.—While in hospital the patient was kept in bed in a warm room and fed well. Arsenic in the form either of arrhenal, sodium cacodylate or arsenate of iron was administered hypodermically. Notwithstanding that the drug was pushed to what appeared to be the limit of prudence it did not seem to have any influence on the parasite or on the disease. Methylene blue was also given with a like result. The visit to Eastbourne, the methylene blue and the cacodylate injections being continued, appeared to benefit the general health.

Laveran² injected human blood serum into mice infected with the trypanosoma of nagana with the result that a proportion of the mice so treated recovered from what is almost invariably in them a fatal disease. Laveran reasoned that as man is immune as regards nagana the immunity may be owing to some property of his blood serum, and that if infected mice be treated with this the trypanosoma concerned may be killed. The experiments referred to seemed, in a measure, to bear out this idea. Accordingly, considering the apparent gravity of the case and the futility of the other means already tried, we felt ourselves justified in attempting treatment on similar lines in our patient. Having ascertained that the human trypanosoma could not live in the horse, we selected this animal as a source of serum supply. The table on p. 1253 embodies our results. It may be stated in explanation of the table that prior to the commencement of the serum injections, temperature ranged from normal in the morning to 101° in the evening. On February 25th, 26th, and 27th 10 c.cm. of horse serum were injected into the flank daily; on the 28th the dose was increased to 15 c.cm., and from March 1st to 5th to 20 c.cm. On the 25th the patient became so depressed, her temperature so high, and her pulse so rapid, and at the same time the haemolytic action of the serum so pronounced, the blood count having dropped by one-third within a week, that it was deemed prudent to suspend the treatment. The parasites did not seem to be affected by the serum. On stopping the injections the general condition improved so rapidly and the

Table of Temperature and Blood Observations during period of Horse-serum Injections.

Date.	Time.	Temperature.	Pulse.	Amount of Horse Serum Injected in c.cm.	Red Blood Corpuscles.	Leucocytes.	Hæmoglobin per cent.
February 24th	M. E.	101.0					
" 25th	M. E.	98.6		10			
" 26th	M. E.	101.0		10			
" 27th	M. E.	98.8					
" 28th	M. E.	101.0		10	3,280,000	2,540	40
" 29th	M. E.	98.0					
" 30th	M. E.	101.6		15			
March 1st	M. E.	99.0		20			
" 2nd	M. E.	101.6					
" 3rd	M. E.	98.0		20	2,330,000	2,500	38
" 4th	M. E.	100.0					
" 5th	M. E.	99.6	88	20	2,370,000	1,800	38
" 6th	M. E.	101.6	100				
" 7th	M. E.	99.6	140	20	2,400,000	6,800	40
" 8th	M. E.	102.4	116				
" 9th	M. E.	101.4	120	20	2,146,000	3,100	36
" 10th	M. E.	103.4	128				
" 11th	M. E.	102.0	120		1,970,000	6,500	36
" 12th	M. E.	101.6	128				
" 13th	M. E.	99.2	116		2,600,000	7,800	42
" 14th	M. E.	102.0	120				
" 15th	M. E.	99.0	98		3,000,000	6,000	43
" 16th	M. E.	103.0	128				
" 17th	M. E.	101.2	110		2,800,000	5,000	45
" 18th	M. E.	101.0	120				
" 19th	M. E.	100.4	110	30	2,920,000	4,000	42
" 20th	M. E.	103.6	120				
" 21st	M. E.	102.0	120	30	2,760,000	3,500	42
" 22nd	M. E.	102.6	130				
" 23rd	M. E.	101.8	128		2,380,000		
" 24th	M. E.	101.8	147				
" 25th	M. E.	99.8	130		2,990,000	11,800	40
" 26th	M. E.	99.6	120				
" 27th	M. E.	97.0	100		2,895,000	4,200	42
" 28th	M. E.	99.4	124				
" 29th	M. E.	97.0	90		3,220,000	6,500	45
" 30th	M. E.	99.6	120				
" 31st	M. E.	98.0	100		3,500,000	1,500	47
" 1st	M. E.	99.6	112				

blood regeneration was so marked, the count having risen within a few days from two to three millions, that it was deemed safe to resume the injections, and in larger doses of 30 c.cm. Two such injections were given, one on March 10th and the other on the 11th. At once the blood count began to drop, the patient to become depressed, and on the night of the 11th, about 11 p.m., alarming symptoms suddenly developed, namely, choreic movements in the legs extending to the hands, arms, and trunk, together with high fever and rapid feeble pulse. At 10.45 a.m. on the 12th severe convulsive movements of the muscles of the trunk set in, and the patient became dull and apathetic; at the same time the erythematous condition of the skin became more pronounced and more dusky. The temperature was reduced by sponging, and by the 13th had fallen to subnormal in the morning, the general condition also undergoing marked improvement, and the blood count, which had again become seriously reduced, rising once more to 3,000,000. Although there had been some reduction in the number of trypanosomes in the finger blood it was not considered to be safe to resume the injections. When discharged on March 27th the patient had quite recovered from what, had it been pushed much further, might have proved a disastrous line of treatment.

