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SLEEPING SICKNESS IN THE LIGHT OF RECENT KNOWLEDGE

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Sleeping Sickness in the Light of Recent Knowledge.

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FOR over a century the mysterious sleeping sickness of Africa has been known to Europeans. It lurked in the back-country of the West Coast, between the Senegal and the Quanza, and, at the time of the slave trade, hundreds of negroes, raided from the interior, died of it on board transport ships, or in the plantations of the Antilles. But the disease did not give rise to any apprehension; it was believed to be strictly confined to the negro race, it did not spread in the places to which it was imported, and was universally regarded as a peculiar form of nostalgia.

Quite recently, possibly in consequence of the great commercial stir which the advent of the white man has created amongst the native tribes of Tropical Africa, sleeping sickness has begun to spread very widely, and has assumed a fearful importance in the pathology of the Dark Continent. Within the last few years it has extended southward throughout Angola, it has spread up the Niger and the Congo, and, proceeding along the new trade routes opened up by Europeans, it has suddenly appeared in East Central Africa, invading the Upper Nile and the shores and islands of the equatorial lakes. In Northern Angola, on the upper Congo, in certain districts of Uganda, its ravages have already been appalling. In many places entire villages have been depopulated. In the Busoga province alone 30,000 natives have succumbed within the last three years.

The appearance of sleeping sickness in the very heart of Africa, its steady, widening progress, call for very serious consideration and for immediate action. The disease may spread along the Nile and menace Egypt, or, reaching the East Coast, it may possibly find its way into India. However, it is not merely its tendency to spread which brings sleeping sickness so forcibly before us, but its terrible, inexorable deadliness. The sleeping sickness of Africa is invariably fatal.

Heretofore, sleeping sickness has been looked upon as a disease of the negro race exclusively, but a number of cases have been reported in half-breeds, and two or three doubtful cases in Europeans. So far the cases amongst Europeans have been disbelieved, chiefly on account of erroneous *à priori* arguments. Latterly, our ideas concerning the relation between race and disease have been totally changed. We know now that there are no purely ethnic diseases. At one time it was believed that the dark races were far more liable to elephantiasis than the white, now we know that when Europeans are placed exactly in the same conditions as the natives, they are quite as liable to acquire it. I have no doubt the same is the case in sleeping sickness.

Symptoms.

The symptoms of sleeping sickness are fairly well known. Clarke,[1] Dangaix,[2] Nicolas,[3] Santelli,[4] Guérin,[5] McCarthy,[6] Corre,[7] Abblart,[8] Forbes,[9] Bettencourt,[10] Cook[11] and Hodges[12] have given us excellent descriptions of the disease as it occurs in various parts of Africa, and Mackenzie[13] and Manson[14] have very carefully described three cases of the disease in Congo natives brought over to England for the express purpose of accurate investigation. Two of the latter cases I had the opportunity of watching myself.

A peculiar feature in sleeping sickness is the occasionally long duration of its incubation period. At times, the disease in its striking somnolent stage may not manifest it-

self until two, three, or five years after the patient has left the endemic centres. A case occurred in England in a Congo boy who had resided in this country for three years without showing any particular sign of unhealthiness. During the time of the slave trade, the disease was not uncommon in the West Indies among the imported slaves, breaking out long after they had left Africa. According to Corre,[7] the natives of Gorée (Senegambia), when obliged to dwell for a time within the endemic centres of sleeping sickness, do not consider themselves quite safe until seven years after their return.

The long incubation period of sleeping sickness may be compared to that of hydrophobia, a disease which offers other points of likeness. The incubation period of hydrophobia may be prolonged for one or more years, but its average length is from six weeks to two months. Probably, in sleeping sickness, the average length of the incubation period does not exceed a few months.

After the onset of the characteristic symptoms, the disease may run a very rapid course. As a rule, it lasts from three to four months, but a large proportion of cases have been known to continue for twelve months or even longer. Not infrequently the fatal issue is hastened by inanition or by an intercurrent disease such as dysentery or pneumonia.

The drowsy stage creeps on slowly and insidiously. The patient is languid, taciturn, slow, dejected ; his customary spirit and activity are gone, he grows dull and listless. He has a feeling of weight or even pain in the head, and occasionally suffers from giddiness. He is unable to carry on his work on account of a great, overpowering lassitude. He may fall asleep while at work, while at his amusements, and even while he is eating. With the progress of the disease, his gait becomes unsteady and tottering, like that of a decrepit old man. He is found lying in the sun, in a state of drowsiness, with the eyes half closed and the limbs extended. He can easily be roused, and replies to questions intelligently, but slowly and in monosyllables. If he

attempts to rise he does so with difficulty, and his movements are accompanied by muscular tremor. There may be some puffiness about the face and a characteristic drooping of the upper eyelids, which give the patient a peculiar heavy expression. The skin has lost its glossiness and looks dry, ash-coloured and scurfy. A closer inspection will almost invariably reveal a papulo-vesicular eruption, especially marked on the front of the chest, over the abdomen, and on the inner surface of the thighs. This eruption gives rise to severe itching, and the patient is nearly always scratching some part of his body. In a large majority of cases the lymphatic glands of the head and neck are appreciably enlarged. Very often other groups of deep and superficial glands are swollen. The swollen glands show no tendency to suppurate. At first the patient is well nourished, and his appetite is fair. He is usually constipated, but may be liable to diarrhœa. His tongue, when protruded, is characteristically tremulous. We have no very definite knowledge of the temperature in sleeping sickness. In some instances the disease is afebrile ; the surface temperature may even be sub-normal. As a rule there seem to be irregular attacks of fever during the course of the disease, the temperature varying from 100° to 103° F. Corre speaks of a regular evening rise. A day or two before death the temperature may fall below normal. Sometimes there is hyperpyrexia.

After a time the drowsiness becomes more marked, the patient appears to be always asleep, and it becomes difficult to rouse him. He does not reply readily to questions, but the replies, when made, are correct and rational. He takes food when it is given to him, but unless constantly prompted he will invariably relapse into somnolence whilst conveying food to his mouth, or with the half-chewed victuals in his cheek. This stage is occasionally attended with remissions, sometimes sudden and sometimes gradual—deceitful appearances of amendment—but invariably it relapses, and these fallacious symptoms of improvement may occur more than once.

At length the muscular debility becomes excessive, the drowsiness almost continuous, and the patient becomes greatly emaciated. His limbs are agitated with tremors or become powerless and contracted, the corneæ of one or both of his eyes may become opaque, bedsores form upon the sacrum, the ilia and the shoulders, his lips swell, and saliva dribbles from the mouth ; he passes the fæces and urine involuntarily, and dies occasionally in convulsions, but oftener without a struggle. These are the broad outlines of sleeping sickness.

