Remarks ON TRYPANOSOME DISEASES.

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[TRANSLATION.]

A NEW department for the investigation of infectious diseases has of late been opened up by bacteriology, that, namely, relating to pathological protozoa. At first small and insignificant, it became in a short time of great importance, and appears to be still increasing.

HISTORY.

The first discovery in this new sphere was that of the malaria parasites, which we owe to Laveran. This was completed and extended by the discoveries of R. Ross, who pursued the intricate course of development of malaria parasites in the body of mosquitos, and proved that malarial infection did not originate in decomposed organic matter nor in marshes, but is transmitted by infected mosquitos to healthy human beings.

The etiology of Texas fever was then discovered by Th. Smith. This also was shown to be due to a protozoon, which, like the malaria parasite, entered the red blood corpuscles, and was transmitted by a blood-sucking insect, the wood-tick.

The third important discovery was by Bruce, who found the trypanosome of tsetse-fly disease in the blood, and showed that a stinging fly, belonging to the genus *Glossina* was the agent in transmitting this disease. In addition to these discoveries there have been numerous others of protozoal diseases in animals, but especially in man. Among these latter may be mentioned: trypanosomiasis and sleeping sickness in Africa; the spotted fever in North America; tropical splenomegaly, in which protozoa have been proved to exist by Leishman, Donovan, and Marchand, and the Oriental boil (called also Delhi, Aleppo, or Biskra boil), the parasites of which were discovered by Wright.

Scientifically and economically the protozoal diseases have nowadays acquired such importance that the practising physician must take notice of them. I have been asked by the directors of the Berlin Medical Society to tell you of my observations and experiences in Africa, to interest you in them, and to choose a subject from the region of pathological protozoa, and so I will give you some information about one of the most interesting groups—the trypanosomes.

"GENERAL MORPHOLOGY AND SYMPTOMS."

Before passing, however, to the principal subject of my discourse, it seems to me important for your enlightenment to give you a short description of the trypanosoma and trypanosome diseases which will come under your notice.

Trypanosomes belong to the flagellata, the ciliated protozoa. If blood containing trypanosomes be examined microscopically in a fresh state it is easy, under a moderate power, to recognize the relatively large and actively moving parasites. Their form, however, can only be distinguished when they are at rest. They then resemble a fish, are twice or three times as long as a red blood corpuscle, have a long flagella, and on one side an undulating membrane.

The finer structure can be made most distinctly visible by Romanowsky's stain (Giemsa's modification). There is then seen a rather large red-stained nucleus, a granule stained very deeply red close to the hinder end, which looks like a centrosome, and, issuing from the latter, a red line extending to the edge of the undulating membrane which passes into the flagella, which is likewise stained red. The body of the trypanosome is shown by the blue staining of the plasma. Trypanosomes do not form pigments as do malaria parasites, from which we may conclude that they do not derive nutriment from the haemoglobin, but from the constituents of the blood plasma. They increase by longitudinal fission. All trypanosome diseases have this in common that, like malarial diseases, they may run a rather acute course, but as a rule drag on for a long time, often for years. In their symptoms, too, they often resemble malaria. They give rise to irregular fever, often interrupted by longer or shorter intermissions, to anaemia, emaciation, weakness, localized oedema, and swelling of the lymphatic glands and spleen.

TSETSE-FLY DISEASE.

The best known and at the same time most important of the trypanosome diseases is the tsetse-fly disease. It was first observed in South Africa, in the valleys of the Limpopo and the Zambesi, where Livingstone became acquainted with it and gave a good description of it. Later it was discovered to be widely spread over the African continent. It was identified on the east coast from Natal to Somaliland, on the west coast as far up as Senegambia, in the German territories of Togo and Kamerun, in the Congo basin, on Lake Chad, and as far as Southern Algeria. The slight variations from the general type of the disease which have been described here and there are to be attributed to differences in the methods of observation of the several observers.

The trypanosomes of the tsetse-fly disease—discovered by Bruce in 1895 and called *trypanosoma brucei*—are distinguished morphologically by the fact that their hinder end—the trypanosoma swims with the flagella end first, which therefore appears to be the front—is blunt, and the centrosoma is situated quite near the end. They are more or less pathogenic for all domestic animals, especially for horses, mules, and dogs, less for cattle, and still less for donkeys; sheep and goats are most capable of resistance. Animals, such as mice, rats, and rabbits, experimented on in laboratories, are very susceptible. Men are very insusceptible to tsetse-fly disease.

