THE ELUCIDATION OF SLEEPING SICKNESS.

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Sleeping sickness has been known to Europeans for over a century, but until quite recently we had no definite knowledge of its etiology. It was believed to be strictly confined to the negro race, and was looked upon as a peculiar form of nostalgia. At times, it caused considerable losses to the slave-traders of the West Coast, notwithstanding the careful isolation of the sick and the weeding-out of all such as presented glandular swellings about the neck. When any of the slaves showed symptoms of the disease on transport ships, they were mercilessly thrown overboard; some developed the malady long after transportation, and died of it in the plantations of the Antilles. But the disease never spread in the places to which it was imported, and therefore it did not give rise to any serious apprehension.

Within the last few years, 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. 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 Africa, invading the shores and islands of the Victoria Nyanza.

Along the right bank of the Quanza, on the Upper Congo, round the northern and eastern coasts of Lake Victoria, the ravages of the dread disease have already been appalling. In many places entire villages have been depopulated.

The appearance of sleeping sickness in the very heart of Africa—the possibility of its spread along the Nile to Egypt, or by way of the coast to India; its terrible, inexorable deadliness—called for immediate and judicious action.

At the instigation of the Foreign Office, a Commission was appointed by the Royal Society to proceed to Uganda, for the purpose of investigating the cause of sleeping sickness. The Commission consisted of Drs. George C. Low,

Aldo Castellani, and Cuthbert Christy. It left London on June 10th, 1902.

In accordance with the instructions received, Dr. Low undertook to ascertain whether *Filaria perstans* had anything to do with the disease. He examined over 3000 natives, some in areas where sleeping sickness was rife, others in areas from which it was absent, and in which it had never been known; and he definitely proved that there was no causal connection between *Filaria perstans* and sleeping sickness.

Dr. Christy studied the distribution of the disease. He found that it did not prevail all over Uganda and Busoga, as reported, but that it was strictly confined to a narrow strip along the coast-line of the Victoria Nyanza, from the Kotanza river right across to Kissumu. There, it skipped a small portion, and then extended to the Gori river. The infection area did not extend for more than 10 miles from the shore. Cases beyond this limit were very rare, and the patients had always a history of having come from the lake shore. The affected area included all the islands, many of which were taxed severely. Dr. Christy made a trip to Buvuma Island, and there mapped all cases in the places in which they occurred. The dots on the map showed that the distribution of the disease on the island corresponded to the general distribution of sleeping sickness. It was confined to the coast-line overgrown with bush, chiefly bananas. Dr. Christy also noticed that there was no connection between *Filaria perstans* and sleeping sickness. He observed that the disease extended about 150 miles beyond the extreme limit of *Filaria perstans*.

Meanwhile, Dr. Castellani isolated a *Streptococcus* from the blood and cerebro-spinal fluid of patients suffering from sleeping sickness. At first he conjectured that this bacterium might be the cause of the disease, but later he noticed that it was found rarely during life, and then only in the last stages.

On November 12th, 1902, while examining some cerebro-spinal fluid, obtained from a case of sleeping sickness by means of the lumbar puncture performed during life, Castellani discovered a *Trypanosoma*. At the moment, he did not attach much importance to this finding. He considered the presence of the flagellate a mere coincidence, and thought that it had probably arisen from admixture of blood during puncture. Subsequently, however, he observed that trypanosomes, though always few in number, were of frequent occurrence in the cerebro-spinal fluid of patients suffering

from sleeping sickness; and he communicated his discovery to Drs. Moffat and Baker, and afterwards to Lieut.-Colonel Bruce, as soon as the latter arrived in Uganda.

Dr. Castellani's discovery was followed up very rapidly by a number of observers; and thus, in a twelvemonth, the etiology and epidemiology of sleeping sickness have been almost entirely worked out, and the deadliest scourge of Africa is under the heel of the white man's foot.

The history of this discovery is a most brilliant proof of the exactness of modern scientific medicine; and the famous boast, "*Veni, vidi, vici!*" could not find a more appropriate application.

Although we are indebted to Dr. Castellani for the discovery of the *vera causa* of sleeping sickness, it is but fair to state that the complete elucidation of the disease has been the work of numerous observers; and we should not forget the researches of the old English and French surgeons who gave us the first accounts of the malady, any more than the latest and most important investigations by Bruce, Brumpt, and Manson. Our modern triumphs have deep roots, not only in the discoveries, but also in the mistakes of the past. The old dictum, "*Errando discitur*," applies to the advancement of science just as truly as it applies to the experience of life.

So far as I know, the first to describe sleeping sickness was Dr. T. Winterbottom, in *An Account of the Native Africans in the Neighbourhood of Sierra Leone*, which he published in London exactly a hundred years ago. Then followed Papers by Clarke, Dangaix, Nicolas, Gaigneron, Karl, Griffon du Bellay, and Santelli, who described fairly well the symptoms and the coarse anatomical features of the disease.

In 1869, Dr. P. A. Guérin published an excellent thesis on sleeping sickness. During a period of about twelve years in Martinique, Guérin had the opportunity of studying 148 cases of the disease in Negroes imported from the Congo. In some cases the period of incubation lasted five years, or more. The disease did not spread to the black Creoles of the Antilles; neither did it spread to other Congolese who had been in the colony some forty years. In his Report to the Royal Society, Dr. Christy questions the correctness of Guérin's observations; but his criticism is futile. Besides, as he owns himself, he read only a summary of Guérin's Paper in the *Archives de Médicine*. The so-called incubation period of sleeping sickness, like that of hydrophobia, may certainly extend over a period of two,

three, or more years. A case occurred in England in a Congo boy, who had resided in this country for three years without showing any particular signs of unhealthiness.

In 1876 and 1877, Dr. A. Corre published some very interesting Papers on sleeping sickness. Corre had made a special study of the disease in the severely-affected districts of Joal and Portudal in Senegambia. He laid special stress on the paludal nature of the sleeping sickness centres, and remarked that the disease may attach itself to a particular house or to a particular group of houses. He referred that a number of patients believed they had contracted the disease during the rainy season. In his first Paper, Corre 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. Corre gave an admirable description of the symptoms of the disease. He noticed that, in most cases, a regular evening rise is the characteristic temperature ; he also noticed an opacity of the cornea in some cases.

In 1891, while examining the blood of a case of sleeping sickness under the care of Sir Stephen Mackenzie in the London Hospital, Sir Patrick Manson discovered the larvæ of a new filaria, which he named *Filaria perstans*, because of the constant presence of its young in the peripheral circulation. Subsequently, he found the larvæ of *Filaria perstans* in films of blood obtained from cases of sleeping sickness on the Congo ; and, in 1898, he again found them in two cases of sleeping sickness which Dr. Grattan Guinness brought over to England for the purpose of study, and which were admitted into Dr. Abercrombie's ward at Charing Cross Hospital. Struck by the constant presence of these blood-worms in cases of sleeping sickness, and by the singular corespondence which seemed to exist between the geographical distribution of sleeping sickness and that of *Filaria perstans*, and paralleling the long incubation period of sleeping sickness with the fact that *Filaria perstans* can remain alive within the body of its host years after the infection area has been quitted, Manson suggested that this Filaria might possibly be the cause of sleeping sickness. When it became evident that *Filaria perstans* was present not only in cases of sleeping sickness, but also in a large proportion of the normal inhabitants of the Congo and of other parts of West Africa, Manson still held to his hypothesis, because it was supported by the pathology of *Filaria bancrofti*. In fact, *Filaria 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 *Filaria perstans* in British Guiana was decidedly 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 wrote that he believed sleeping sickness to be amongst their ailments; indeed, he stated that a Buck woman was brought to him for treatment, because, as her friends said, she was always asleep.

Low's recent researches in British Guiana, and the numerous and accurate observations he made in various parts of Uganda, have definitely proved that there is no causal association between *Filaria perstans* and sleeping sickness.

Drs. Hodges and Wiggins had already shown, before the Commission arrived in Uganda, that, though sleeping sickness was very prevalent in the Kavirondo Islands, *Filaria perstans*, on the other hand, was very rare. Besides, the distribution of *Filaria perstans* is very wide throughout intertropical Africa, wherever the œcological conditions are favourable. But all this information is very recent.

The suggestion that *Filaria perstans* might be the cause of sleeping sickness has proved erroneous; but the suggestion was very reasonable; and, indeed, it led to the discovery of the true cause of the disease, just as an analogous mistake led to the discovery of America.

Other nematodes have been incriminated as causative agents in sleeping sickness, but on very poor grounds. Forbes ascribed the disease to *Strongyloides intestinalis;* Fergusson to *Uncinaria duodenalis.* Both worms have a very wide distribution. *Uncinaria* is almost cosmopolitan.

It would be idle to discuss the various theories put forward by the older authors 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-traders and planters. Others ascribed it to malaria, to sunstroke, to amenorrhea, to inanition, to the immoderate drinking of palm wine, to the eating of raw manioc, or to the smoking of Indian hemp.

The food-intoxication theory, suggested first by Corre, then again by Pereira do Nascimento and Calmette, was revived last year by Ziemann, who ascribed 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. In controverting Ziemann's theory, I must begin by stating that his premise is wrong. 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 an analogous poison in 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, certainly they 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 and topographical distribution of sleeping sickness. Another reason against the manioc theory is the occurrence of sleeping sickness among Negroes far and long removed from the endemic centres of the disease, as in the West Indies and in Europe.

Various kinds of bacteria have been described in connection with sleeping sickness, and claimed to be the specific agents of the disease. In 1897, Cagigal and Lepierre found a bacillus in the blood of a case of sleeping sickness imported 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, who procured a culture of the bacillus, were unable to confirm these observations.

In 1899, Marchoux suggested that *Fränkel's diplococcus* might be the cause of sleeping sickness. He performed the autopsy of one case of the disease at Saint Louis (Senegal) and found a *Diplococcus* on the pericardium, but was unable to detect its presence within the cerebro-spinal system. Pneumonia was very prevalent at the time.

In 1901, Broden examined several cases of sleeping sickness at Leopoldville (Congo), and found in the blood and in the cerebro-spinal fluid (*post-mortem*) a bacillus which grew abundantly on potatoes. This bacillus, possibly *Bacillus solanacearum*, 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 isolated a *Streptococcus* from the cerebro-spinal fluid obtained by means of

the lumbar puncture performed during life, or *post-mortem*. The lumbar puncture was performed in nine cases. In six of these it gave positive results, the bacteria being easily isolated; in the other three, both the examination of the direct preparations and of the cultures gave negative results. The *streptococcus* was also found in the blood and in the lymph glands.