REFERENCES.

¹ BRITISH MEDICAL JOURNAL, 1902, vol. II, p. 881. ² Annales de l'Institut Pasteur, November, 1902.

PURE DRUGS.—A Bill has, according to *American Medicine*, been introduced into the New York Legislature to prohibit the sale of defective, stale, or otherwise deficient drugs, and to punish persons who make substitution of another drug for the one called for by a customer. The Bill provides that drugs likely to deteriorate in time must be marked with the date of manufacture, and with a statement showing the quality, strength, and genuineness of the drug. A time limit must also be fixed after which the drug will be unfit for use. The Bill was introduced at the instance of the Medico-legal Society of New York.

ON THE POSSIBILITY OF THE OCCURRENCE OF TRYPANOSOMIASIS IN INDIA.

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THE recent discovery of trypanosomiasis in man by Dr. Dutton and Dr. Forde,¹ and the report of further cases by Dr. Manson,² naturally lead one to question the possibility of the occurrence of this disease in other parts of the world than those originally reported—viz., the Congo and the Gambia. In the following remarks I hope to show that there is at least some ground for the belief that it may occur in India, and that a species of trypanosoma may be the cause of one of the indefinite varieties of fever occurring in that country, in which the presence of malaria parasites in the blood is not determined or is, at least, only incidentally noted.

The case upon which this theory is based belonged to such a class, whose general features I shall briefly describe before going into details with regard to the individual patient. For want of a better name I may speak of them as cases of "Dum-dum fever," because, as far as my experience goes, the patients usually came either from this cantonment or its immediate neighbourhood. This station of Dum-dum lies about seven miles from Calcutta and is notoriously unhealthy, malarial fevers of all types, dysentery, and enteric being rife. It is excessively damp, and, in the rains, is practically a morass from the fact of its lying so low; it is said to be even a few feet below the level of the Hoogley, which flows within a mile or two of the cantonments. I had a short personal acquaintance with this station in 1890, but the present remarks refer to the features of this form of Indian fever as presented by soldiers invalided on account of it from Dum-dum to the Royal Victoria Hospital, Netley, during the past three or four years. The cases were, as a rule, regarded as having been malarial in origin, and presented, on admission to Netley, an extreme degree of cachexia; it was, in fact, the severity of this cachectic condition and the frequency of its association with Dum-dum—and, more rarely, its immediate neighbours, Calcutta and Barrackpore—which gave rise to the idea that we were dealing with a specific type of fever, whose cause was unknown. Clinically, these cases presented no very definite features distinguishing them from other and commoner forms of tropical cachexia, the chief symptoms being an irregularly remittent type of fever, grave anaemia, progressive muscular atrophy, and great enlargement of the spleen. Digestive and bowel derangements were frequent, the latter often a legacy of previous dysentery. In none of these Netley cases were malaria parasites found in the blood, nor were there any records of their having been found at an earlier stage of the disease.

The difference, then, between these cases of Dum-dum fever and other cases of tropical cachexia, associated with a low form of fever, was chiefly one of degree, and this was so marked that one of the first questions one asked a patient suffering from a particularly severe form of cachexia was as to whether he had served recently at Dum-dum. Time after time the reply was either that he had been invalided directly from this station, or that he had quite recently served there. It was at the necropsy of one of these cases of Dum-dum fever that the appearances described below were noted in the spleen, which I now think to have been due to trypanosoma infection.

Private J. B., 2nd Royal Irish Rifles, aged 23, who had been invalided from Dum-dum for dysentery, was admitted to Netley in April, 1900, and died there seven months afterwards. He had not served in any other tropical country. During these seven months he presented in an extreme degree all the general features of the class of cases I have just described, and, in addition, suffered from chronic dysentery for some time after his admission, though this had improved considerably before his death. I examined his blood on many occasions, but never detected any signs of malaria. His temperature was seldom normal, but his chart showed no regular features. At the necropsy, made 38 hours after death, beyond the intense emaciation, the only gross lesions found were in the large intestine and the spleen. The walls of the colon were deeply pigmented and greatly thickened, and were covered with the cicatrices of old dysenteric ulcers; a few unhealed ulcers were found in the neighbourhood of the sigmoid flexure. The spleen was greatly enlarged, weighing 2 lb. 7 oz., and was much congested, the spleen pulp was extremely soft and friable, the organ was sterile on cultivation. 100 oz. of clear serum were removed from the peritoneal cavity.

On making smear preparations from the spleen pulp, I was struck by the curious appearance, among the spleen cells and