The tsetse trypanosomes may be carried, as Bruce has shown, by *Glossina morsitans*: this is a stinging fly, not much larger than our house-fly. Bruce thinks that the infection passes immediately through the proboscis of the fly, which is something like a vaccinating needle, and this presents no difficulty if the blood be rich in trypanosome. Bruce himself found—and later on we will see other examples of the same—that in South Africa the big game (big antelopes and buffaloes), the usual source of tsetse infection, have only a very small proportion of tsetse parasites in the blood. Under these circumstances, I may assume that, to make infection possible, the trypanosomes increase in the *Glossina* or undergo some

* In dogs and donkeys race seems to make a difference. In South Africa there is an indigenous breed of dogs, I am told on reliable authority, which is immune from tsetse. In the case of donkeys I have found that Massai donkeys get over inoculation with virulent trypanosomes without becoming ill. Some have doubted this; I therefore give here some instances from the accounts of African travellers who have had similar experiences. The accounts are from the work of Austen, *A Monograph of the Tsetse Flies*.

David Livingstone: "The bite of this insect does not affect the donkey as it does cattle." "The mule, ass, and goat enjoy the same immunity from the tsetse as man and the game."

David and Charles Livingstone: "This fly invariably kills all domestic animals except goats and donkeys; man and the wild animals escape. We ourselves were severely bitten on this pass, and so were our donkeys, but neither suffered from any after-effects."

James Chapman: "The bite of this insect is fatal to cattle, horses, sheep, and dogs; but there is a peculiar breed of the latter, known as Makoba dogs, which are exempt from the effects of its poison, the breed having from time immemorial been reared in the 'fly' country."

Dr. B. F. Bradshaw: "All domestic animals perish if bitten, sooner or later, with the exception of the goat; the donkey seems to resist it longest."

F. J. Jackson: "This fly is perfectly harmless to human beings, but its effect on domestic animals is of the most disastrous nature; in fact, as far as my knowledge goes, all domestic animals, with the exception of goats, and perhaps of the grey donkey, when struck by this fly, are bound, sooner or later, to die."

F. C. Selous: "The donkey resists the poison (of the tsetse fly) far better than any other domestic animal, and will pass through belts of 'fly' country without taking much harm, his constitution being so strong that he will recover from the effects of the poison if not kept too long in the infected district, whereas an ox or a horse, if once impregnated, will almost to a certainty pine away and die."

Commissioner Johnston: "The southern shore of Lake Tanganyika is infested with the fly, which kills, even dogs, goats, and donkeys, the two latter beasts generally escaping."

W. Cotton Osell: "Wild animals are not affected, but all domestic ones are, save the ass and the goat."

Sir H. H. Johnston: "Donkeys are far less subject to the poisonous character of its bite than horses and mules; indeed, it is said that the domestic donkey of East Africa, which is only one degree removed from the Abyssinian wild ass, is impervious to its attacks, and certainly none of those animals have died from tsetse bite in British Central Africa. Major Lugard, I believe, has found on his expedition to Lake Ngami his donkeys were the only animals that survived the attacks of the tsetse."

Aurel Schulz, M.D., and August Hammer: "Donkeys show more resistance to fly-bite than any other domestic animals. It has often been asserted, not without mild proof, that the donkey of all domestic animals is the only one that will survive the tsetse-fly bite. I myself have seen them traverse safely the distance from Delagoa Bay to Lydenburg when that country was thickly infested with flies that killed cattle, horses, and even the few camels that were imported as an experiment."

Captain A. St. H. Gibbons: "Of all domestic animals the lowly donkey alone makes a good fight of it—that is, the poison of the tsetse fly."

Other travellers have occasionally made contrary observations. It is probably a case of imported donkeys, and not of the indigenous race. To this belongs the later-given cases of donkeys stung by tsetse flies on the Zambesi which were unaffected, while a horse stung at the same time got ill.

process of development, similar to the malaria parasite in the mosquito.*

SURRA.

A trypanosome disease, the surra—analogue to tsetse-fly disease in Africa—is found in Asia. Its special district is Upper India. It extends, however, west to Persia and east to Further India. Of late years it has spread to the Philippines, Java, Mauritius, and Abyssinia. It attacks chiefly horses and camels; elephants, too, succumb to it. Cattle in India resist it pretty well, but in Mauritius, where it was brought from India by a cattle transport, it proved very virulent.

The surra trypanosome was discovered by Evans in 1881. Morphologically, there is no distinction between it and the tsetse trypanosome, nor in its pathogenic properties, for it may be carried to all species of animals obnoxious to the tsetse trypanosome. Infection takes place apparently by means of stinging flies of the genera *Stomoxys* and *Tabanus*. At present, however, there is not complete certainty on this point.

MAL DE CADERAS.