Castellani also found a *streptococcus* in the blood and cerebro-spinal fluid of patients suffering from sleeping sickness, but 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 cerebro-spinal 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.

Probably, Castellani's *streptococcus* is identical with the microbe described by the Portuguese Commissioners. The latter 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. After Castellani's publication, however, they modified their statements, and affirmed that their *streptococcus* grows very well on gelatine.

Castellani believes that the *Streptococcus* he has found in cases of sleeping sickness is merely a variety of *Streptococcus pyogenes*. He is inclined to think that this organism may play a part in the etiology of sleeping sickness, similar to that of the *streptococci*, associated with the complications of scarlet fever and rheumatic polyarthritis.

The bacteria so far described in connection with sleeping sickness have probably no casual connection with the disease; they are seldom found in the early stages of the disease; they are often absent in the last. The two cases of sleeping sickness which were brought to London in 1898 were very carefully examined with regard to bacteria. Dr. Bullock 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 ordi-

nary micro-organisms were contained in the blood or glands. At *post-mortem* the cerebro-spinal fluid was examined for micro-organisms by cultures, etc., and various organisms, including *diplococci, streptococci,* and *bacilli* were found; but, of course, no importance could be attached to these observations.

The question of the *rôle* played by *streptococci* in scarlet fever and other infections is a very difficult one, and recent researches by Aronson and others show that we are further than ever from its solution.

A very important step in our knowledge of sleeping sickness was the study of its minute anatomical features. The first detailed microscopical examination was that which Regis and Gaid published in 1898. These authors correctly 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, Dr. Frederick Mott 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 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, especially on account of starvation. 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 sub-archnoidal space. In some rapid cases the exudation may be considerable in amount. As a rule, it is slightly turbid, but never purulent unless the disease be complicated by *streptococcic* invasion. 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 cerebro-spinal fluid may be slightly turbid, but seldom in excess. The ventricles are rarely dilated.

The brain-substance is of normal consistence, and, as a rule, 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 vesssels.

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 toxin.

Castellani's discovery of a trypanosome in the cerebro-spinal fluid of patients suffering from sleeping sickness marked a new era in the study of this fearful disease, and suggested a very definite line of research with regard to its etiology, epidemiology, and prophylaxis.

For some years trypanosomes had been the object of very active researches, and a large amount of knowledge had been accumulated. Castellani's discovery brought all this knowledge to bear on sleeping sickness; and, thus in less than a year, the elucidation of sleeping sickness becomes the boast of modern scientific medicine.

The genus *Trypanosoma* was established by Grubey in 1843; but the wimble-like *hæmatozoa*, included in this division, were first described in 1841 by Valentin, who discovered them in the blood of a trout (*Salmo fario*), and the following year by Gugge, who found them in frogs. Since then numerous species have been described from fish, batrachians, and birds.

The first to find these parasites in mammals was Dr. Timothy Lewis, who, in a sadly short career, has so largely contributed to the advancement of Tropical medicine. Lewis found them in 1879 at Calcutta, in the blood of rats (*Mus decumanus* and *Mus rufescens*). The rat-trypano-

some, very appropriately called *Trypanosoma lewisi*, has a world-wide distribution corresponding with the cosmopolitanism of its mammalian host. But its prevalence varies greatly in different localities. The researches of Rabinowitsch and Kempner, and those of Laveran and Mesnil, have greatly advanced our knowledge of this flagellate. Similar parasites have been found in hamsters, guinea-pigs, rabbits, and other rodents.

In 1880, in the Punjab, Griffith Evans discovered in the blood of horses a trypanosome of a far greater pathological importance. The horses examined by Evans were suffering from Surra, a disease known to the natives of India from time immemorial, and ascribed by them to the bite of certain *Tabanidæ*. The Surra parasite (*Trypanosoma evansi*) is not limited to horses and mules, but attacks also camels, elephants, buffaloes and dogs. Experimentally it has been transferred to monkeys, rabbits, rats, mice and guinea-pigs. "Surra" has a very wide distribution in Southern Asia and in Malaya. It has been described by the Germans in East Africa, and, quite recently, by the Americans in the Philippine Islands. Evans was favourable to the popular opinion which ascribed the transmission of the disease to certain blood-sucking flies; but subsequent authors, and especially Lingard, considered food and drinking-water to be the true vehicles of the infection.

The discovery of a trypanosome in Surra, the fly-disease of India, was followed by the discovery of a trypanosome in Nagana, the fly-disease of Africa.

The fly-disease of Africa has been known as long as the fly-disease of India. James Bruce, in his famous *Travels to Discover the Source of the Nile*, mentions a blood-sucking fly, probably a tsetse fly, under the name of "Tsaltsalya," or "Zimb," and describes its terrible ravages amongst horses and cattle, during the rainy season, on the Upper Atbara river, on the confines of the Sudan and Abyssinia. In South Africa "Nagana" has long been known to Europeans as the "Fly-disease."

Dr. Livingstone, in his *Missionary Travels and Researches in South Africa*, gives much information regarding tsetse flies and the disease they inoculate. After describing the symptoms of Nagana, he very correctly says: "These symptoms seem to indicate what is probably the case—a poison in the blood, the germ of which enters when the proboscis is inserted to draw blood. The poison-germ, contained in a bulb at the root of the proboscis, seems capable, although very minute in quantity, of reproducing itself."

In 1879, Dr. J. J. Drysdale, after referring to Manson's discovery of the transference of *Filaria bancrofti* by mosquitoes, says :—"It is possible that we have here an explanation of the destructive power of the tsetse fly, for it may be the intermediate host of some similar blood parasite; or it may be the carrier of some infective poison. It is highly improbable that any mere poison or venom should exist so powerful as to cause the death of a large animal in such small dose."

A Swiss entomologist named Schoch, in 1883, and A. Laboulbène, in 1888, again expressed the opinion that the tsetse is not poisonous in itself, but that it acts as a carrier of pathogenic micro-organisms.

In the short time at my disposal it would be impossible for me to mention the numerous authors who have contributed to our knowledge of the African fly-disease. These authors described very accurately the symptoms of Nagana —its coarse anatomical lesions, its peculiar distribution, the immunity of local wild animals, the structure, distribution, and life-habits of its carrier, the tsetse fly.

At last, in 1895, Surgeon-Major—now Lieut.-Colonel—David Bruce went to Zululand to investigate Nagana, and found that the specific parasite of the African horse-disease was a trypanosome similar to the one found by Evans in Surra fifteen years previously. Drs. Kauthack, Durham, Blanford, Plimmer and Bradford made a more complete study of the parasite, and the latter two named it *Trypanosoma brucei*. Then followed numerous investigations by Laveran and Mesnil, by Koch, by Rabinowitsch and Kempner.

Lieut.-Colonel Bruce made several experiments to prove that the disease was transmitted from infected to normal animals by means of the bite of tsetse flies. This point, however, had already been investigated some time ago. In fact, in 1857 Livingstone wrote: "The curious feature in the case—that dogs perish, though fed on milk, whereas the calves escape so long as they continue sucking—made us imagine that the mischief might be produced by some plant in the locality, and not by the tsetse. But Major Vardon, of the Madras Army, settled that point by riding a horse up to a small hill infested by the insect without allowing him time to graze; and though he only remained long enough to take a view of the country, and catch some specimens of tsetse on the animal, in ten days afterwards the horse was dead."

In Southern Europe, and right round the Mediterranean

basin, we also find a trypanosome infection peculiar to horses, and known since the beginning of the nineteenth century under the names of Dourine and *Maladie du coit.* The parasite *Trypanosoma equiperdum* was first discovered by Chauvrat in 1892.

Another trypanosome disease of horses is the *Mal de caderas,* which ranges over a wide area in South America. The parasite was discovered in 1901 by Dr. Elmassian, an old student of the Institut Pasteur. Voges gave it the name of *Trypanosoma equinum.*

To complete the list of trypanosomes so far described in the domesticated mammals, I must mention the large trypanosome found by Theiler in 1903, in the so-called "gall-sickness" of South African cattle, and named by Colonel Bruce *Trypanosoma theileri.*

A very important question is to determine whether these variously-named and variously-distributed diseases are distinct morbid entities or not.

The "gall-sickness" of South Africa appears to be a specific disease affecting only cattle. Its parasite, *Trypanosoma theileri,* attains greater dimensions (30—65 μ) than the other trypanosomes.

We should not forget, however, that the same species of *trypanosoma* may present very different dimensions in different host-species. Thus, *Trypanosoma brucei,* which measures about 26 μ in the rat, attains a length of from 28 to 33 μ in the horse.

Mal de caderas seems likewise to be a separate disease. Its parasite *Trypanosoma equinum* is easily distinguished from the other trypanosomes by the fact that its micronucleus is almost invisible on account of its very small size and does not acquire a deep colouration in stained specimens, but stains faintly, like the flagellum.

As to the trypanosomes of Surra, Nagana, and Dourine it is not possible to distinguish them morphologically Dourine seems to differ somewhat symptomatically from Surra and Nagana. Dogs may recover from its attacks, and the animals which have acquired immunity against Dourine are not immune to Surra or Nagana.

Surra and Nagana are strikingly alike. They affect the same animals, they give rise to the same symptoms, they cause the same anatomical lesions. Their identity, suggested by Koch, Schilling and Rogers, seems, therefore, quite possible.

In distinguishing between trypanosomes, much importance has been attached to experiments of inoculation into

other animals; but we should not forget the frequent fallaciousness of such experiments. Different investigators have often obtained opposite results. Different species of oxen, horses, or dogs may exhibit a very different degree of susceptibility. Then again the passage of the parasite through certain animals may greatly alter its virulence, and even modify its aptitude for the original host. This all-important fact, which has been thoroughly ascertained in the laboratory, should not be lost sight of in epidemiological investigations.

It is a general law in parasitism that parasites become more and more adapted to the host-species they repeatedly inhabit. In time, they become so specialised—so greatly modified and changed—that they are absolutely dependent upon such hosts, and are unable to thrive in any others. Sometimes the limitation to certain hosts is not associated with any apparent structural change; and naturalists have proposed to call "biologic species" those species which cannot be distinguished by morphological characters.