Morbid Anatomy.

The coarse anatomical features of sleeping sickness were described many years ago by Clarke,[1] Dangaix,[2] Gore,[15] Guérin,[5] and others. In 1898, Regis and Gaid[16] published a detailed microscopical examination, and attributed the symptoms of sleeping sickness to a diffuse meningo-encephalitis, but their observations referred to a single case in the region of Timbuctoo. In 1900, Mott[17] published the changes he had found in the central nervous system of two cases of the disease, and remarked that sleeping sickness is due " to a poison, of micro-parasitic or other source, which affects especially the lymphatic system, and in particular that portion of it pertaining to the central nervous system." Mott's excellent observations were confirmed by the Portuguese Commissioners in 1901, and by Warrington[18] in 1902.

The chief characteristics after death from sleeping sickness are : general emaciation, enlargement of the lymphatic glands, slight opacity and thickening of the pia-arachnoid, and serous effusion into the meshes of the pia mater or into the ventricles. The microscope reveals an intense chronic meningo-encephalo-myelitis. The emaciation is very marked in certain cases, the enlargement of the lymph glands is constant, and may be noticed in the cervical, axillary, mesenteric, and inguinal groups. In the cerebro-spinal system the macroscopical changes are seldom marked. In most cases there is only a slight opacity of the pia

arachnoid over the convexities and some serous exudation in the subarachnoidal space. In some rapid cases the exudate may be considerable in amount. As a rule it is somewhat turbid, but never purulent. The vessels of the brain do not show any appreciable abnormality, but there may be a marked congestion of the arteries and veins of the dura mater. The cerebrospinal fluid may be slightly turbid but seldom in excess. The ventricles are never

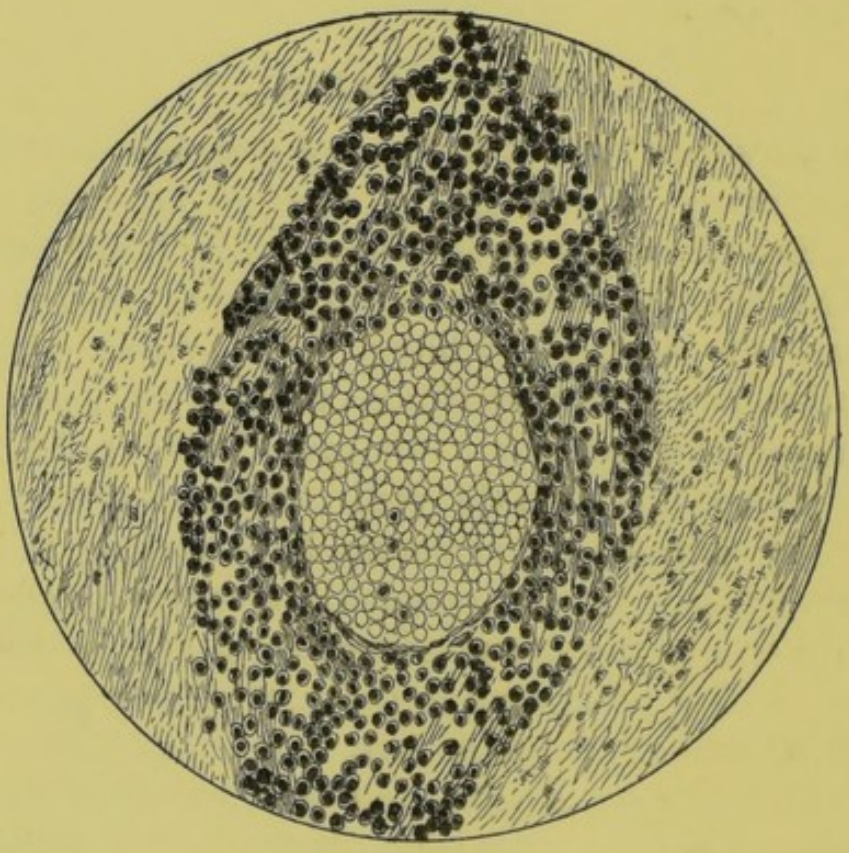

FIG. 1.

dilated and the ependyma is not granular. The brain substance is of normal consistence and the convolutions are neither flattened nor wasted. *Puncta cruenta* are rarely marked in the cut surface of the cerebrum. The medulla shows to the naked eye marked congestion of the vessels. In one of Mott's cases the roots of the cauda equina were surrounded by a gelatinous yellow deposit.

The microscope shows the pia-arachnoid infiltrated

with mononuclear leucocytes ; the inflammation is seen throughout the whole central nervous system, but especially in the medulla and at the base of the brain. It can be traced along the blood-vessels and septa into the substance of the nervous system. The perivascular lymphatics around both large and small vessels are crowded with these lymphocytes. The cells of the cerebral cortex show a normal outline, but scattered through the substance, especially in the pericellular spaces, are the small round nucleated cells.

The enlargement of the lymph glands throughout the body, and the enormous accumulation of mononuclear leucocytes within the perivascular lymphatics of the cerebro-spinal system, indicate that the specific agent of sleeping sickness is essentially a parasite of the lymphatics, but that it is capable of damaging the nervous elements, either by mechanical action, or, possibly, by elaborating a special toxine.

Epidemiology.

The epidemiology of sleeping sickness is as yet very imperfectly known, but it presents several remarkable peculiarities. The disease is strictly connected with water. It prevails along rivers and streams or on the shores of lakes. Several people have remarked that its endemic centres correspond as a rule with the worst malaria stations, and Corre lays special stress on the paludal nature of the sleeping sickness centres of Joal and Portudal in Senegambia. In Uganda, where it has only just appeared, it is confined to the northern shores of Lake Victoria Nyanza and to the adjacent islands. Another characteristic feature is its patchy distribution. The disease is not generally diffused throughout a river valley or other endemic district, but affects particular foci, clings to particular villages, and is not observed in places near by. Corre has frequently remarked that sleeping sickness may attach itself to a particular house or to a particular group of

houses. It may suddenly appear in villages hitherto immune and cling to the place for years. As to season, the only information is that of Corre, who states that in Senegambia a number of patients believed they had contracted the disease during the rainy season. Neither age nor sex seem to have any special influence. Sleeping sickness may make its appearance at any epoch of life, but it is more commonly found between the ages of 12 and 20 years. It is very rare at an earlier age than 3 years, but this does not prove a protective influence of the period of lactation as conjectured by Ziemann and others. Males and females are equally affected.

Old Theories.

Various theories have been put forward at different times to account for this strange and formidable disease. Some believed it to be a kind of nostalgia intensified by the ill-treatment suffered at the hands of slave-dealers and planters. Other equally irrelevant theories are those which ascribe the disease to malaria, to sun-stroke, to sorcery, to the immoderate drinking of palm-wine, or to the smoking of Indian hemp.