America also has its trypanosome disease, mal de Caderas, found in South America from the Argentine to the Amazon. It is chiefly dangerous to horses, but behaves otherwise like tsetse and surra. The trypanosoma, discovered in 1901 by Elmassian, should be distinguished from the parasites of tsetse and surra in that its centrosoma is small and stains slightly. I have not yet been able fully to convince myself as to the cause of this peculiarity, which is probably dependent on variations in preparation and colouring. Mal de Caderas is carried by a species of *Stomoxys*.

SLEEPING SICKNESS.

Until recently it was hoped that man was immune to trypanosomes. This, unfortunately, has proved to be a fallacy, for in Gambia in 1901 Dutton discovered by microscopic investigation trypanosomes in a man who was looked upon as suffering from malaria and treated ineffectively with quinine. This discovery was soon confirmed on several occasions, but its significance was first understood when in 1903 trypanosomes were found in sleeping sickness. They were first seen by Castellani in the centrifugized cerebro-spinal fluid of a patient. He, however, looked upon it as an accidental discovery; and it was reserved for Bruce, the discoverer of the etiology of tsetse, to show the importance of trypanosomes in sleeping sickness, and to prove that here again a stinging fly, the *Glossina palpalis*, was the medium of infection. At first one was inclined to look on both trypanosome discoveries in men as things apart, but soon one had to convince oneself that they belonged together and were connected with only one disease—the trypanosomiasis of man. As knowledge developed one was obliged to add to this the conviction that in sleeping sickness not only are there trypanosomes in the cerebro-spinal fluid but also in the blood, and, vice versa, that persons who have trypanosomes only in the blood may later on develop sleeping sickness. Sleeping sickness is therefore only a symptom of the trypanosomiasis of men, which sets in when the trypanosomes have found their way into the cerebro-spinal fluid. Only when this has happened do the cerebral symptoms peculiar to sleeping sickness develop themselves, and, according to experience, always end in death. Whether in every case of trypanosomiasis sleeping sickness develops seems questionable, but there are cases in which the disease ends in death without cerebral symptoms and through exhaustion. Spontaneous cure of trypanosomiasis has not been established up to the present in any single case. These are questions which can only find their answer in further exhaustive experiments.

As to the proportion in which trypanosomiasis affects the population of an endemic region, such as Uganda, we know that in 80 apparently healthy natives Bruce found that 23, or 28.7 per cent., had trypanosome in the blood.

As regards the usual symptoms of the trypanosome disease in man, it has been observed that, as in animals after infection, there may be good health for a long time, till symptoms of irregular fever set in, accompanied by anaemia, loss of strength, emaciation, local oedema, and erythema. Swelling of the lymphatic glands, especially of the neck, and of the spleen, usually ensues. The symptoms of so-called sleeping sickness are so well known that I need not describe them again.

This disease was known in the beginning of last century.

* These remarks apply naturally to trypanosomiasis in men also, and, as a rule, trypanosomes are found very sparingly in the human blood.

It was especially seen among negro slaves on the West Coast of Africa, often too among slaves transported to the West Indies, and it was deduced that they were attacked by sleeping sickness from five to eight years after they had left the African coast. For this period they must have been suffering from simple trypanosomiasis. The disease never got a footing in the West Indies, evidently because there are no stinging flies there capable of transmitting the parasites. At that time the infected district extended from Senegambia to the borders of Angola. It is only lately that, owing to the development of trade, it spread to the Congo basin, and from thence in 1896 it was conveyed to Uganda by the survivors of the Emin Pasha expedition, who, coming from the Congo, settled in Busoga on the Victoria Nyanza. It seems to have found here favourable conditions for development, for in a few years 200,000 persons were carried off. That Europeans may also be attacked is seen from not a few examples. Owing to the swift course which the epidemic took from West Africa to Uganda, we may certainly expect a further spread.

The trypanosomes of men cannot be distinguished from those of tsetse and surra, either morphologically or in their pathogenic properties in relation to domestic and experimental animals.

THEILER'S TRYPANOSOME.

There is one other trypanosome disease to be mentioned, that discovered by Theiler in 1902 in cattle in South Africa. The trypanosoma theileri, as the parasite which causes this disease is called, is easily recognized from its size, being twice or three times as long as any of the trypanosomes already mentioned. Further, it has this peculiarity, that it is pathogenic to cattle only. The animals become very anaemic, but generally recover. The mortality averages only about 5 per cent.

The disease seems, on the other hand, to be more general than at first supposed; for Schilling found the trypanosoma theileri in Togo; Panse found it in cattle on the island of Mafia, belonging to the German East African territory, and I myself have met with it in cattle from Mafia Island, and among cattle at the experimental station in Rhodesia.

THE RAT TRYPANOSOME.

Lastly, I have to instance trypanosomiasis in rats. This is widespread; in fact, it may be found everywhere if rats be examined. Usually it has been shown that 10 to 30 per cent. of the rats examined are attacked, sometimes as many as 90 per cent. The rat trypanosome is scarcely at all pathogenic for its host; at least animals which have trypanosome in the blood do not appear ill. These trypanosomes cannot be transmitted to other species, and are therefore restricted to this single host.