An example, which shows how such limitations may arise, is that of the stem eel-worm (*Tylenchus devastatrix*). This nematode lives and reproduces in various cultivated plants, such as rye, oats, stored onions, hyacinths, buckwheat, potatoes, and clover; and in wild plants such as *Poa annua*, *Anthoxanthum odoratum*, *Dipsacus silvestris*, and *Polygonum persicaria*, but not to the same extent in all. However, eel-worms of which the progenitors have developed for many years exclusively in rye and buckwheat are not easily transferred to another kind of plant; or, at any rate, they do not multiply vigorously there.

Various blood-sucking insects have been incriminated as carriers of the different trypanosome infections, but the information so far at hand is very scanty and most unsatisfactory. Rat-fleas are believed to be the carriers of *Trypanosoma lewisi*, because living trypanosomes have been found in the mid-gut of these insects. McNeal and Novy saw living specimens of *Trypanosoma lewisi* in the stomach of rat-lice. Dourine is generally believed to be acquired by direct contact with the secretions of the œdematous genital mucosae of infected animals; but Rabinowitsch and Kempner found the trypanosomes of Dourine in the stomachs of fleas. They think, therefore, that Dourine may be also due to the agency of blood-sucking insects. For the Surra trypanosome certain horse-flies (*Tabanidae*) have been incriminated by Rogers as its carriers in India. Curry found the Surra trypanosome of

the Philippines in the mid-gut and proboscis of *Stomoxys calcitrans*. In 1898, Captain A. C. Haslam, at Machakos, found the living trypanosomes of Nagana in the stomach of specimens of two species of *Stomoxys*, caught sucking the blood of mules suffering from the disease. Lignières found the trypanosomes of *Mal de caderas* in the stomach of *Stomoxys calcitrans*, and Sivori and Lecler stated that they allowed sound horses to be bitten by these flies, and obtained positive results. Lignières, however, was unable to obtain infection of horses with *Mal de caderas*, by means of either *Tabanidae* or *Stomoxys calcitrans*. Lastly, Theiler found living trypanosomes in the stomach of specimens of *Hippobosca rufipes* and *Hippobosca maculata*, fed on cattle suffering from "gall sickness." He decided, therefore, to try the infection of cattle by the medium of the fly's bite. For this purpose some flies were fed on the groins of an infected calf, and then placed on a healthy animal. To give the experiment every chance of success, the place where the flies were put to feed was first shaved, as was also the spot on the normal animal where they were placed for infection. Feeding by turns on a sick and on a clean animal was thus repeated several times. Out of four experiments made in this way, two were successful.

Turning now to the discovery of trypanosomes in man, we find that the first to describe trypanosomes in man was Dr. Nepveu.

Dr. Nepveu found these flagellates in Algeria, in 1890, while studying malaria parasites. In a paper published on December 24th, 1898, in the *Comptes Rendus des Séances de la Société de Biologie*, he says: "This trypanosome presents all the characters of the genus; general shape, a homogeneous colourless membrane, one border of which is thinner, hyalin, and presents characteristic undulatory movements. This membrane bears a nucleus, and a slender flagellum which is placed anteriorly, and the undulations of which follow in rapid succession." Nepveu describes segmentation forms with two flagella at one of their extremities, and correctly considers them to represent a developmental stage of the trypanosome. "In conclusion," he says, "trypanosomes must be classed amongst the parasites of human blood."

On May the 10th, 1901, at Bathurst, Gambia, Mr. R. M. Forde, while examining the blood of a patient suffering from an anomalous form of fever, discovered some small worm-like, actively-moving bodies, the nature of which he was unable to ascertain. The patient, master of a

Government steamer on the Gambia, went home on sick leave, and on August 12th entered the Royal Southern Hospital, Liverpool, where he suffered from "three short periods of pyrexia," and other symptoms. Here Dr. J. Everett Dutton examined his blood for malarial parasites on two occasions, with negative results. Having considerably improved, the patient returned to Bathurst in the early part of December, 1901. At about the same time, Dr. Dutton also arrived at Bathurst, and Mr. Forde asked him to examine the blood of the patient once more, because he was sure it contained some extremely active worm-like bodies, which might prove of great pathological interest. On doing so, Dr. Dutton, who had previously found nothing in the patient's blood, now succeeded in detecting the parasite, recognised it to be a trypanosome, and named it *Trypanosoma gambiense.*

To Mr. Forde we are indebted not only for the discovery of trypanosomes in Gambia, but also for the first description of the symptoms peculiar to the early stage of *Trypanosoma* infection.

The description of the parasite and the clinical symptoms of Forde's patient were published first by Dr. Dutton in the Thompson-Yates Laboratory Reports, and later by Forde himself in the *Journal of Tropical Medicine.*

On October 3rd, 1902, Sir Patrick Manson examined a lady, the wife of a missionary who had just returned from Monsambe on the Upper Congo. Struck by the fact that the symptoms presented by this patient (daily recurring fever, enlarged spleen, patchy œdema, erythema multiforme) closely resembled those he had noticed two months previously in Forde's case, he made a provisional diagnosis of *Trypanosoma* fever, Manson's diagnosis was subsequently confirmed by Dr. Daniels who, after a long search, found trypanosomes in the blood of this patient.

Other cases were soon afterwards described by Drs. Broden and Brumpt on the Congo. Meanwhile, a commission consisting of Drs. J. E. Dutton and J. H. Todd was despatched to the Gambia by the Liverpool School of Tropical Medicine, to ascertain the extension and prevalence of the disease in the colony. Dutton and Todd examined over a thousand persons, and found the parasite in six natives and one white man (quadroon). The history and clinical examination of the native cases revealed nothing important. In the younger cases the usual enlargement of the spleen was met with. Enlargement of the lymphatic glands was present in some, but not in

others; parasites were very scanty. The disease, as it occurred in natives, was a peculiarly mild one. This absence of marked clinical features in natives corroborates Nepveu's observations, because the latter failed to recognise in his patients any symptoms characteristic of *Trypanosoma* infection. I mention this because, in an article contributed to the *Lancet* on February 21st, 1903, Professors Boyce, Ross and Sherrington endeavoured to disprove Nepveu's observations, and pointed to the latter's statement of the non-pathogenetic nature of the parasites as a strong argument against the veracity of his observations.

Drs. Dutton and Todd examined various animals in Gambia, to ascertain whether any were infected by trypanosomes, but this parasite was found only in horses. Out of thirty-six horses examined ten were infected. The symptoms noticed were: loss of vigour, periodical rises of temperature, marked emaciation, and, at times, a slight watery discharge from the eyes. The diseased animal wore an apathetic, chronically-tired expression which was most characteristic. In none of these horses did they observe the marked œdemas and the changes in the coat described as characteristic of Nagana. There was a general enlargement of all the lymphatic glands.

No morphological distinction could be made between *Trypanosoma gambiense* and the horse trypanosome. Therefore, it was impossible to decide whether the parasites found originally in the horse and man were the same or different. Several experiments of inoculation into lower animals were made with both parasites. These experiments seemed to indicate a marked distinction between *Trypansoma gambiense* and the horse parasite.

As soon as Castellani discovered a trypanosome in the blood and cerebro-spinal fluid of patients suffering from sleeping sickness, the idea of a fly as the carrier of the infection came very naturally to all those who had any knowledge of *Trypanosoma* diseases.

The first to publish any definite opinion on the matter were Dr. Brumpt and myself. It would be idle to discuss priority in the matter. I expressed my views in a lecture on sleeping sickness, delivered at the Livingstone College, and subsequently published in the *Journal of Tropical Medicine* of July 1st, 1903. Dr. Brumpt's observations were published on July 2nd. However, the idea came to both simultaneously and independently the day we learnt that a trypanosome was possibly the cause of sleeping sickness.

Dr. Brumpt incriminated *Glossina morsitans*; I suggested a West African species, and more especially the widely-distributed *Glossina palpalis*; but I attach no great importance to this, because Brumpt was in the wilds of the Congo, and therefore unable to identify his specimens. Besides, various species of the genus *Glossina* may be capable of transmitting sleeping sickness just as various species of the genus *Anopheles* are able to disseminate sub-tertian fever. Our respective communications did not merely suggest the possibility of a *Glossina* as the carrier of sleeping sickness, because a trypanosome had been described in connection with sleeping sickness, and because Nagana was known to be disseminated by a *Glossina*; but, inversely, they were intended to support Castellani's discovery by a number of facts gleaned from a careful study of the distribution and life-history of tsetse flies, as well as of the distribution and epidemiology of sleeping sickness.

At first, Castellani's discovery met with little favour in this country. At the last meeting of the British Medical Association, in Swansea, when the subject of trypanosomiasis was thoroughly discussed, I was the only one to uphold a causal relationship between Castellani's trypanosome and sleeping sickness. My opinion was based on the many analogies between sleeping sickness and the various *Trypanosoma* diseases of cattle in their symptoms, course, and anatomical features; and more especially on the striking connections which exist between the peculiar distribution of sleeping sickness and that of tsetse flies, between the epidemiology of the disease and the bionomics of the *Glossinæ*.

I stated quite clearly that I could see no morphological difference between Castellani's trypanosome and *Trypanosoma gambiense*. I pointed out that the so-called anterior extremity of trypanosomes is really their posterior extremity, and that the true anterior extremity is the one which encloses the micro-nucleus, and from which arises the flagellum. The most cursory examination of the various flagellates, and more especially of the free-living forms, suffices to prove that the tapering end of the trypanosome, continued by the free extremity of the flagellum, is the posterior extremity. Authors have called it "anterior," because the parasite moves more frequently and more rapidly with this extremity foremost; but the mode of progression is not a sound argument, otherwise we should have to term "posterior extremity" the well-defined head

of cephalopods, because these animals are capable of a very rapid backward motion, and in this way they usually escape the animals that prey upon them.

I also expressed the opinion that the *Glossinæ* do not merely transfer the trypanosomes in a passive way, as suggested by Lieut.-Colonel Bruce, but that, somehow, they play the part of alternative hosts in their propagation.