Corre, in his first paper on sleeping sickness, conjectured that the disease might be a kind of food poisoning analogous to ergotism and lathyrism, but later he put it down to scrofula on account of the frequent occurrence of glandular swellings. Calmette, in 1888,[19] compared the disease to pellagra, and Ziemann[20] revived again last year the food-intoxication theory by ascribing sleeping sickness to the eating of raw or unsuitably prepared manioc. Ziemann says that he was led to this theory by a previous study of pellagra and beri-beri, which, he affirms, are known to be diseases of intoxication. But so far no one has actually proved that pellagra is caused by some specific toxic substance contained normally in maize, neither has anyone proved that beri-beri is due to the consumption of rice. Both maize and rice are perfectly healthy foods

under ordinary conditions, and whatever their part may be in the natural history of pellagra and beri-beri, they certainly do not stand in the direct relation of cause and effect. Like many other food-plants now extensively cultivated in West Africa, the bitter cassava (*Manihot utilissima*) and the sweet cassava (*Manihot aipi*) were imported from South America. The areas of their cultivation and consumption in Africa do not in any way coincide with the geographical distribution of sleeping sickness. Another reason against the food theory is the occurrence of the disease among negroes far removed from the endemic centres, as in the West Indies and in Europe.

Bacteria.

Various kinds of bacteria have been described in cases of sleeping sickness and claimed to be the specific agents of the disease. In 1897, Cagigal and Lepierre[21] found a bacillus in the blood of a case of sleeping sickness from Angola, and claimed that it was the cause of the disease. They stated that by inoculating rabbits with cultures of this bacterium they produced a disease resembling sleeping sickness and yielding the characteristic organism. Brault and Lapin,[22] who had a culture of the bacillus sent to them, were unable to confirm these observations.

In 1899, Marchoux[23] suggested that *Fränkel's diplococcus* might be the cause of sleeping sickness. He made the autopsy of one case of sleeping sickness at Saint Louis (Senegal), and found the pneumococcus on the pericardium, but was unable to detect its presence within the cerebrospinal system. Pneumonia was very prevalent at the time.

In 1901, Broden[24] examined several cases of sleeping sickness at Leopoldville (Congo), and found in the blood and in the cerebrospinal fluid (*post mortem*) a bacillus which grew abundantly on potatoes. This bacillus was not agglutinated by the blood of patients suffering from sleeping sickness. The same year the Portuguese Government sent a Commission to Angola to investigate the

etiology of sleeping sickness. Bettencourt and his colleagues[10] isolated a *diplo-streptococcus* from the cerebrospinal fluid which they obtained by means of the lumbar puncture made during life or *post mortem*. Lumbar puncture was performed in nine cases. In six of these it gave positive results, the bacteria being easily isolated; in the other three the examination of the direct preparations and the cultures gave negative results. This streptococcus was also found in the blood and in the lymph glands.

Quite recently a similar streptococcus has been seen by Castellani who, together with Low and Christy, was sent by the Foreign Office and the Royal Society to study the disease in Uganda. Castellani[25] found the streptococcus in the blood and cerebrospinal fluid of patients suffering from sleeping sickness, but he found it very rarely during life, and then only in the last stages of the disease. Indeed, he grew it once only from the blood, although he examined bacteriologically the blood of thirty-seven patients, and in each case repeated the investigation several times, and with different methods. He examined the cerebrospinal fluid obtained by lumbar puncture in twenty-eight patients, but only five cases gave a positive result, and four of these were examined a few hours before death. Out of six bacteriological examinations of urine, he grew the microbe once. Bacteriological examinations of enlarged lymphatic glands removed during life were negative, and the examination of the spleen juice obtained by puncture during life was likewise negative.

It is difficult to say whether Castellani's streptococcus is identical with the microbe described by the Portuguese Commission. The Portuguese physicians first stated that their diplo-streptococcus grew very poorly on the ordinary culture media, and that they had never succeeded in obtaining cultures on gelatine. Recently, however, they have modified this statement and affirmed that, like the streptococcus isolated by Castellani, it grows very well on gelatine.

Castellani believes that the streptococcus he has found

in cases of sleeping sickness is simply a variety of *Streptococcus pyogenes*. He thinks that its rôle in the etiology of sleeping sickness may be similar to that of the streptococci in scarlet fever and rheumatic polyarthritis.

The bacteria so far described in cases of sleeping sickness have probably nothing to do with the disease, and, indeed, the extensive bedsores which form towards the close of sleeping sickness fully explain the presence of secondary parasites.

The two cases which were brought to London in 1898 were very carefully examined with regard to bacteria. Dr. Bullock[17] attempted to make cultures from the blood and from some enlarged cervical glands which were removed during life, but none of the cultures had grown at the end of three weeks; he therefore came to the conclusion that no ordinary micro-organisms were contained in the blood or glands. At *post mortem* the cerebrospinal fluid was examined for micro-organisms by cultures, &c., and various organisms, including diplococci, *Streptococci pyogenes*, and bacilli were found, but of course no importance could be attached to these observations.

Filaria Perstans.

In 1891, while examining the blood of a case of sleeping sickness, under the care of Dr. Stephen Mackenzie in the London Hospital, Manson discovered the larvæ of a new filaria, which he called *F. perstans*, because it observes no periodicity while in the peripheral circulation. Later he found the larvæ of *F. perstans* in films of blood obtained from other cases of sleeping sickness on the Congo, and, in 1898, he again found them in the two cases of sleeping sickness which were admitted into Dr. Abercrombie's wards at Charing Cross Hospital. Struck by the constant presence of these filariæ in cases of sleeping sickness, and by the singular correspondence which seemed to exist between the geographical distribution of sleeping sickness and of *F. perstans*, and paralleling the long incubation period of sleeping

sickness with the fact that *F. perstans* can remain alive within the body of its host years after the infection area has been quitted, Dr. Manson, without committing himself, very reasonably suggested that this peculiar blood-worm might possibly be the cause of sleeping sickness. When it was discovered that *F. perstans* was found not only in cases of sleeping sickness, but also in a large proportion of the inhabitants of the Congo and of other parts of West Africa, Dr. Manson still held to his hypothesis, because it was supported by the pathology of *F. Bancrofti*. In fact, *F. Bancrofti* does not always cause chyluria, yet there can be no doubt that it is, within the Tropics, and in many sub-tropical countries, a frequent cause of chyluria.

The discovery of the presence of *F. perstans* in British Guiana was very much against the theory of a connection between this nematode and sleeping sickness, but the diseases of the natives of British Guiana are very little known, and Dr. Ozzard[26] wrote that he believed sleeping sickness to be amongst their ailments, and stated that a Buck woman was brought to him for treatment because, as her friends said, she was always asleep.