Morphologically their characteristic is that the hinder end is long and pointed, making it appear like a beak. It is also worth noticing that the centrosoma does not lie near the end, but at the junction of the last and middle third. By these morphological peculiarities they may easily be distinguished from other trypanosomes. Even when they are present in the blood of a rat which has rat trypanosomiasis, and in addition has been infected with tsetse, it can easily be determined whether a parasite is a rat or a tsetse trypanosome. The different action of the rat and tsetse parasites may be shown by inoculating a dog with the blood of a rat which contains both. The tsetse trypanosome alone should develop in the dog, because it alone is pathogenic to the dog. In an experiment which I made of this kind, the dog only developed the kind of trypanosome which was pathogenic for it. If, on the other hand, the blood of the same rat had been inoculated into a rat, then both kinds would have developed. The dog forms somehow a filter through which only one kind can pass, and in this way the two kinds may be separated the one from the other.

CLASSIFICATION OF TRYPANOSOME DISEASES. 3

If we look at these characteristic trypanosome diseases, we see at once that they fall into two different groups. One group is composed of the last-mentioned diseases, trypanosomiasis of rats and the trypanosome disease discovered by Theiler in cattle. They are to be distinguished by the fact that their trypanosomes are constant in their more important characters and sharply separated from other trypanosomes. Among these most important properties I reckon their morphological characters, their virulence, and their relations to the domestic animals.

As regards morphological characters, we have seen that rat trypanosome and Theiler's trypanosome are distinctly charac-

terized and can easily be distinguished from other trypanosomes. In their virulence also they show no variations. It has never been noticed that they increase or diminish in virulence by further inoculation. Rat trypanosomes, when they multiply in rats, and similarly Theiler's trypanosome have always shown the same characteristics when again inoculated into cattle. Their relationship to the host is quite distinct; rat trypanosome can be passed on again exclusively to rats, and Theiler's trypanosome to no other species of animal but cattle.

From the very characteristic behaviour of these two kinds of trypanosome I think I may draw the conclusion that for a long time they have been exclusively restricted to their own particular host, and consequently are most particularly suitable to this host, thereby acquiring special properties and becoming a distinct species. In this respect they resemble malaria parasites and piroplasma.

Quite different are the relations of the trypanosome of the second group of diseases to which tsetse, surra, mal de Caderas, and trypanosomiasis in man belong. They are, in the three leading characters mentioned, fluctuating and variable; they are not sharply separated morphologically from each other, their virulence fluctuates over a wide range, and they are not exclusively found in one host.

From this I would draw the conclusion that the parasites of this second group have lived a proportionally short time in their host, that they are not completely adapted to it, and have not yet developed into a distinct species. This gives the impression that we have here to deal with conditions similar to those which de Vries found in his classical discoveries on the mutation of the *Cenotheca*. It would therefore appear that the trypanosomes of the second group are in a stage of mutability.

I will endeavour to give some reasons in support of this conception of the peculiar character of the second group of trypanosomes. It would lead me too far were I to go into all the representatives of this group, and I will therefore limit myself to the tsetse trypanosome, as this is to some extent typical and is the best known.

I have already directed attention, in my description of trypanosome disease, to the fact that tsetse parasites cannot easily be distinguished morphologically from the other trypanosomes. Moreover, in size and form they vary greatly when passed on to other animals. They are comparatively small, and in the blood of rats, cattle, and dogs the posterior end is blunt. On the other hand, in the blood of horses they are large, and have a pointed, elongated end, making them similar to the rat trypanosome. In the blood of rabbits and dogs the flagellae are usually long, in that of pigs very short, as Martini has shown.

So much for the morphological characters. Much more important for us are the variations in virulence. Already under natural conditions extremes of virulence is known to exist, as shown by the two following examples:

First Example.—Two horses coming from the interior of Togo, a stallion and a mare, were to go to the Zoological Gardens in Berlin, and on the way had to pass the border of a tsetse-infected region. They must have caught the infection here, as the stallion about six weeks after its arrival in the Zoological Gardens appeared ill. Surgeon-Major Martini who examined the animal found tsetse trypanosomes in the blood. We have to thank the director of the Zoological Gardens, Dr. Heck, for his kindness in letting us take both animals to the Institute for Infectious Diseases, where we could continue to observe them. The stallion became very ill indeed; was feverish, anaemic, and emaciated. Gradually it grew worse, oedema followed, and about four months after catching the infection the animal died. While it lived frequent microscopic examinations of the blood showed trypanosomes. Horses, donkeys, monkeys, rats, and mice, infected with its blood, developed tsetse disease and died in a relatively short time. The trypanosome in the blood of the stallion must therefore have been very virulent.