Considering the very remarkable mode of development which obtains in tsetse flies, I further suggested that both Nagana and sleeping sickness might be transmitted, not directly by the fly that sucks the blood of infected animals, but by its progeny, as is known to be the case in the transmission of Red-water fever by the cattle tick, *Rhipicephalus annulatus*, and in the transmission of the malignant jaundice of dogs by another tick: *Haemaphysalis leachi*.

In August, the Royal Society published a Progress Report, by Lieut.-Colonel David Bruce and Dr. David Nabarro. These two gentlemen fully confirmed Dr. Castellani's discovery. They stated that whilst Dr. Castellani had found the trypanosome in about 70 per cent. of cases, they found it almost in every case of the disease, even in the early stages; and not only in Uganda, but also in other districts affected by the sickness.

Castellani had already observed that trypanosomes were not present in the cerebro-spinal fluid of natives suffering from other diseases, but free from sleeping sickness. Bruce and Nabarro examined fifteen more cases, and proved the statement correct. Dr. Wiggins also examined seven natives free from sleeping sickness in Kissumu, and likewise failed to find trypanosomes.

Castellani had found the trypanosome also in the blood of one of his cases of sleeping sickness. Bruce and Nabarro asserted that the presence of trypanosomes in the blood could be demonstrated almost in every case of sleeping sickness.

As cases of "*Trypanosoma* fever" had been described by Drs. Baker and Moffat in Uganda, Bruce and Nabarro considered the question of a possible connection between the two conditions. However, they did not venture any definite opinion, but merely described certain morphological differences, which, they thought, seemed to separate Castellani's trypanosome from *Trypanosoma gambiense*. They stated that the flagellate found in sleeping sickness was shorter, had chromatic dots more frequently, and the

micro-nucleus was situated nearer the extremity than in *Trypanosoma gambiense.*

Numerous experiments were carried out in monkeys, dogs, rats, and other animals, both with trypanosomes from sleeping sickness cases and from *Trypanosoma* fever. Both sets of experiments gave positive results, but did not lead to any definite conclusion.

From the analogy suggested by Nagana, Bruce and Nabarro suspected that a tsetse fly might be the carrier of the disease. Two "varieties" of *glossina* were obtained from the Botanical Gardens at Entebbe, and experiments at once commenced. One monkey, after having been bitten on successive days by 215 tsetse flies, showed trypanosomes in its blood 14 days after the first day of experiment.

In November appeared a "Further Report" by Lieut.-Colonel Bruce, Dr. Nabarro, and Captain Greig. In this report the Commissioners stated that they were inclined to consider *Trypanosoma* fever as the first stage of sleeping sickness. They described two cases of *Trypanosoma* fever which, after a short period of improvement, developed symptoms suggestive of sleeping sickness. At the same time, the parasites, which had been confined to the blood, appeared in the cerebro-spinal fluid.

In this second report the Commissioners retracted their previous statement concerning the morphological differences between *Trypanosoma castellanii* and *Trypanosoma gambiense.* They stated that the differences mentioned in the Progress Report have no specific importance, but only show that the parasites find the cerebro-spinal fluid not so favourable for their growth as the blood. Trypanosomes from the cerebro-spinal fluid injected into the blood of monkeys became quite as long as the trypanosomes found in the blood of man.

Numerous experiments were described in monkeys, dogs, guinea-pigs, donkeys, oxen, sheep, and goats. The experiments were carried out with trypanosomes taken both from cases of sleeping sickness and *Trypanosoma* fever. The inoculations were performed into the brain, into the vertebral canal, or sub-cutaneously. The monkeys showed the greatest susceptibility, and exhibited symptoms resembling those of sleeping sickness, no matter whether inoculated with the cerebro-spinal fluid of sleeping sickness cases or the blood of *Trypanosoma* fever cases. Rats and dogs were only partially susceptible; oxen, donkeys, goats, sheep and guinea-pigs were absolutely refractory. These experiments tended to prove the identity of the

trypanosomes found in sleeping sickness and *Trypanosoma* fever.

Other experiments were made to determine whether the Uganda tsetse flies are able to convey sleeping sickness.

Five monkeys were submitted to the bites of tsetse flies. The flies were collected in the neighbourhood of Entebbe; they were fed on patients suffering from sleeping sickness, and after eight, twenty-four, or forty-eight hours they were made to bite the monkeys. Hundreds of flies were used in each experiment, and the monkeys were bitten every day by ten, thirty, sixty or a hundred and forty flies until a positive result was obtained.

A second set of experiments with tsetse flies and monkeys was also carried out, to ascertain whether flies freshly caught in the vicinity of Entebbe were actually carrying the trypanosomes of sleeping sickness.

Three monkeys were submitted to the bite of large numbers of flies caught in the vicinity of the hut-tax labourer's camp in Entebbe. The flies were fed only on the monkeys soon after being caught.

Both sets of experiments gave positive results, with a very striking difference, however; because, while trypanosomes appeared in the blood of the monkeys eight weeks after the first bite, in those animals which were bitten by flies previously fed on cases of sleeping sickness, they appeared after only two weeks in those which were bitten by flies not artificially infected.

From these experiments the Commissioners concluded that they had proved :—

(1) That *Glossina palpalis* is capable of conveying trypanosomes from sleeping-sickness cases to healthy monkeys, up to at least forty-eight hours after feeding.

(2) That the flies collected in the vicinity of Entebbe were actually carrying the trypanosomes of sleeping sickness.

I dispute the conclusions arrived at by Colonel Bruce and his collaborators. Their experiments did not prove that the flies conveyed the trypanosomes of sleeping sickness from the patients on which they were fed to the healthy monkeys. On the contrary, the presumed artificial infection only served to deprive the flies of the majority of the trypanosomes they were harbouring. From the positive results obtained in the second set of experiments, we learn that the flies were already infected with trypanosomes when caught. When the flies were allowed to bite the monkeys immediately after being caught, the infection in

the latter manifested itself in about two weeks; but when the flies were first fed on sleeping-sickness cases the monkeys experimented upon did not show trypanosomes in their blood until after EIGHT WEEKS. This singular fact proves very clearly that the flies, instead of drawing trypanosomes from the blood of the sleeping-sickness patients, who had very few, if any, in their peripheral circulation, actually discharged in the blood of the latter all, or most, of the parasites they were carrying.

Then, again, I do not consider that the Commissioners proved that the flies caught in the vicinity of Entebbe were carrying the trypanosomes of sleeping sickness. They only proved that the flies were carrying trypanosomes; but who can tell whether these trypanosomes were those of sleeping sickness? The Commissioners state themselves that they examined some oxen in Entebbe, and found in the blood of these animals a trypanosome, which was neither *Trypanosoma brucei* nor *Trypanosoma gambiense*. And surely many other species of trypanosomes are to be found in the blood of the mammals, birds, batrachians, and fish of Uganda.

Lastly, I do not consider that they proved that the fly is merely a passive carrier of the infection. The experiments made by Colonel Bruce on Nagana with tsetse flies (*Glossina pallidipes* and possibly *Glossina morsitans*), those made by Rogers on Surra with *Tabanidae*, those made by Theiler on "gall sickness" with *Hippoboscidae* (*Hippobosca rufipes*, *Hippobosca maculata*) prove perhaps (though I am inclined to explain them in a very different way), that a fly disturbed while sucking a *Trypanosoma*-infected animal *may* convey the disease to a healthy animal by means of its blood-soiled proboscis, just as malaria may be conveyed by a needle soiled with malaria-infected blood. But this mode of transmission does not seem to be the usual one. It does not explain why Nagana is carried exclusively by a *Glossina*, and not by any of the many other blood-sucking insects which attack horses and cattle outside the tsetse stations, or "fly-belts" as they are called. It does not explain why sleeping sickness is likewise strictly confined to the tsetse tracts, and is not propagated by the numerous blood-sucking insects and acarida which swarm in the huts of the natives or cover their bodies.

But there are many other objections against the Commissioners' experiments at Entebbe.

The monkeys used for the experiments were kept in the

open without any protection from blood-sucking diptera or any other source of infection; and this in a district in which sleeping sickness was prevalent. Some of the monkeys used for the experiments belonged to an Asiatic species (*Macacus rhesus*), and were purchased in England. The majority, however, were specimens of a local *Cercopithecus*. The Commissioners do not tell us whether any of the Uganda monkeys presented trypanosomes in their blood, or whether there was any sickness amongst these animals, under natural conditions. A careful examination of the local monkeys would have been very important. The Lokoja natives, knowing nothing of trypanosomes, assert that the tsetse extracts from a certain small red monkey the poison with which it inoculates the bush-cow or dwarf buffalo.

The flies were not reared for one or more generations in the laboratory, as should have been done, in conformity with the numerous and masterly experiments which have been carried out in connection with the intermittent fevers of man and the hæmoglobinuric fevers of cattle. They were collected at random, and hundreds of flies belonging to two or more varieties (species ?) were indiscriminately used in each experiment.

All these experiments will have to be repeated in a thoroughly scientific way. Meanwhile, I believe that the bond of association between the trypanosome of sleeping sickness and *Glossina palpalis* is far more intimate than Colonel Bruce suspects.

At the same time as the publication of the "Further Report" by Colonel Bruce, Dr. Nabarro and Captain Greig, though it was received long before, the Royal Society published several other reports by the members of the first Commission. One of these reports, by Drs. Low and Castellani, is devoted to the clinical aspects of sleeping sickness. The symptoms of the disease and its morbid anatomy, both macroscopical and microscopical, are fully and admirably described. There is one point, however, on which I cannot agree with the authors. They state that polyadenitis is a common condition amongst natives, and cannot, therefore, be regarded as a special symptom of sleeping sickness. They say that it is difficult to determine what produces this polyadenitis, but that perhaps frequent skin diseases, syphilis, and verminous invasions may be responsible. Fully admitting that syphilis and other diseases may be in Africa, as elsewhere, a fruitful cause of glandular enlargements, I believe,

nevertheless, that the glandular swellings met with in natives suffering from sleeping sickness, or living within the affected areas, are decidedly symptomatic of the trypanosome infection. An analogous polyadenitis is met with in Surra, in Nagana, in Dourine and in *Mal de caderas*. Kauthack, 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. Indeed, the trypanosomes are present in the glands from one to three days before they are discoverable in the blood, and they may be very abundant in the glands when still scanty in the blood. From time immemorial the enlargement of the cervical glands has been considered a premonitory sign of sleeping sickness by the natives of various parts of Africa affected by the disease. Winterbottom tells us that slave-traders considered these swollen glands as a symptom of sleeping sickness. "They either never buy such slaves, or get quit of them as soon as they observe any such appearances." Dr. McCarthy, Surgeon-Major Gore, and Dr. Corre, report that the natives of Senegambia believe that sleeping sickness may be cured by a timely cauterisation or extirpation of the swollen glands. Dr. Christy discovered that the area of distribution of enlarged cervical glands in equatorial East Africa agrees with that of sleeping sickness.