Low's[27] recent researches in British Guiana, and the observations he made in Uganda, together with those of Moffat, Cook and Hodges, have definitely proved that *F. perstans* cannot be regarded as the cause of sleeping sickness. *F. perstans* is very common in British Guiana and probably extends over a much wider area in South America, but sleeping sickness is unknown. On the other hand, sleeping sickness is now very prevalent in Kavirondo, along the north-east shores of the Victoria Nyanza, but the filaria is quite exceptional.

Trypanosoma Castellanii (Kruse).

On November 12, 1902, while examining the cerebro-spinal fluid obtained from a case of sleeping sickness by lumbar puncture during life, Castellani discovered a trypanosome. At first he did not give much importance to this

finding. He considered the presence of the flagellate a mere coincidence, and thought it had probably arisen from admixture of blood during puncture. Later, however, he observed that trypanosomes were of frequent occurrence in the cerebro-spinal fluid of patients suffering from sleeping sickness, and he was able to demonstrate their presence in twenty out of thirty-four examined, that is to say, in 70 per cent. of cases. He found them also twice in the cerebro-spinal fluid obtained *post mortem* from the lateral ventricles. Once he found the active trypanosome in the blood.

Besides the ordinary forms, he found in the blood and in the cerebrospinal fluid certain roundish bodies which, stained by the Romanowsky-Leishman method, show the chromatin gathered in two or more points. They measure from 12 to 14 μ, and resemble amœbæ, but do not project pseudopodia; he compares these forms to those described by Kempner-Rabinowitsh in rats infected by *Trypanosoma Lewisi*. He also found in the cerebrospinal fluid some very small (4 to 6 μ) pear-shaped bodies with macro-nucleus, micro-nucleus, and sometimes a short flagellum originating apparently from the micro-nucleus. They correspond to the "amœboid forms" described by Bradford and Plimmer in *Trypanosoma Brucei*.

Castellani's trypanosome closely resembles *T. Brucei* and *T. Nepveui*,* but Castellani mentions certain slight morphological peculiarities by which, he thinks, it may be distinguished from the latter. The points of difference are: a more or less rounded anterior extremity (posterior extremity

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* This trypanosome was first discovered by Nepveu in Algeria, in 1898. Dr. Forde found it again in 1902, and Dr. Dutton proposed to call it *T. Gambiense;* Dr. Manson, in his book on "Tropical Diseases," calls it *T. hominis*. The geographical name given by Dutton is objectionable, because the parasite is not confined to the Gambia, nor was it found for the first time there; besides, there is nothing more unstable than geographical distribution. The name *T. hominis* is likewise objectionable, because several species may attack man. I think that by right of priority Nepveu's name should be associated with the discovery of trypanosoma in man.

of most authors†), the centrosome outside the vacuole and much closer to the extremity, the larger vacuole placed before the centrosome, the longer free portion of the flagellum, and fewer granules at the posterior extremity.

The distinguishing features enumerated by Castellani are far from being constant, as he owns himself, and we know that both *T. Brucei* and *T. Nepveui* vary considerably in size, in shape, in the relative position of centrosome and vacuole, and in the form of the anterior

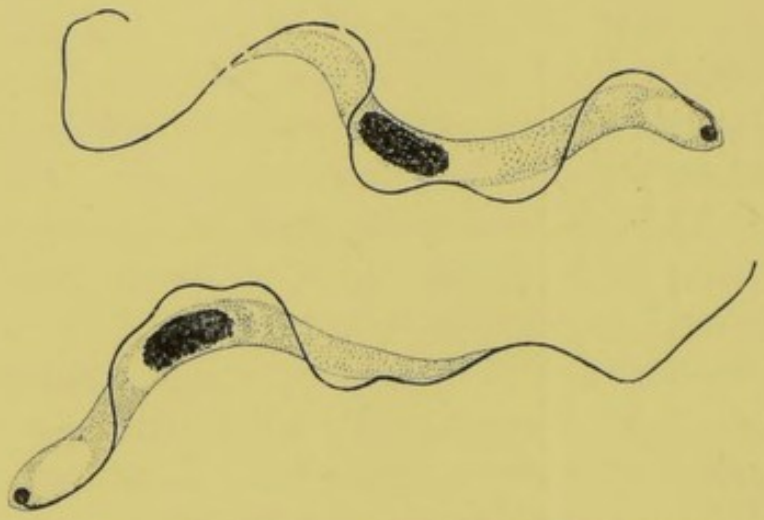
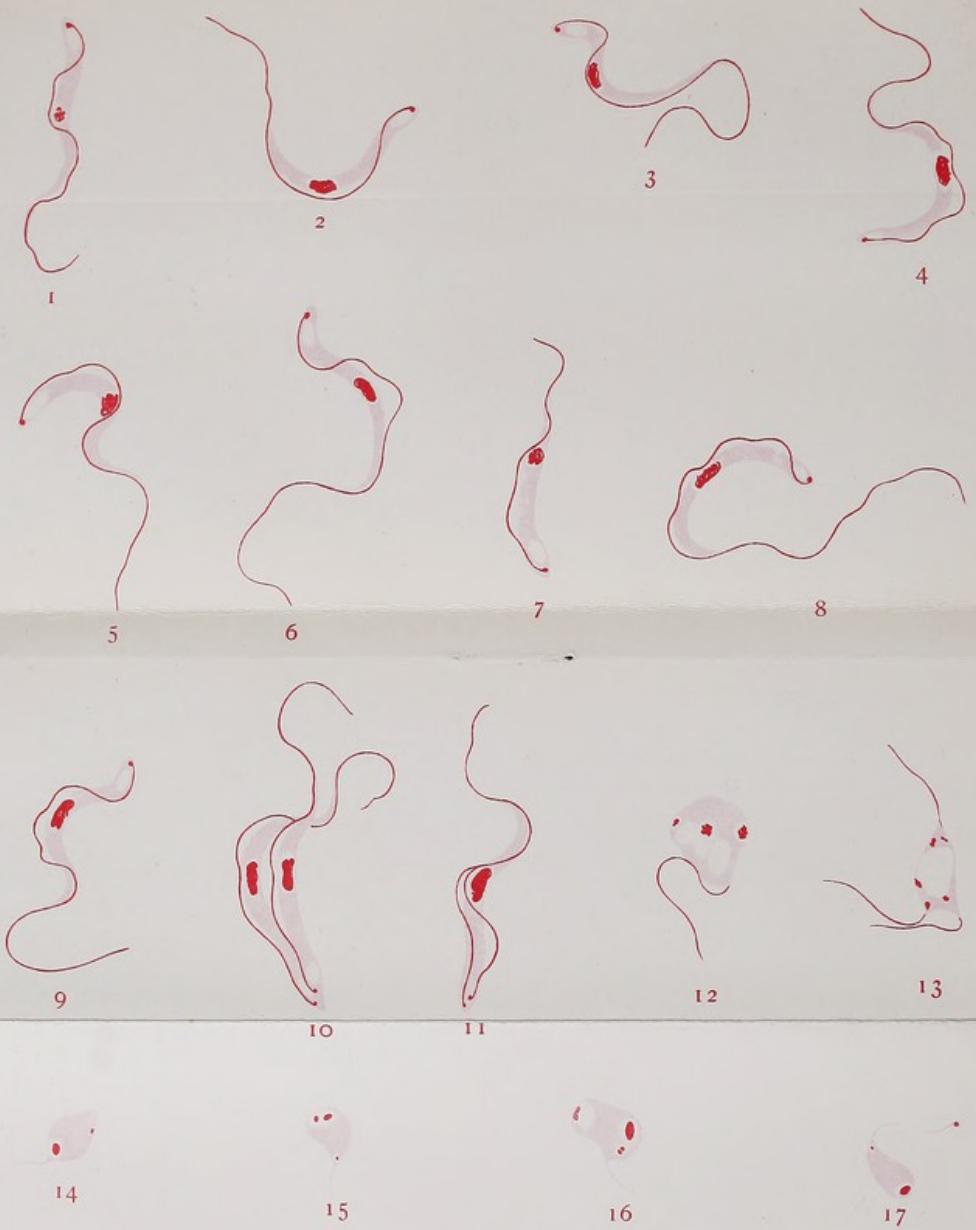