The other animal, the mare, showed on the other hand not the least sign of tsetse-fly disease. All the same it was examined to see if trypanosomes were not, even in very small quantity, present in the blood, as at that time similar cases were known. Many careful microscopic examinations were made but not a single trypanosome was found. Some of the blood was injected into rats, but with no result. It was only after injecting the blood into the abdomen of a large number of young dogs that there was any sign of trypanosome. To show, however, how small was the number of trypanosomes in this animal, 20 c.c.m. of blood were injected into two dogs after they had already been injected with 5 c.c.m. without making them ill. Nine dogs in all were infected with the Togo mare's blood. While those dogs that were inoculated with the stallion's blood always succumbed in a short time to severe tsetse-fly disease, those inoculated with the mare's blood were only temporarily and slightly ill. One only died after 102 days' illness. The others soon got perfectly well, and later on, as far as microscopic examination showed, there was no sign of trypanosome in the blood.

Horses, rats and mice inoculated with the Togo mare's blood were rendered only slightly ill and in some cases not at all.

The trypanosomes of the mare were very slightly pathogenic or not at all virulent, and yet both these animals, in which the virulence of the trypanosome showed such extreme difference, were most probably infected at the same time and in the same place. How is this to be accounted for? The possibility of a varying predisposition in the two animals suggested itself. But this idea was quickly rejected, seeing that the mare, after remaining in continuous good health for a year, proved just as little able to resist the trypanosome of the stallion as the stallion itself. The mare was ultimately infected with the trypanosome of the stallion, became very ill, and succumbed to the disease in a short time. The only conclusion is that the original trypanosomes differed very much in virulence.

Second Example.—In Rhodesia a mining expedition was undertaken to the Zambesi—that is, into the classical tsetse area. The expedition, which included one horse and six donkeys for riding and transport, went astray and found itself in a "fly-belt"—that is, in a neighbourhood where tsetse flies abound. Before the party recognized their mistake and were able to extricate themselves from the danger many of the animals had been stung by tsetse flies. Eventually the donkeys remained perfectly well, but the horse developed pronounced symptoms of tsetse, and the incident was mentioned to me on this account. Surgeon-Major Kleine examined the horse and proved the existence of tsetse parasites in the blood, whereupon a cow and a dog were inoculated with the blood. The horse soon recovered so much that it could be ridden. Six months after the infection I had the animal brought to our experimental station at Bulawayo, to keep it under observation for a week. During this time it showed no visible symptoms of disease; on the contrary, it appeared perfectly well, and on microscopic examination no trypanosomes were to be seen in the blood.

The trypanosomes which were taken from the blood of this horse and injected into dogs, rats, and mice acted just in the same way as those of the Togo mare: they were almost non-virulent. From experience we know that in the very region in which this horse was infected there is a very virulent form of tsetse-fly disease, so that in this case again we have side by side very virulent and almost non-virulent trypanosomes.

The virulence of the trypanosome can be very easily influenced artificially, it can be considerably increased and abated at pleasure. The almost non-virulent trypanosome coming from the Togo mare was inoculated first into a horse and then into a dog by Surgeon-Major Martini, and by this means attained to a considerable degree of virulence. As already mentioned, a dog inoculated direct from the mare died in 102 days, another of the second generation inoculated from a horse died in 113 days. Eventually death after inoculation followed more and more rapidly in from ten to fifteen days, the same period as we get after inoculation of our most virulent tsetse germs.

On this occasion another very interesting observation was made. Three dogs which had recovered from the first infection with the trypanosome direct from the Togo mare were eventually infected successfully after it had been made highly virulent by passing through dogs. They developed tsetse disease, recovered, and behaved just as if nothing had happened to them. It may also be remarked that the increase in virulence by transmission through dogs had the same result in another experiment. Artificial diminution of virulence is proved by the following experiment which I made in Dar-es-Salaam. I passed trypanosomes which were very virulent for cattle through a rat, and then through a dog. They were then inoculated into two cows, which were made only slightly ill, and quickly recovered. From these observations and experiments the variability of the virulence of tsetse trypanosome is easily seen.

It appears, therefore, that they are not completely adapted to their host. Nearly all mammals that have been experimented on have reacted to inoculation. But here, too, there are variations; sometimes they are more virulent for cattle, sometimes for horses, sometimes for camels, etc., and from this it must be concluded by observers who relied on these characters alone that we have to do with a separate disease. In reality it evidently has to do with the natural evolution of the tsetse parasite, which possibly, if the trypanosome in time becomes limited to a single host, would lead to the development of constant characters. Meanwhile the diseases of the second group present characters which vary so much that it is at present difficult, sometimes impossible, to make a sharp distinction between them.