My rapid survey of the work which has unravelled the mysteries of sleeping sickness would be incomplete if I did not mention Mr. E. Austen's admirable monograph of the tsetse flies. Mr. Austen's book, with its careful description of the various species, with its copious information on the bionomics of these flies, with Mr. Terzi's illustrations, will certainly prove of invaluable aid in future researches.

The last step in the history of sleeping sickness is one of great importance. The lady patient examined by Sir Patrick Manson on October 3rd, 1902, and so sagaciously diagnosed as a case of *Trypanosoma* fever, began to show symptoms of sleeping sickness about two months ago, and died of the disease on November 26th, 1903—two years and three months after the presumed date of infection. At the autopsy, and subsequent microscopical examination of the brain, Drs. Mott and Low found unequivocal evidence of sleeping sickness. The history of this case proves beyond doubt that Europeans are liable to sleeping sickness; that the disease is a *Trypanosoma* infection; and that the so-called "*Trypanosoma* fever" is only a pre-

cursory stage of "sleeping sickness." The trypanosomes from this case, in its early stage, were the very ones I had compared with those found by Castellani in sleeping sickness cases and declared morphologically identical.

If sleeping sickness is a *Trypanosoma* disease, if a tsetse is the means of its dissemination, the study of the bionomics of the *Glossinæ* is the most important step with regard to prophylaxis. Mr. Austen, in his valuable Monograph, has given us a very full account of the information so far collected with regard to the life-habits of tsetse flies. I also have studied the bionomics of the *Glossinæ*, but my conclusions are somewhat different from those of Mr. Austen. Tsetse flies are confined to Africa. As a genus they have a wide range throughout the greater part of the continent, but the limits of the various species are very imperfectly known. Far more definite and important is the knowledge of their local distribution. This, however, must be considered collectively because, hitherto, writers have not distinguished between species. No doubt the habits of different species will be found to differ, and perhaps these differences will explain some of the discrepancies between various observers. But whatever the species, and whatever the part of Africa in which they have been observed, authors are unanimous as to the location of the tsetse stations. The *Glossinæ* are never found on mountains; they are seldom seen above 3000 ft.; they are absent from extensive plains, or other open places; they are rarely found in cultivated patches. Their habitat is always in the neighbourhood of water: along the banks of rivers, round the coasts of lakes, on low riverine islands, in swamps and meres, especially at the foot of mountains. They are most numerous along the water's edge; they become scarcer and scarcer as one advances inland, and disappear entirely within a few miles of the water. The places they occupy are sharply defined and permanently established. These places or stations are called "fly belts," and the natives know their limits precisely. The fly belts vary greatly in disposition and extent. Not infrequently they occur on one side of a stream, but not on the other. Along the courses of rivers, or in the low country bordering a coast line, so-called "fly belts" may extend for hundreds of miles, varying greatly in width according to the nature of the country. In such cases, however, tsetse flies are not found at every point throughout the belt, but in particular patches, the area of which may be quite small. Thus, according to Bains, "the fly is extremely local, and

extensive districts in which it prevails may be passed through by the aid of guides who know the 'patches' of fly, just as a pilot knows the shoals of an estuary." These fly patches are usually confined to reed swamps, to strips of jungle, to banana bushes, or to patches of mosani or mimosa forest. In short, the essential condition of a tsetse station are: the presence of water, a thickly-wooded district, and a loose, fragmentary soil. The nature of the soil is probably of great importance. As a rule, the fly patches are in rich sandy ridges, near marshy spots. The limitation of the tsetse to definite tracts or "belts" has given rise to much speculation. The prevalent opinion is, that the fly waits near the water to feed on the animals that come down to drink. Mr. Austen advances a new hypothesis. He says: "The limitation of the tsetse to 'belts' is not as remarkable as might at first sight appear. There can be little doubt that it is due to a characteristic social tendency of the order to which these insects belong, which, though frequently overlooked, is exhibited by the majority of species of diptera, and has attracted special attention in the case of the tsetse, owing to their blood-thirsty nature, and the fatal consequences of their bites." He further says that, in spite of the fact that the distribution of most species of diptera is remarkably wide, it will be found in the majority of cases that individuals of the same species do not occur everywhere throughout its area, but are confined to particular spots, and wherever they are met with, they are usually to be found in some numbers. I do not think we can class tsetse flies among the "social insects." I can see no purpose for the association. As to the confinement of diptera to particular spots within the area of their distribution, it is in conformity with the general laws of distribution. All animals, whether social or not, are confined to particular stations which offer the necessary œcological conditions. Besides, although Mr. Austen thinks that "the occurrence of tsetse flies in belts is not difficult of explanation," he says himself that "the fact that animals may be in perfect safety on one bank of a stream, when bushes on the other side are full of the fly, is exceedingly hard to understand." Mr. Austen, although fully aware of the peculiar distribution of tsetse flies, is not unfavourable to the theory, often propounded by travellers and sportsmen, that the fly follows the big game. I think I may safely state that the distribution of the tsetse fly is in no way connected with big game. The tsetse fly is not found in open plains,

although such plains may be literary swarming with big game; and, on the other hand, places devoid of game may be very dangerous "fly zones." The marked peculiarities shown by the distribution of tsetse flies exclude altogether the big game theory. The invariable association of the tsetse with streams, rivers, or other bodies of water, is undoubtedly a very important feature in the natural history of *Glossinæ*, and one which needs careful investigation. Two main facts determine the distribution of animals: their breeding habits and the nature of their food. In the pupiparous genus *Glossina*, the association with water can only be related to food habits. I therefore suggested in my earlier Paper that it may be related to the habit of feeding on fishes. A large proportion of the fish inhabiting the African rivers and lakes are air-breathers. There are several species of *Anabas*, three species of *Protopteros*, three species of *Ophiocephalus*, and no less than 100 species of siluroids. All these fish spend a great part of their life out of water, and even when they are in water, they are constantly obliged to ascend to the surface to breathe. They are quite incapable of supporting life by breathing water. When dry weather deprives their usual haunts of all moisture, these fish bury themselves in the mud, or migrate in large numbers to the nearest swamps. The siluroids of the *Genera clarias, Clariallabes*, and *Chaunallabes* are of special interest; they live in burrows, like rabbits, coming out towards evening in quest of food. The flesh of most of these fish is much esteemed by the natives, and in many places the women go and dig them out of their burrows. A connexion with the air-breathing fish would explain most satisfactorily the peculiar patchy distribution of the tsetse flies, and their limitation to the borders of marshes or river banks. Of course, the connexion might be indirect: that is to say, the fly might not be after the fish, but after some marsh rodent like *Aulacodus;* or after a fish-eating mammal, like *Potamogale velox*, which inhabits the Gaboon; or after an otter, such as *Lutra inunguis* or *Lutra maculicollis*, which have a wide distribution in Africa. I say this, because in South America the natives point to a large water mammal *(Hydrochoerus capibara)* as the original source of *Mal de Caderas.* Dr. Christy, who is now investigating sleeping sickness on the Congo, has promised me to elucidate this point. From what we know of the life-history of the tsetse flies, I think I may state that it will be easier to eradicate the *Glossinæ* than it is to destroy the *Culicidæ.*

Lately there has arisen some disagreement on questions of priority concerning the discovery of a *Trypanosoma* in sleeping sickness, and the suggestions of the part played by tsetse flies in the propagation of the disease. I have endeavoured to adhere very scrupulously to the exact facts, so as to avoid any quarrel. I hope, therefore, that the discussion will not lapse into a worthless controversy, but that it will lead to useful suggestions for the prevention of the deadly African scourge.

Gentlemen, a great scientific triumph has been achieved; let us bestir ourselves to do justice and honour to those who, heedless of danger, have wrought this noble work.

Discussion on Dr. Sambon's Paper.

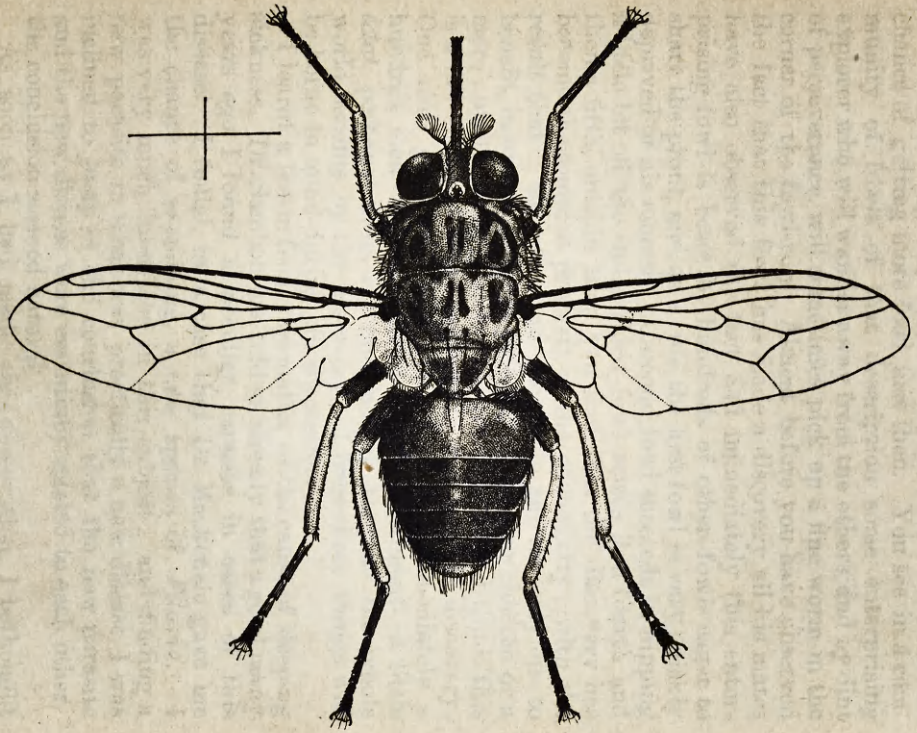
The President said he thought that Dr. Sambon's Paper, and the discussion which it was hoped would follow, would form a most valuable contribution to the *Transactions* of the Society. He considered that they had listened to a most interesting Paper, and one which would give rise to considerable discussion, in which it was hoped that a great many eminent men who had had great facilities for studying this question would take part.