FIG. 2.—Trypanosoma found in sleeping sickness.

extremity, which may be pointed, rounded, or sharply truncated. Indeed, it is still a moot point whether the parasites of nagana, surra and mal de caderas represent one or more species.

The different geographical and zoological distribution of nagana and sleeping sickness show that *T. Brucei* and *T. Castellanii* are somehow distinct. I can see no morpho-

† *T. Castellanii* moves with the more rounded extremity foremost, besides, analogy with other non-parasitic flagellates points to this extremity as the anterior—the flagellum in the latter subserving nutrition as well as locomotion. The micro-nucleus or centrosome probably represents the eye-spot which in other protozoa, such as the *Euglenæ*, is placed at the base of the flagellum, and in contiguity with the contractile reservoir (vacuole).



TRYPANOSOMA Castellanii (Kruse).

1-9. Adult forms; 10, 11, Division forms; 12, 13, Various developmental forms; 14-17, Amœboid forms.

(See article by Dr. ALDO CASTELLANI, published in the JOURNAL OF TROPICAL MEDICINE, June 1, 1903.)

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logical distinction between Castellani's trypanosome and the trypanosome previously found in man by Nepveu,[28] Forde,[29] Dutton,[30] and Manson,[31] but it is quite probable that the two do represent different "biologic species," and, indeed, we have several examples, both in mammals and fishes, of different species or "tribes" of the genus *Trypanosoma* infesting the same vertebrate host. Besides, so far as we know at present, the disease produced by *T. Nepveui* has its own peculiar clinical features, and it is said to be almost non-pathogenic in natives.

As to the relation between *T. Castellanii* and sleeping sickness, Castellani says: "From the whole of my researches, I am inclined to come to the conclusion that sleeping sickness is probably due to the trypanosome I have described."

Personally, I think there is much to be said in favour of this connection. Of course, the deposition of *F. perstans* will cause many to hesitate before they accept a new pretender, but we should consider that whilst the filariæ are, frequently, almost harmless to their hosts, the trypanosomes are, as a rule, very dangerous parasites.

A comparison between sleeping sickness and the various diseases of animals caused by trypanosomes is decidedly in favour of the trypanosome theory.

The duration of sleeping sickness varies from a few weeks to perhaps two years, its characteristic somnolent stage may be preceded by a very long period of latency (so-called incubation period). Surra, nagana, mal de caderas vary considerably in duration, according to the species affected. In rats, mice and dogs, nagana takes the course of an acute and fatal disease; in horses, donkeys, rabbits and guinea-pigs, it is not so rapidly fatal; in oxen, sheep and goats, it assumes a more chronic course and is not invariably fatal. Dourine resembles very much nagana, but it has a more chronic course.

Œdema is not a very prominent symptom in sleeping sickness, although Clark, in 1840, named the disease "Sleeping

Dropsy," but as a rule there is a certain amount of puffiness about the face, especially in the earlier stages, and sometimes slight œdema round the ankles. In nagana, œdema is very marked in horses and rabbits, but it is slight or totally absent in oxen, dogs, sheep, goats and guinea-pigs. In dourine, the œdema is very marked in horses, less so in donkeys. In mal de caderas, Elmassian states that he never observed œdema or ulceration of the genitals in the horse.

Emaciation is a very characteristic feature in the various trypanosoma-diseases of animals, it is likewise a marked symptom in sleeping sickness. The great muscular weakness of sleeping sickness is found also in nagana, in surra, in dourine, in mal de caderas. The unsteady gait of sleeping sickness corresponds to the peculiar swaying and unsteadiness of the hind quarters of animals suffering from dourine or mal de caderas. Paresis may be found in any of these diseases, and the characteristic drowsiness of sleeping sickness is seen in horses, donkeys, dogs, monkeys or mice suffering from nagana.

The swelling of the lymphatic glands is no less constant in nagana than in sleeping sickness. Kanthack, Durham and Blanford, as well as Plimmer and Bradford, have laid special stress on the hypertrophy of the lymph glands in nagana, and especially about the region of inoculation. They have also shown that the swollen glands contain the parasites.

We have no definite knowledge of the temperature in sleeping sickness but in animals the temperature varies considerably according to the disease and the species inoculated. Nagana does not affect the temperature of rats, it gives rise to irregular fits of fever in rabbits, and produces a continued remittent fever in horses, dogs, and guinea-pigs. In dourine, the temperature of horses rises at first then becomes normal.

Digestive symptoms are absent alike in sleeping sickness and in the various trypanosoma-diseases of animals. The

papulo-vesicular eruption of sleeping sickness might be paralleled with the various skin eruptions of nagana and mal de caderas. A striking feature of nagana in the horse are the eye symptoms. There may be only a slight opacity of the cornea due to turbidity of the aqueous fluid in the anterior chamber, or complete blindness. In rabbits, the eye symptoms are also frequently marked. In cattle and dogs there may be some discharge from the eyes and nose, perhaps some opacity of the cornea, but never blindness. In cases of sleeping sickness, Corre, and others have noticed a similar opacity of the cornea.