For this reason in 1897, after comparing surra and tsetse disease, and failing to find any certain distinguishing marks, I expressed the opinion that these two diseases might be identical. I encountered much lively opposition, but I again

occupied myself with this question later on, and always obtained the same result. I must abide by my conclusions the more because the marks of distinction alleged to exist between the two diseases on the score of recent researches have been proved to be unsound. It has been asserted, for instance, that surra in India is little virulent and tsetse in Africa very virulent for cattle. But we have seen that in Africa there are forms of tsetse which are very little virulent, and, on the other hand, that the slightly virulent surra of India, if carried to other countries, may become very virulent, as has been observed in an especially striking way in Mauritius.

In recent times, most authorities have accepted my conclusions. Musgrave, who made some very thorough investigations of trypanosome diseases in Manila goes even further, and would identify mal de Caderas with tsetse and surra. Laveran and Mesnil, on the other hand, to whom we owe an excellent monograph on trypanosome diseases, defend the contrary opinion. They would not only distinguish sharply between the various diseases of the second group, but would also divide tsetse disease into several forms. They appeal to their experiments in immunity, in which they found it possible to infect animals with surra, after they had been rendered immune to tsetse. If these experiments, however, are closely examined, it is seen that they are not conclusive. The experiments were made on goats, animals almost insusceptible to both diseases, and therefore unsuitable for experiment on surra and tsetse; the experiment had the only result which could be expected. The goats infected with surra did not become ill, trypanosomes were not once found in the blood on microscopical examination, and it was only by experiments on animals that it was shown that trypanosomes were sparingly present for a short time. Further, it was not ascertained whether these trypanosomes were acquired from the first or second inoculation. It may happen that, as we shall see later, trypanosomes may persist in the blood of immune animals for a long time.

But even if the experiments of Laveran and Mesnil were free from objection their method would not suffice to distinguish between the several trypanosomes. We should be obliged to regard our stocks of trypanosome in the Togo mare—the non-virulent and the very virulent—as two separate diseases, for dogs which had resisted inoculation with the first stock, that is, were immune to it, succumbed to inoculation with the second. In our cases we did not meet with trypanosome infection uncertain and hardly to be noticed, as in Laveran's experiment; but, on the contrary, the animals became very ill after infection, and eventually died.

If we accepted these principles we should have to recognize an interminable number of trypanosome diseases, and the confusion which already reigns would only grow worse. We have had a similar experience with regard to malarial diseases. There was a time when it was thought necessary, on account of specious and trifling differences continually, to invent new kinds of malarial diseases, but thorough investigation showed that there were only three kinds—the quartan, tertian, and tropical—each presenting very constant characters by which they might with certainty be distinguished the one from the other. So should it be with trypanosome diseases, and those only accounted distinct which possess fixed and unalterable characters. Thus, for example, I would consider mal de Caderas as distinct from tsetse and surra if the varying relations of the centrosome in the Caderas trypanosome was quite constant; but this, as I have said, is not yet certainly established.

The question of the difference or identity of these trypanosome diseases, which, of course, must be settled some day, has, however, only a theoretical importance. On this point I agree with Musgrave, who rightly remarks that in practice it is not a question of what the trypanosomes are, but of what they do.

EXPERIMENTS IN IMMUNIZATION.

This observation leads me to another point which is of more practical importance. It is this. You will remember the experiment in which virulent trypanosomes, after being inoculated into a rat and a dog, were so reduced in virulence that they caused only a slight infection in two cattle. It stood to reason that these two animals having recovered, and no trypanosomes being discoverable in their blood on microscopical examination, ought to be experimented upon to ascertain how they would now behave towards trypanosomes the virulence of which had not been reduced. Together with some control animals, they were at once inoculated with very virulent tsetse blood; the control animals

sickened in the usual way, but the two previously inoculated showed for a few days only a few trypanosomes in the blood, and on the whole remained quite well. This showed that they were immune to the tsetse stock employed. It remained to inquire whether this immunity would persist for any length of time. I could not test the animals further, as I was obliged to leave Africa. But I asked Veterinary-Surgeon Schmidt, who went to Africa shortly afterwards, to look out for the animals and investigate their immunity afresh. He was only able to find one of them; he repeated the experiment, inoculating control animals at the same time. The animal was immune to this inoculation also. During my last visit to Dar-es-Salam this animal again came under my observation, and I was able to assure myself that it remained perfectly healthy. Its immunity had thus lasted for six years. Nocard, Schilling, and Martini subsequently rendered cattle immune by the same method. It seemed indeed that these observations would place in our possession a method of protecting cattle against tsetse disease—a matter of great importance in those extensive areas where nowadays, on account of tsetse, no cattle-breeding can be carried on. At first I gave myself up to this hope, but from further study of the pathological protozoa I have arrived at quite a different conclusion.