He had had letters expressing regret at being absent from Professor Clifford Allbutt, Sir Michael Foster, and others; and he would now ask Sir Patrick Manson to open the discussion.

Sir Patrick Manson: I feel a great responsibility in opening this discussion, because I cannot but recognise that the subject is one of very great importance, not only to Africa—where it is really one of primary importance—but to pathology in general; for the entrance of these protozoa into the field of pathology promises to give new light in places where darkness formerly prevailed, and one must be extremely careful in expressing any opinion or view upon the subject, just when it begins to break upon the medical mind.

I was especially pleased with the last part of Dr. Sambon's Paper: that in which he expresses a hope that questions of priority will not occupy the meeting. They are always thorny questions, and they lead to a good deal of bad feeling, and do not, so far as my experience goes, conduce to general profit. Sometimes, on a Sunday, I have an opportunity of contemplating the manners and customs of a

GLOSSINA PALPALIS.



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fowl-run. My observations are usually conducted in the afternoon, between the morning meal and the afternoon meal, when the fowls are at leisure: they have picked up the last grain of the maize that has been thrown to them, and have nothing very much to do, as there is little or no chance of getting more food just then. You see in a community of fowls of that description some enterprising explorer who will wander away from the others, and by dint of perseverance, will sometimes pick up a fine worm in the corner of the fowl-run. Almost before you have observed the fact that this fowl has made a discovery all his mates have also observed the fact, and immediately this enterprising fowl is beset by hundreds of other fowls eager to share the profit, and, as a rule, the first fowl is very quickly deprived of his morsel. A second fowl succeeds in nipping a little bit off the end, a third fowl seizes it, a fourth and then a fifth, until in time you find that the discovery has become the common property of the community; with the result that I, the owner of the fowls, am the only one to benefit, inasmuch as I get probably a plumper chicken or a more nutritious egg the next morning. Now I think this is a fair simile of what happens in the field of discovery. One man gets hold of a new fact, and immediately a hundred men seek to extract a little nutriment—a little *éclat*, perhaps—from his find, and in the end the whole world benefits by the discovery. I hope these things will be borne in mind during our discussion.

I learnt a lesson from this matter of the cause of sleeping sickness. Dr. Sambon has told us already that a good many years ago I found a peculiar parasite in cases of this disease. I found, in a case that Dr. Mackenzie gave me the chance of examining, a new species of *Filaria*. I was very much interested in this subject; and finding a new parasite in what was practically a new disease, I was inclined to jump to the conclusion that the new parasite and the new disease were essentially related to each other the conclusion seemed natural.

As soon as I had made the observation, I bethought myself how I should pursue the subject, and I determined to send to all the corners of Africa for specimens of blood from the natives. I sent about 10,000 slides to Africa, and I got about 300 back; but a good many came from cases of sleeping sickness, and in every case of sleeping sickness I found *Filaria perstans*. By-and-bye, Mr. Grattan Guinness imported two cases of sleeping sickness into England for purposes of study, and was kind enough to put them at my

disposal. I was much gratified to find in the blood of these two cases also *Filaria perstans*. Now, with evidence of that sort at my disposal, I think it would have been beyond the powers of resistance of most human natures to say that *Filaria perstans* was not the cause of sleeping sickness. Yet even then I resisted the temptation. I said it was very likely: at all events, we had some ground for pursuing the subject further; and when afterwards the same parasite was found in British Guiana I was somewhat disappointed, because at that time we had no knowledge of sleeping sickness in British Guiana. I wrote to a friend there, and asked him if he knew of any cases resembling sleeping sickness in British Guiana, and he wrote back and said that a patient had been brought to him suffering from a condition of somnolence from which her friends had great difficulty in awaking her. This information somewhat encouraged the idea that, possibly in this very little-known country sleeping sickness might exist, and the existence of sleeping sickness there would further endorse the possibility as to the filaria being the cause of the disease.

By-and-bye, when Drs. Low and Castellani went out to Uganda to investigate the subject, they went out with distinct instructions from the Royal Society to ascertain as to how far this particular Filaria might be connected with sleeping sickness. Their first reports and private letters were distinctly in favour of regarding this parasite as the cause of the disease, for Drs. Low and Castellani found something like 95 per cent. (I forget the actual figures) of the natives of Uganda who were suffering from sleeping sickness to be the hosts of *Filaria perstans*. By-and-bye, on extending their observations, they made the somewhat disconcerting discovery that although in Uganda itself, or rather in the particular part they were investigating, *Filaria perstans* and sleeping sickness seemed to occur together, yet in a district where the sickness was epidemic, *Filaria perstans* seemed to be entirely absent. Thus at one stroke was destroyed a hypothesis from which I had begun to think I might derive a little credit, and I am now compelled to disavow any connection of *Filaria perstans* with sleeping sickness further than accidental.

As regards the connection of this new parasite, *Trypanosoma*, with sleeping sickness, we have to bear in mind my experience with *Filaria perstans*. My creed is—my belief is—that sleeping sickness is caused by *Trypanosoma gambiense*, but I will not say that this has been proved. My creed at one time was that sleeping sickness

was caused by *Filaria perstans*, but I could not say that it had been proved. I still think there is room for further proof on the subject of a distinct and definite connection between *Trypanosoma gambiense* and sleeping sickness. Observe that there is a difference between belief and knowledge—I believe it is the cause, I do not know for certain that it is. Lastly, the case to which Dr. Sambon has referred, a patient of mine who died recently of sleeping sickness, has added another reason for our believing in the close relationship of the parasite with the disease. But even that additional evidence is not sufficient for the scientific mind. Concurrence even in that case may have something to do with the matter.

When Dr. Castellani's discovery and Colonel Bruce's extension of that discovery were first made public, I was extremely sceptical as to the relationship of the two parasites, and for this reason : Colonel Bruce distinctly states that 28 per cent. of the whole population of Uganda have got the *Trypanosoma* in their blood. Now, sleeping sickness is a disease that certainly predisposes the human body to many kinds of parasitical invasion ; inasmuch as, in consequence of its paralysing effects on the sensory nerves, and especially on the cutaneous sensations, and the indifference to what goes on outside the patient which is characteristic of the disease, such carriers of parasites as flies, ticks, bugs, and so on, can make bites with impunity and not be brushed away. One can understand that a patient afflicted with the indifference and languor so characteristic of sleeping sickness would be extremely prone to be infected with the parasite when in this condition of physical languor, and therefore is just the person who would exhibit parasites of that character. In the same way, I believe he is specially subject to invasion of *Filaria perstans*. Therefore, it seemed to me that our evidence was nothing approaching what could be regarded as satisfactory from a scientific point of view. But when this poor lady, in whom I had found (or rather Dr. Daniels had found) the *Trypanosoma* a good many months ago—long before she exhibited symptoms of the languor of sleeping sickness (the parasite was the cause of the initial fever contracted on the Congo)—when this lady developed sleeping sickness, I thought we had a much more cogent argument than has been supplied from Uganda. She had no opportunity of being bitten while in a torpid condition, no opportunity of being bitten by *Glossina morsitans* or *palpalis*, and no opportunity of subsequent infection following the primary act of

infection, whatever it may be, that introduced the *Trypanosoma*. Therefore, I think that this case is one of very great importance, as affording, not complete but additional proof that *Trypanosoma* is the cause of the disease. Still, it is conceivable that even in her case the two conditions — *Trypanosoma* in the blood and independent disease—might concur; and, until we have obtained constant results from inoculation with pure cultures of the *Trypanosoma*, I say the subject is not closed, and we still ought to maintain an open mind as to the relations of the *Trypanosoma* and of the disease. My belief—founded on a consideration of the probabilities (nothing more)—is, that this parasite is the cause of the disease; but I cannot say that it has been scientifically and conclusively demonstrated. I hope that the cultivation experiments that have been made lately by two American scientists on the growth of *Trypanosoma lewisi* in pure culture will be applied to the decision of this question: for, until the thing is positively decided one way or another, I think one incurs a certain amount of responsibility and danger in advising anything like expensive measures with a view of counteracting *Trypanosoma* in connection with sleeping sickness. To base expensive measures on what may be only a speculation and not a fact, is somewhat dangerous ground for men responsible for the conduct of public affairs. So I would urge on those who are interested in this question to undertake these cultivation experiments. And then, if we find that pure cultures of *Trypanosoma gambiense* in an animal, or in a human subject, if anyone is sufficiently self-sacrificing to offer his own person, produce symptoms of sleeping sickness—then I should say the thing is mathematically proved, and we should be content.

I should like to point out one or two things that have struck me in connection with this matter as worth deciding. Colonel Bruce has distinctly proved that the monkey (and his experiments have been repeated in Paris and elsewhere) —or a certain species of monkey, at all events—is susceptible to *Trypanosoma* infection. This being so, is there any proof that the monkeys of Uganda have got sleeping sickness? I do not think those experiments by Bruce of injecting blood or cerebro-spinal fluid of patients infected with sleeping sickness, and subsequently inducing sleeping sickness in the monkey, along with *Trypanosoma* in the blood, are at all conclusive of the connection of *Trypanosoma* with the sleeping sickness. Supposing we assume

that this is an independent disease, and that there is no connection between *Trypanosoma* and sleeping sickness, you take the blood of a patient suffering from sleeping sickness, and having *Trypanosoma* in his blood, and you inject this into the monkey, and you produce two diseases—*Trypanosomiasis* and sleeping sickness: Suppose you had a patient suffering from plague, and at the same time from relapsing fever, and you take a little of that patient's blood and inject it into a sound man's veins: in that sound man you produce two diseases—plague and relapsing fever. You would find *Bacillus pestis*, and you would find *Spirillum obermeieri* in that man's blood; but it would not follow that the *bacillus pestis* was the cause of the relapsing fever, or that the *Spirillum obermeieri* was the cause of the plague. Neither does it follow from Bruce's experiments that a definite relationship between the *Trypanosoma* and sleeping sickness has been established.