The Tsetse Fly.

The discovery of a trypanosome in sleeping sickness suggests a very definite line of research with regard to the etiology, epidemiology and prophylaxis of this fearful disease.

We know that trypanosoma infection may be contracted either by direct contact (dourine), or through the intermediation of blood-sucking insects (nagana, surra, rat-trypanosomiasis). In dourine, or "Maladie du Coït," the disease is acquired, like syphilis, during sexual congress. Schneider and Buffard produced dourine in a bitch by simply smearing the vulva with blood containing *Trypanosoma equiperdum*. Subsequently two dogs covered this bitch, and both contracted the disease in about a fortnight. Nagana and surra are spread by blood-sucking flies. Major Bruce[33] proved that *Glossina morsitans* is a carrier of nagana in Zululand, and Rogers[34] found that a horse-fly (*Tabanus*) disseminates surra in India. *Trypanosoma Lewisi* is propagated amongst rats by the fleas peculiar to these rodents.

The heretofore limitation of sleeping sickness to West Africa, the peculiar patchy distribution of the disease along the large river valleys, its failure to spread in the West Indies, in South America, and in other countries, though frequently imported with negro slaves, and the probability

that, like nagana, it is caused by a trypanosome, suggest a fly of the genus *Glossina* as the carrier.

The genus *Glossina* comprises several species, some of which have a wide distribution in West Africa. The carrier of sleeping sickness should be sought amongst the latter.

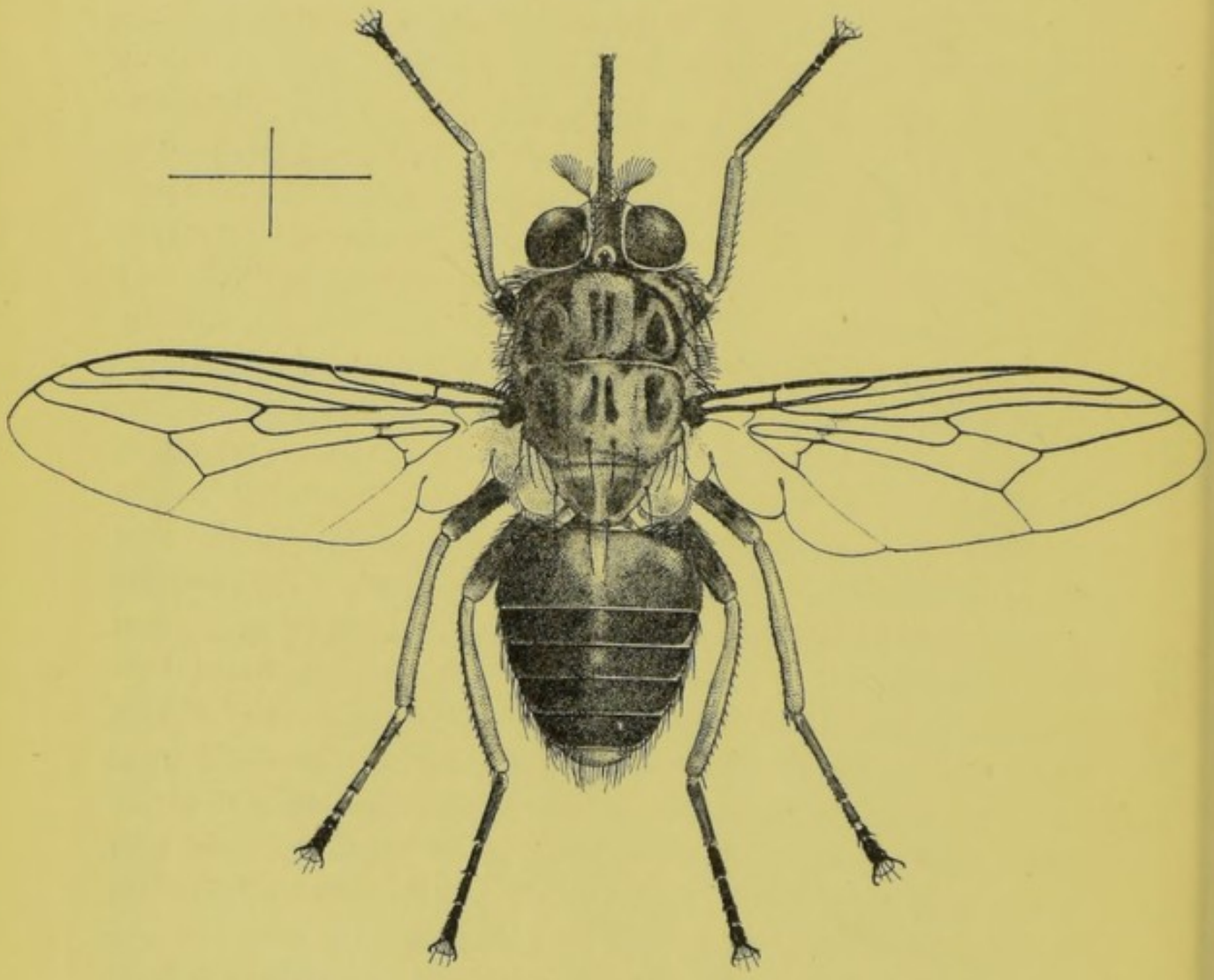

FIG. 3.—*Glossina palpalis*, a widely distributed West African species.

A most interesting and important point which, so far, has not been definitely ascertained is the manner in which the tsetse fly conveys the trypanosome.

In South Africa, nagana has long been known to Europeans as "the fly disease." In 1895 Major Bruce proved that tsetse flies are not venomous, but that, like

the cattle-tick (*Ripicephalus annulatus*) in Texas fever, they inoculate, with their bite, a deadly protozoal organism. By infecting susceptible animals in Ubombo with flies gathered in the low country where nagana prevails, Major Bruce was able to prove that the *Glossina morsitans* is a carrier of the distemper.

Taking into consideration that an animal suffering from nagana does not communicate the disease to other animals in places devoid of tsetse flies, and that both the distribution of the disease and the distribution of the tsetse flies show the same striking peculiarities, it may be reasonably surmised that other blood-sucking ecto-parasites are, as a rule, unable to convey the nagana flagellate. So far, very few experiments have been made to settle this point, and the various species of the genus *Glossina* have not been tested.

Major Bruce states that *Glossina morsitans* carries the nagana parasites from affected to healthy animals much in the same way as the vaccinating needle carries the infection of vaccinia from child to child. He further remarks that the fly is capable of inoculating living trypanosomes twelve, twenty-four and even forty-eight hours after having sucked the blood of an infected animal. I very much doubt that this can be the usual mode of transmission. If the tsetse fly acted merely in the way suggested by Major Bruce, it would be difficult to understand why the disease is not spread by other blood-sucking animals, such as mosquitoes, fleas and ticks, all of which are known to be capable of transmitting blood parasites.