At that time it was believed that in an immune animal the parasites could not exist, and that such an animal must on that account be quite free from parasites. But even in the case of bacterial diseases in connexion with which this idea originated, we were obliged to admit in the course of time that even in immune individuals—in cholera, diphtheria, typhus, for instance—parasites could continue to exist, sometimes for a considerable time, and it became necessary to modify materially our prophylactic measures.

In the case of pathological protozoa, this condition seems to be the rule. This was shown first and most clearly in Texas fever. Cattle which remained immune to Texas fever, either because they survived the disease, or because they grew up in a district where Texas fever is enzootic, could yet carry Texas fever to susceptible cattle, although they themselves appeared perfectly healthy. This is possible only if these animals are affected with the blood parasite peculiar to Texas fever, the piroplasma. Much pains was taken to discover the piroplasma in the blood of such immune cattle, but with success in isolated cases only. We were able, however, in Rhodesia, where we had to get our cattle for experiments from a similar Texas-fever infected neighbourhood, either on account of a better system of investigation or of larger opportunities, to prove the presence of the piroplasma in 15 to 20 per cent. of the cattle. This percentage would undoubtedly have been increased considerably, if the animals had been examined more frequently, or if the examination, which had proved so essentially useful in the discovery of isolated trypanosomes, could have been applied on a larger scale.*

In the coast fever with which I occupied myself in Rhodesia, I was able to prove the same thing. In this disease the parasites can as a rule be found in the blood of immune animals on microscopical examination. In regard to other diseases allied to Texas fever (piroplasma of dogs and horses, the cattle disease of Transcaucasus first described by Dschunkowski), sufficient evidence exists to enable us to assert that in them, too, the same conditions obtain.

Under these circumstances, the question arises whether in the blood of animals immune to the trypanosome parasites do not exist, even though in small numbers. The question undoubtedly finds an answer in some of the facts already mentioned. I may remind you of the case of the rats apparently quite sound but yet having trypanosomes in the blood; further, I may remind you of the Togo mare which appeared sound while under observation during nearly a whole year, but all the time had isolated trypanosomes. The discovery of Bruce, too, that healthy antelopes and buffaloes are infested by trypanosomes in a tsetse-infected district must be noted here. We can, however, come nearer the answer to this question from our own investigations. We have at our disposal the oft-mentioned case of the cow at Dar-es-Salam which remained immune for six years; this experiment was specially important in so far that it might possibly afford a method of immunizing other animals artificially. This animal was thoroughly examined by

* In one case we succeeded with the blood of an animal immune to Texas fever in which no piroplasma could be found microscopically in producing Texas fever in a calf kept constantly in a stall, and thus protected from any other source of infection.

Surgeon-Major Kleine, and in spite of repeated microscopical examinations no trace of trypanosome could ever be discovered. But the dog experiment in this case, as well as in that of the Togo mare, proved the existence of trypanosomes. This artificially-immunized animal, in spite of apparent good health, retained the trypanosome for years. It was in the same condition as the large antelopes and buffaloes which are, according to those most experienced in the tsetse regions, the principal source of tsetse infection. If we were to attempt to make whole herds of cattle immune in this way we would produce more permanent sources of infection, and tsetse disease, which we hoped to exterminate by artificial immunization, would in this way be permanently retained. Under these circumstances it will be clearly understood that I do not think it advisable to combat tsetse disease by artificial immunization.

PROPHYLACTIC MEASURES.

We must look for other means of attacking this epidemic, and these are, fortunately, not wanting. Action might be taken either against the intermediary, the stinging fly, or the parasites themselves. Whether anything can be done against the *Stomoxys* and *Tabanus* species, which it is alleged carry the infection in India, the Philippines, Java, Mauritius, and South America, cannot at present be said, for too little is known of their habits, mode of life, and conditions of existence to render it possible to frame measures for their extermination. But it seems possible to do something against the African stinging flies, the *Glossinae*. It has often been observed that with the disappearance of large game tsetse flies and tsetse disease disappear too. Whether the disappearance is due to the drying up of the fountain of infection, the big game, must remain doubtful. But in every instance the cessation of tsetse disease in all places where wild game has been shot out or removed is an indisputable fact of which use should be made in the districts where tsetse disease and big game exist together. We must be clear on this point—which is the more profitable, a good stock of game or a good stock of cattle. Both cannot live together on African soil.

The measures taken against trypanosomes seem to work very successfully. With this object all animals which harbour trypanosomes must be sought out, and the danger removed by their extermination or slaughter, or, if kept to be slaughtered, they should be so isolated that they may no longer infect other animals. To ensure that all animals infected with trypanosome are included, not only must those actually ill be examined, but all those still apparently well but suspected.