I should very much like to know whether monkeys are subject to sleeping sickness, and whether there has been any epidemic of the disease amongst these animals.

Prof. RAY LANKESTER: May I venture, not as a member of the medical profession, but as one who takes a great interest in the subject from what I may call the natural history point of view, to make a few remarks.

My own interest in this matter began with the study, some years ago, of the *Trypanosoma* which occurs in the blood of the frog; and I believe that I was the first to study this, and to write about it, after Grubey. It had not been mentioned in the interval, and at the time (1870) I missed Grubey's account (it was a very old one), and described it as a new parasite. It subsequently turned out that this parasite was the one called *Trypanosoma* by Grubey; and since then I have always taken great interest in these parasites of the blood—rather, I should say, from the naturalist's point of view. I very much doubt, for one thing—although I see that Laveran and Mesnil take the opposite view—whether it is really right to call these parasites of the mammalia by this name *Trypanosoma*. I think zoologists would say that there is a generic distinction between the characters of the original *Trypanosoma* and the forms allied to it, which occur in mammalia and in birds; and therefore it is rather awkward that this long word has become so commonly used. I think zoologists would say that the name

"Herpetomonas," which was given by Savile Kent to Lewis's parasite (the one he got from the rat), must become that of a genus for the species of mammalian *Trypanosoma*.

May I say that I listened with great pleasure to Sir Patrick Manson's statement, which was an extraordinarily interesting account of his views and theory on the matter, and was the statement of a really scientific attitude as to the outcome of this question. He had had strong presumptive evidence with regard to *Filaria perstans*; but he did not commit himself about it; and I think that the doubt he has pointed out to us with regard to the *Trypanosoma gambinese* is absolutely correct and sound. There is a great deal of converging evidence, which amounts to cumulative evidence in favour of *Trypanosoma* being the cause of sleeping sickness, but it is not absolutely proved to be so. The possibility of another parasite accompanying the present one in the blood has to be borne in mind. We are getting to know such extraordinarily minute and varied parasites in the blood of the mammals in tropical countries, that we have to be very careful as to the conclusions which we form.

I think it is not desirable to discuss questions of priority on the present occasion; but I think that Dr. Sambon should correct the statements in his Paper by reference to the Report of the Commission of the Royal Society, in which he will find that Dr. Castellani did not attach any importance to the fact that his sleeping sickness patients had *Trypanosoma* in their blood until Colonel Bruce pointed it out; and it was Colonel Bruce who initiated and carried out the investigation which proved the invariable presence of *Trypanosoma* in sleeping sickness.

Another point which struck me was that in one or two matters Dr. Sambon seems inclined to put in some claim for himself for priority for some suggestions that he has made: a claim which I feel inclined to call in question. I refer especially to the suggestion that the *Glossina palpalis* is the carrier of the sleeping sickness *Trypanosoma*. It occurred to Dr. Sambon, as it would occur to anybody who knew the facts, that this might be so. The real interest in the matter is that Colonel Bruce found the *Glossina palpalis* where it was not previously known, and showed that its distribution coincides with that of sleeping sickness, and that it does and can carry the parasite; and he did this, of course, quite independently, and without suggestion from Dr. Sambon.

Similarly, the suggestion that a change goes on in the *Trypanosoma* whilst in the interior of the *Glossina*—that there is some further development—is a suggestion which everybody who has ever heard of a parasite undergoing a change in the body of its host will, of course, entertain. It is no use claiming priority for a platitude of that kind—the thing is to show that a change occurs. It is a possibility that observers who have *Trypanosoma* and *Glossina* under their observation are bound to entertain. But the suggestion that there is this possibility is not worth putting on record as a matter of priority—that is my opinion.

I think there is no doubt a very great deal more to be done in the study, not only of this particular *Trypanosoma* and its connection with sleeping sickness, but with regard to many other forms of the same kind. We must not be impatient. I think that a very extraordinary rapidity has been shown in the growth of our knowledge about the relation of *Trypanosoma* to sleeping sickness, when you remember that it was only the beginning of last March that 70 per cent. of the patients were found to have the *Trypanosoma* in their cerebro-spinal fluid—only last March. Well, there has not been much time lost in the investigation since then, and it is still in progress.

The PRESIDENT: I think the time has now arrived when I must consult the Society as to what they will do. We have every promise of an animated discussion on this very interesting subject; but we have nearly reached ten o'clock, and our rules will not allow us to go on after half-past. What I would submit is this: that we should adjourn the discussion—the greater part of it, with one exception, which I will name in a moment—to our next meeting on January 15th, in the hope that it will be convenient to Dr. Sambon to be with us again on that occasion; and that, in the meantime, we have the Paper and so much of the discussion as has been already contributed, together with the exception that I am about to mention, set up in type; we should then be in a position to do more justice to the subject when we return to it.

I want to make one exception. We are honoured to-night with the presence of Dr. Brumpt, who has come from Paris; and, although we should be only too pleased to have Dr. Brumpt with us again at our next meeting, it is rather too much to ask of him to postpone what he has to say to us until then. I would, therefore, suggest that we should continue for a sufficient time after ten o'clock to

hear what Dr. Brumpt may be able to tell us, and that we should then go into the next room and look at the specimens that have been prepared for us. Is it your pleasure that we adjourn the discussion, with that exception, to our next ordinary meeting on January 15th?

(The resolution was carried.)

The PRESIDENT: Then, that I understand to be carried. Dr. Sambon's Paper and the discussion which has already taken place, shall be put up in type; and may I ask those members and others who are present who desire to have copies of it, to communicate with the Honorary Secretary, Dr. Bulstrode?

Dr. E. BRUMPT: Professor Ray Lankester is quite right in saying that the tsetse fly hypothesis is of little importance, as a consequence of Castellani's discovery, when based merely on the analogy of Nagana. But there is a great difference between a mere suggestion and the arguments adduced by Dr. Sambon and myself.

Having noticed on the Congo, in December and January, 1902, that neither water, nor fish, nor manioc could be incriminated in the causation of sleeping sickness—because within the same region, whilst the inhabitants fed exactly on the same diet, but living close to a river, were decimated, those inhabiting the interior were spared; and that, on the other hand, the disease, though frequently imported to America, had not become acclimatised in that part of the world—the idea suggested itself of an intermediary host living by the water-side, and thus permitting the extension of the disease along the river margins. It is for this reason that, on hearing of Castellani's discovery, without the slightest hesitation I incriminated the tsetse flies, which alone could explain the epidemiology of the disease.

With Dr. Sambon and Sir Patrick Manson, I also consider that Colonel Bruce's experiments lack in scientific accuracy. There ought to have been control animals remaining immune after the bite of flies having fasted for a sufficiently long time, and others succumbing to the bites of infected flies. However, I consider Bruce's experiments of great interest; and were it possible to prove that the trypanosomes which developed in the monkeys were really those of sleeping sickness, Bruce would have solved one of the most important problems, especially as regards prophylaxis, which in this malady, as in many other tropical diseases, has a far greater importance than treatment.

My own researches are due to the great discovery that Castellani made while in Uganda, on behalf of the Royal Society. I think, the tsetse fly theory explains the whole epidemiology of sleeping sickness. All tsetse flies must be able to play a part in this disease, as well as in the other trypanosome diseases of Africa. These flies owe their great virulence to their voracity; to the habit of piercing the skin very frequently before settling definitely to feed; and, lastly, to the blandness of their gastric juices, which allow the trypanosomes to remain alive in their stomachs for a very long time.

The geographical distribution of *Glossina palpalis* is very wide. I found it on the River Omo, in the vicinity of Nimulé, and all along the Congo, from the sources of the Onelle to Matadi.

Sir Patrick Manson, with perfectly scientific caution, has expressed the idea that the trypanosome and sleeping sickness may possibly represent two very different morbid entities, and that by inoculating the trypanosome one inoculates at the same time the germ of sleeping sickness. The experiments I made on animals in the Congo, and those I am now carrying out in Paris, together with Professor Wurtz, dispose, I think, of Manson's objection.

A monkey (*Macacus rhesus*) was inoculated with the blood from three cases of sleeping sickness, in the abdomen and beneath the skin of the thighs, as well as with the cerebro-spinal fluid of these patients into the vertebral canal. Repeated examinations during six weeks proved negative. The animal presented neither trypanosomes nor symptoms of sleeping sickness. The same monkey inoculated with the blood of another monkey which had been successfully inoculated, presented in eight days trypanosomes, and simultaneously, symptoms of sleeping sickness.

The inoculations which remain negative as regards trypanosomes are equally negative as regards the symptoms peculiar to sleeping sickness.

ADJOURNED DISCUSSION, JANUARY 15TH, 1904.

THE PRESIDENT: We will now continue the discussion of the Paper which Dr. Sambon read before us at our last meeting, and the discussion of which was commenced but not finished. We have before us in print the full text of that Paper, and the remarks made by Sir Patrick Manson, Professor Ray Lankester, and Dr. Brumpt.

I will, in the first place, call upon Dr. Nabarro, whose name is so honourably associated with the recent researches in Uganda, to open the discussion.