I am inclined to believe that *Glossina morsitans* acts as a definitive host to *Trypanosoma Brucei* just like *Anopheles costalis* acts as a definitive host to *Hæmamœba Laverani*. Two important facts suggest this theory. First, the limitation of nagana to the so-called "fly belts"; secondly, the probability of a double alternating cycle in the life-history of the trypanosome.

The probability of a dual life-cycle in trypanosomes is not only suggested by the analogy of other parasitic pro-

tozoa, but by a very general law which limits the continuancy of growth by asexual reproduction, and, indeed, under certain conditions the trypanosomes are known to assume peculiar forms which may be the representatives of a sexual or resting stage.

In studying the natural history of the tsetse flies, I was struck by certain facts which I think may help us in elucidating the etiology and epidemiology of trypanosomiasis.

Major Bruce noticed that "the tsetse fly does not lay eggs as do the majority of the Diptera, but extrudes a

FIG. 4.—Puparium of tsetse fly.

yellow-coloured larva nearly as large as the abdomen of the mother. This larva is furnished with a black hood at one pole and two minute spikes at the other. It is annulated and consists of ten segments. Immediately on being born this larva creeps about with a good deal of activity, evidently searching for some cover or hole in which to hide. Having found a resting-place, it immediately begins to change colour, and after a few hours has turned into a jet-black hard pupa or nympha."

This description clearly shows that the method of reproduction in the tsetse flies is like that of the *Hippoboscidæ*, the eggs hatching, and the larvæ developing and moulting within the body of the parent, so that when extruded they have practically reached the pupa stage. In fact, the extruded larva becomes almost immediately a pupa, the larva skin becoming a hard *puparium*

The nourishment of the growing larva requires a large amount of food, and the avidity with which blood is imbibed by the gravid female is really astonishing. This peculiar mode of development suggests, I think, the possibility that the transmission of nagana may take place not directly by the fly that imbibes the blood of an infected animal but by its progeny. Several facts are in favour of this hypothesis. Like mosquitoes, the tsetse flies usually suck blood only once every two or three days. In the transmission of cattle hæmoglobinuric fever (Texas fever) by *Ripicephalus annulatus*, and in that of the malignant jaundice of dogs by *Hæmaphysalis Leachi*, we have examples of the transmission of protozoal parasites by the progeny of ticks fed on infected animals. The parasites in these two cases probably reach the young when the latter are in the egg stage, with the food reserve which is derived from the infected blood imbibed by the parent tick.

It has been stated by a number of travellers and sportsmen, and it is also the opinion of the natives, that the tsetse fly follows the big game, and that the prevalence of nagana in a district is proportionate to the number of wild animals. Indeed, it has been asserted that both the fly and the disease disappear as the game is killed off or driven away, and some people have gone so far as to urge the destruction of big game, and more especially of the buffalo, in order to protect imported domestic animals. Major Bruce has clearly proved that *Trypanosoma Brucei* affects in a comparatively harmless way the indigenous wild animals. Of thirty-five wild animals examined ten contained the parasite. These comprised one buffalo, three wildebeests, three koodoos, one bush-buck, and one hyena. It is also quite likely that the fly follows the herds within certain areas, and that it may settle for a time on its host. Major Bruce one day killed a wildebeeste and found a large number of tsetse flies on the dead animal. And again on a dead buffalo he counted as many as forty flies. However, we should not misunderstand the bearing of these facts,

because the distribution of the tsetse fly is in no way connected with that of big game. The tsetse fly is not found in open plains, although such plains may be literally swarming with game, and on the other hand, places devoid of game may be very dangerous "fly zones." The association between buffalo and tsetse is more apparent than real, both inhabiting densely-wooded, damp, secluded districts; and, indeed, tsetse flies occur in districts where there are no buffalo, and in these places, in which both formerly co-existed, the almost total destruction of buffalo by rinderpest has made no appreciable difference in the number of flies. The distribution of the tsetse fly shows marked peculiarities which exclude altogether the big game theory. The most important features are the invariable limitation to the borders of marshes or river-banks, and the formation of small, scattered stations, only a few hundred yards in extent, called "fly belts" or "fly zones." Sometimes the tsetse is confined to one side of a river in thousands, whilst on the opposite bank not one can be found. The constant association of the tsetse with streams, rivers, or other bodies of water, is, undoubtedly, a very important feature in the natural history of this fly, and one which needs investigation. The only explanation so far advanced to account for it is that the fly waits near water to feed on the animals that come down to drink! In Freetown, Mr. Austen[35] noticed that *Glossina palpalis* always occurred along the beds of streams, and frequently settled on stones projecting from the water. On one occasion he saw quite a number of these tsetse flies congregated on a fisherman's canoe.

The association between mosquitoes and water is very obviously explained by the fact that these Diptera have aquatic larvæ. In the pupiparous genus *Glossina*, the association with water can only be related to food-habits, and I venture to suggest that it may be related to the habit of feeding on fishes. This suggestion will probably appear extraordinary to some, but I will endeavour to show that it is quite

reasonable. In the first place, we know that certain blood-sucking flies can and do feed on fishes. Mr. C. H. Murray[36] saw mosquitoes alight and immediately transfix the fry of trout by inserting their proboscis into the head of the young fish as they came to the surface of the water. "I was so interested in this before unheard of destruction of fish," says Mr. Murray, "that I watched the depredations of these mosquitoes for more than half an hour, and in that time over twenty trout were sucked dry and their lifeless bodies sent floating away with the current. From this observation I am satisfied that great numbers of trout, and perhaps infant fish of other varieties in clear waters, must come to their death in this way." Mr. Theobald has observed a small blood-sucking fly, *Simulium reptans*, settled on the bodies of roach while these were lying on water-plants in shoals during the spawning season.

Turning now to the fish of the African rivers and lakes, we find that the suggestion of an association between tsetse flies and fish is supported by the peculiar habits of various fish belonging to the great family of *Siluridæ*, which, according to Mr. Boulenger,[37] is represented in Africa by twenty-nine genera comprising no less than a hundred species. The Siluroids are characterised by having a naked skin and two or more long feelers or barbels on each side of the mouth. The genera *Synodontis*, *Clarias*, *Clariallabes* and *Channallabes* are of special interest to us; they are found very abundantly all over tropical Africa. The siluroids of the genus *Synodontis* have the curious habit of swimming on their backs with the belly above the surface of the water as if they were dead. In one species (*S. membranaceus*) this habit appears to have brought about a reversion of the coloration, which is dark on the abdomen and light on the back. The fish belonging to this genus can lead an amphibious life, and it is stated that occasionally they feed on grain. Even more interesting are the siluroids of the genera *Clarias*, *Clariallabes* and *Channallabes*. During the dry season, when there is no longer any water in the meres

they inhabit, these fish live in burrows, like rabbits, coming out towards evening in quest of food. The flesh of these siluroids is much esteemed by the natives, and the women go and dig them out of their burrows.