The example of Java and Mauritius shows how useful is the diligent carrying out of such important measures, and how by neglecting them much harm may arise. In Mauritius, surra, which had been introduced from India by a cattle transport, was not known until recently, and, when recognized, no rational measures were at first taken. The result was that in two years all the horses and mules and most of the cattle died. In Java, on the other hand, the epidemic was quickly diagnosed and immediately taken in hand. The stalls were examined, diseased animals slaughtered, and those suspected efficiently isolated by sending them either to places where there were no stinging flies or to a neighbourhood where no cattle were. Thus the epidemic, which was quickly taken in hand, was checked, and the mortality kept within narrow bounds. By these means and by the precautionary measures taken against every infectious disease, we must in the future fight against trypanosome diseases.

Unfortunately these measures cannot be applied to trypanosome disease in men. It would not, of course, be difficult to isolate adequately in hospitals those pronounced to be suffering from sleeping sickness. Little, however, would be gained by this, for it is not these sick persons but the thousands of apparently healthy people who are already afflicted with trypanosome who are the cause of the infection in this sickness, and how would it be possible to isolate thousands of healthy people? If we had a drug which would destroy the trypanosome in the blood, as malaria parasites are destroyed by quinine, then we might arrange a battle against trypanosomiasis on the pattern of the attack on malaria which has led to such good results. At present no such drug is at our disposal, but there are certain indications that it will yet be found.

For some time the use of preparations of arsenic has been attended by a not wholly unsuccessful result. Then Ehrlich discovered a remedy in a drug he called trypanoth, which

gave decidedly better results than arsenic. Laveran and the members of the Liverpool School of Tropical Medicine succeeded still better with a combination of trypanoth and arsenic. Further, Wendelstadt has found that malachite green has a destructive effect on the trypanosome in the blood of experimental animals. All these investigations, however, are still in the stage of trial by laboratory experiments, and it is not yet known how they will work out in practice. They show, however, that a keen effort is being made to find a remedy against trypanosomiasis, and we can only hope that one may soon be discovered.

At all events, it is important that the inquiries into trypanosomiasis in man, begun so successfully by the English expeditions under Bruce, Dutton, and others, should be furthered by every means, and that all nations interested in combating this epidemic should lend assistance. The German nation is one of these. In Kamerun and Togo the existence of the disease has already been proved, and sleeping sickness quickly spreading from Uganda has already reached the borders of German East African territory, has perhaps already got beyond them. It is high time, then, that something should be done, and we would express the earnest hope that Germany may soon follow England's example.

The Bradshaw Lecture

ON THE

TREATMENT OF ENTERIC FEVER.

Delivered before the Royal College of Physicians of London on November 15th, 1904.

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[ABSTRACT.]

[AFTER some introductory remarks, in the course of which reference was made to the fact that the case-mortality of enteric fever remained to-day at a height of more than 15 per cent., and that in this country alone some 5,000 or 6,000 people annually died from the disease, Dr. Foord Caiger proceeded as follows:]

From a therapeutic point of view it may be stated broadly that the treatment of a case of enteric fever will probably be conducted on one of two lines: an active remedial method or a passive or so-called expectant method, each of which has its firm adherents.

ACTIVE OR REMEDIAL METHODS OF TREATMENT.

The methods of treating enteric fever by means of remedies which are assumed to be capable of exerting a direct controlling influence over the natural course of the disease may be appropriately referred to as either (1) specific, (2) antipyretic, or (3) antiseptic, according to their conception and to the nature of the agents employed, and they may conveniently be discussed under these headings.

Specific Treatment of Enteric Fever.

The remarkable success which has attended the treatment of diphtheria by the injection of antitoxic serum not unnaturally encouraged the hope that a curative serum might be prepared which would prove equally efficacious in the case of typhoid fever. In the case of typhoid fever, however, the serum of a horse after repeated inoculations with the virus, though possessed of antibacterial properties, as in the case of diphtheria and tetanus, is found to be practically devoid of any antitoxic value, and consequently useless as a curative serum.

It should be mentioned, however, that Chantemesse claims to have produced a serum the nature of which is unknown, with which remarkable success in the treatment of enteric fever is stated to have been obtained.

[Reference was made to the protective method initiated by Professor A. E. Wright, consisting of the inoculation of sterile cultures of the typhoid bacillus which had been attenuated by exposure to heat. The Lecturer then continued:]

An investigation as to the value of Professor Wright's method of antityphoid inoculation was undertaken by the College of Physicians last year at the request of the War Office, and a special Committee of the College was appointed to inquire into it. Careful examination of the whole of the