Fish is an important article of food throughout tropical Africa, not only amongst the riverside populations, but also amongst the inland tribes which barter it with manioc, bananas, or charcoal. The fish is usually parboiled in palm oil, and eaten with baked manioc leaves. Much of it is smoked, then kept in baskets and eaten raw.

Having thus suggested a possible connection between fish and tsetse flies, I will draw attention to the fact that trypanosomes are very common parasites amongst fish. They have been found chiefly in freshwater fish, but quite recently Laveran and Mesnil[38] found them in soles (*Solea vulgaris*) and rays (*Raja punctata* and *R. mosaica*) from the British Channel. Lingard, who examined the freshwater fish of India, states that trypanosomes are especially common amongst those species which live in the mud. It is also important to remark with Laveran and Mesnil that the trypanosomes of fish are strikingly like those of mammals, and very different from those of the closer related Batrachians.

Lastly, to connect the above observations with sleeping sickness, I will point out that the natives of various parts of Africa believe fish to be the cause of the dread disease. Thus, while the Sussus or Sossé (south of the Pongo river) ascribe sleeping sickness to the sting of a fish, the Congo negroes believe it to be due to the consumption of diseased fish with swollen gills.

Another theory somewhat prevalent amongst natives is that infection takes place by means of the saliva of the patient. The natives always eat with their hands out of the same family dish and lick their fingers after each mouthful. A similar theory is held with regard to nagana, the diseased animals are supposed to contaminate the grass or drinking water by their saliva. This mode of infection is also in

accordance with the trypanosoma theory of sleeping sickness, because we know that dourine can be acquired by direct contact with the secretions of the œdematous genital mucosæ. But, in sleeping sickness, direct contact is certainly not the usual means of transmission. On the other hand, dourine is probably also inoculated by blood-sucking insects.

In sleeping sickness the glands most frequently enlarged are those of the neck. In connection with this, it is interesting to remark, that it is precisely on the neck and behind the back between the shoulders that the fly most frequently bites man. Of course it may bite any exposed part, and the naked legs of the natives are frequently assailed. Horses and cattle are sometimes bitten on the back, but preferably inside the thighs, beneath the belly or below the tail. The tsetse darts suddenly on its hosts, making a loud buzzing noise. Its flight is rapid and straight. The tsetse will bite at any time, but (according to Bruce) preferably at sunset. It is known to bite by moonlight. In man the bite causes a sharp prick which draws one's attention suddenly to the spot, but the pain is trifling and the subsequent swelling and irritation very slight.

Prevention.

I fear that for the present in sleeping sickness Ιατρος ἰᾶται Θανατος. The physician that cures is death. Numerous remedies have been tried, but they were suggested by erroneous theories, and have proved invariably useless. The natives have no better treatment; they administer cathartics and diaphoretics, but in early cases they sometimes extirpate or cauterise the swollen glands to prevent the further progress of the disease. This bold surgical interference is common to various populations in West Africa and deserves investigation.

In 1873, in a letter to Dr. J. W. Ogle, Dr. M'Carthy,[39] Assistant Surgeon at Accra, says: "In every case of 'sleeping sickness' there is invariably a chronic thickening of the

deep cervical glands of the neck. I mean those glands commonly called the 'glandula concatenata,' and which form a chain from the base of the skull to the clavicle. The treatment adopted by the native 'doctors' consists in removing these thickened glands. I have never seen the operation performed, but it is said to be always followed by cure. In one man I counted no less than thirteen cicatrices in the neck."

Surgeon-Major Gore[40] says: "I had just returned from shooting, when a native was brought to my bungalow with an enlargement of the glands of the neck, which he was anxious to have removed. My servant, a Portuguese, informed me that he stated he was afraid he was about to get the 'sleeping sickness.' Upon further inquiry I found that this was really the case, and that among the people of the neighbourhood (Portuguese Senegambia) this enlargement of the glands was considered a premonitory sign of African lethargus. My servant, who appeared to be quite *au fait* with the subject, further informed me that the native doctors always excised or destroyed the enlarged lymphatic glands as a measure of prevention, a process accounting for the many scars which marked the necks and other parts of the bodies of their patients."

According to Corre, the natives of Rio Nunez distinguish two forms of sleeping sickness. One form they ascribe to the poison of a plant known to the sorcerers only—it is, of course, incurable—the other they connect with the enlargement of the lymphatic glands, and believe it can be cured by the cauterisation or extirpation of the swollen glands.

Possibly, during the long period of incubation, the virus of sleeping sickness remains shut up in the lymphatic glands, and only becomes destructive when, under certain obscure conditions, it is set afloat in the circulation. This seems to be the case in hydrophobia, the characteristic stage of the disease being always preceded by irritation, pain or numbness about the part bitten, weeks, months, or years before by the rabid dog.

The natives unanimously believe that sleeping sickness is a communicable disease, and in accordance with this opinion they usually isolate the patients, especially in the more advanced stages of the disease. Dangaix tells us that, in his time, slave-dealers invariably isolated any slave that showed symptoms of the disease. And even in Uganda, where the disease has only recently appeared, we see the natives attempting a primitive form of isolation. Dr. Hodges tells us that they drive away into the bush such persons as are suspected of having the dread disease, and that "they have hitherto hidden their sick from the sight of Europeans, probably from the unfounded fear that they themselves may be likewise driven away or disturbed on account of sickness among their people. Even now (at the time of the expedition), in spite of its prevalence, all signs of sleeping sickness might easily escape a casual observer passing through the country. It is only when the poor creatures are stimulated by the hope of medicine or cure, that the sad crowds emerge from their huts and enclosures, or from their improvised shelters in the jungle."

The trypanosome theory of sleeping sickness suggests: (1) The extermination of tsetse flies by suppressing the conditions favourable to their increase; (2) the prevention of tsetse fly bites either by avoiding the "fly zones" or by using appropriate covering; (3) the screening of patients, or their removal from the fly country, to prevent a wider infection of tsetse flies; (4) the careful avoidance of infection by the saliva and other secretions of the patient.

But whatever may be the cause of sleeping sickness, the segregation of patients in suitable camps, and under proper supervision, would be far more humane and judicious than their dispersal in the bush. The spread of sleeping sickness is a serious menace to the development and prosperity of the great African continent, and no pains should be spared, no money withheld, no stones unturned in order to elucidate as soon as possible the etiology of this formidable disease.

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