Dr. Nabarro: Mr. President and Gentlemen—I am sorry that I had not returned from Africa when your first meeting on this subject was held, and that I have not had the opportunity of fully reading Dr. Sambon's Paper. I do not intend to go into controversial points to-night, but perhaps I may be able to make a few remarks which will be of interest to this Society, especially as since Col. Bruce's return from Uganda we have continued the work which was started last March. When we arrived in Entebbe we were told two facts: one by Dr. Castellani—as probably you have heard—that he had examined the cerebro-spinal fluid of patients suffering from sleeping sickness, and he had found *Trypanosoma* in 5 out of 15. The second fact was communicated by Dr. Baker, of the Uganda Service, and it was that he had found the *Trypanosoma* in the blood of one of the natives of Uganda. These two facts were extremely interesting, because so very unexpected, and they at once led us to think that possibly the *Trypanosoma* had something to do with sleeping sickness; and although it would not have done to jump at once to a conclusion, it led us to carry out the investigations which we did in the subsequent months that we were in Entebbe. While Dr. Castellani was in Entebbe we carried out a number of lumbar punctures, and thereby increased his percentage from 5 out of 15 to 19 out of 34: which works out, I think, to 56 per cent. and not 70, as erroneously stated in the Royal Society's Report. During the next few weeks Dr. Baker, curiously enough, came upon four other cases of *Trypanosoma* in the blood of natives not suffering from sleeping sickness. That was very interesting, and it showed us that *Trypanosoma* was not so rare as one might have expected. Patients with the *Trypanosoma* in their blood came to the dispensary because they had an attack of fever, and really there was very little else the matter with them. We had them under observation during the whole time that we were in Entebbe; I saw all the men two months ago, before I came away, and they were all practically well and at their work. We punctured them every month: they did not mind the operation, and it did not seem to do them any harm; we always gave them chloroform, and they generally got up about fifteen or twenty minutes afterwards and went away. If you read

the Report published by the Royal Society, you will find that in the early months they had enough *Trypanosomata* to show in blood films; but later on we had to take large quantities before we could find *Trypanosoma*. This would last for several days, or perhaps a week or two, but on no occasion did they show *Trypanosoma* in the cerebro-spinal fluid—that is, in the early months. Later on, in July, two of them showed *Trypanosoma* in the cerebro-spinal fluid. Of course we were rather pleased at that, because we had then in our minds the theory that *Trypanosoma* was possibly the cause of sleeping sickness. So we looked carefully for any signs of sleeping sickness in these patients, but beyond very indefinite symptoms we could find nothing the matter with them. Therefore we examined them again in a month's time, but we could not find *Trypanosoma* present then, unfortunately. I examined them afterwards three times at intervals of a month, and there was no *Trypanosoma*. I think it is possible that when we found the *Trypanosoma* in the cerebro-spinal fluid there was an appreciable amount of blood, and that was one objection that we had to consider, namely: the likelihood of blood being mixed with the cerebro-spinal fluid; but that does not apply to a large number of cases. These patients are still under observation by Captain Greig, whom I left in Entebbe, and I am thinking that these people will still develop sleeping sickness.

Then, after Dr. Castellani left, the theory being a very suggestive one, we devoted our attention practically exclusively to the *Trypanosoma*. We did several *post-mortems*, and looked for *Streptococcus*, which was found in the heart blood and lateral ventricle fluid in some of the cases. A *Diplococcus* was found in two of the *post-mortems*, but we did not do a very large number, because the *Trypanosoma* theory seemed a suggestive one, and we devoted all our energies to that part of the subject.

The first point in that connection is the result obtained by lumbar punctures in cases of sleeping sickness. In practically every case — I cannot remember the exact number—we found *Trypanosoma* in the lumbar fluid of sleeping sickness patients. True, it is sometimes extremely scanty, and on more than one occasion we have had to repeat the lumbar puncture two, three, and four times before finding *Trypanosoma;* but on the fourth occasion we have found it present. Again, in some of them we found a large number of *Trypanosomata*. We drew off 10 c.c. of the fluid, centrifuged it, and poured off the super-

natant liquid. Sometimes a drop of the residue will show two or three in the very first field, although there might not be a single red corpuscle in twenty fields of the microscope—and that point I would emphasise. I am practically sure that the *Trypanosoma* does not get into the lumbar fluid owing to leakage of blood. In fact, I did a case of a Persian (the first known case in a non-African race), and his cerebro-spinal fluid was simply teeming with *Trypanosomata*, and yet there were no red corpuscles in twenty fields of the microscope.

I would point out that this question applies not only to Uganda proper, for Dr. Wiggins examined a large number of cases in Kavirondo, on the north-east of Victoria Nyanza; and he found *Trypanosoma* in every case of undoubted sleeping sickness.

We examined the cerebro-spinal fluid of a Persian who had the disease, and his fluid was teeming with *Trypanosomata*. I have already told you that one does not always get it on the first occasion; sometimes one has to repeat the puncture two, or even three and four times. At times there is a good deal of fluid present, and it seems that the dilution renders it rather more difficult to find *Trypanosoma*, because there is so little deposit. Another point which we have not mentioned, and which rather struck me, was this. The flow of the lumbar fluid was at times very slow and irregular; so it was suggested to start the flow by aspiration with a syringe, and one was surprised then to see the fluid spurt out. That happened on several occasions, and one managed in that way to save a good deal of time. No blood was obtained with the fluid, and so it did no harm to the patient.

Next, as to lumbar punctures in controls, that is, in patients who did not show obvious signs of sleeping sickness. It is rather difficult to get a large number of these; it is difficult to persuade a native to come and take chloroform, and submit to a lumbar puncture. I think the numbers are: 15 which we did in our laboratory at Entebbe, all with a negative result, and 7 by Dr. Wiggins, giving a total of 22. Then there were 5 with *Trypanosoma* in their blood—they were extremely interesting, because we lumbar-punctured them once a month regularly from March to July. In the case of 2 of them, they never showed the *Trypanosoma* until July. Well, that I think is very important to bear in mind, because we know that these patients had a considerable number of *Trypanosomata* in their blood, and on several occasions an appreciable deposit

of blood in the cerebro-spinal residue; and in spite of that there was no *Trypanosoma* to be seen. So that although there were a number of *Trypanosoma* in the blood, and an appreciable quantity of blood in the lumbar fluid, there were no *Trypanosomata* to be seen in the fluid itself.

Leaving the lumbar fluid, we come next to the blood of patients suffering from sleeping sickness, and the blood of controls. When I tell you that to find the *Trypanosoma* in the blood we very often had to draw off 10 c.c., and centrifuge it three or four times, you will understand that after having done about 25, we had had about as much as we found to our taste. It took quite a long time to do this, and in 15 out of 16 we found *Trypanosoma:* in the 16th, we tried seven times, but could not find it. Then we had to do controls, *i.e.*, healthy people: and this, perhaps, I had better split up into different categories. The first, that of healthy people from non-infected areas in Uganda. There are parts of Uganda, especially in the interior, where there is no sleeping sickness, and it was from one of these that these people came. They came into Entebbe to do a month's work, and ten of them used to be sent to us every day to have their blood examined. Our method was to draw off 10 c.c. and centrifuge it three or four times: we used to have three or four going at the same time, and in that way managed to get through several of them in a day.

We examined sixty-six of these people, and they were all negative. That, I submit, is a very interesting and important fact which ought to be borne in mind.

Similarly from a non-infected area in East Africa, where Captain Greig went to make some observations on *Glossinae*, fifty natives were examined, and in every case with a negative result. Therefore, you have 116 observations of healthy individuals in a non-infected area, and all showing absence of *Trypanosoma* from the blood.

I think I may say that all, except perhaps one or two, were examined by centrifuging the plasma after it had been pipetted off. This operation was repeated three times, and the residue examined again, and the *Trypanosoma* seen in the third or fourth residue.

The third category were those natives from the infected areas, viz.: the shores of the Victoria Nyanza, and especially the islands. We find that of seventy-four natives examined from these districts, *Trypanosomata* were present in 17 cases; in other words, 23 per cent. These numbers are slightly different from those given in our Report, but I think they are a little more accurate. I have altered them

a little, because they included other cases which do not come in this category: for example, you will find that, in our Report, five patients of Dr. Baker's are included in them. But they themselves were selected from a number of other natives. These—the seventy-four—were taken at random, and the *Trypanosomata* were found in seventeen of them, in other words, 23 per cent.

Then, lastly, we have these five natives, in whom they were found by accident when they had fever on them; and one European who had been exposed to the bite of the tsetse fly: he developed *Trypanosomiasis*, and was sent home.

We began to think that *Trypanosoma* had something to do with the disease, and we turned our attention to the tsetse fly. We inquired whether they had the tsetse fly in Entebbe, and we were told "No." But a few days after, we sent out into the forest, and found the tsetse fly: this showed us that we could not rely on what we were told; and after that flies were brought in by hundreds every day.

While on the subject of flies, perhaps I may say a few words about the distribution of the fly in Uganda. Very soon after finding the fly in Entebbe, we thought it would be interesting to ascertain, if possible, whether these flies were found throughout Uganda; and a circular letter was sent out to missionaries and others, to ask the natives to collect flies and send them in; and in that way large numbers of flies were sent in to us, sorted out, and a map was made, which has been published by the Royal Society, showing the distribution of the fly throughout Uganda; and it is interesting to note that in one part of Uganda, in the district of Busoga, the fly goes a long way inland. Why that is we have not been able to make out; but on the left bank of the Nile, the Uganda provinces, the tsetse fly is practically never found in the interior. Just before I left, I sent word asking the collector to send flies from the left bank of the Nile, and I did not get a single tsetse fly, although on the right bank they are found a long way down the Nile itself.

If you look at the map showing the distribution of the disease, and also at the map showing the distribution of the fly, you find a very close similitude between them, and you see that practically the distribution of the fly and the distribution of the disease are identical. I think myself that that is a very strong argument in favour of *Glossina* being the cause of dissemination of the disease. I travelled up the country, and I was struck by the fact that the fly

is extremely localised to forest areas and to the water's edge. The three most constant features in these fly areas are water, forest and dense undergrowth : I have never found them in papyrus swamps nor in grassy plains. The islands in the lake are full of the fly, and the islands are hotbeds of the disease. Some of the islands are practically depopulated, and the curious distribution of the fly certainly adds to the probability that it is the carrier or disseminator of the disease.

Then, as to experiments performed on animals. We used a large number of animals—monkeys, dogs, guinea-pigs, rats, sheep, goats, donkeys, oxen and a jackal. Unfortunately, the animal experiments were not very satisfactory. We found that only four animals took the *Trypanosoma* at all: that is, were at all affected by injections of *Trypanosoma*, viz., the monkey, the dog, the rat and the jackal. The others—sheep, goats, oxen, etc.—were not affected by *Trypanosoma* injections. They were still alive and well when I left, although they had been injected three or four times with *Trypanosoma*. The monkeys behaved very curiously. A few weeks after the injection, *Trypanosoma* appeared in the blood, but not very abundantly; it then became very numerous, but after a short time began gradually to disappear; and when I left, practically all the monkeys failed to show the *Trypanosoma* in the blood, and I am sorry to say they were all in a very good state of health. A few of them, however, died, as you have read in our Papers. One of them died of tuberculosis, and three others died after the inoculation of *Trypanosoma*, but whether as a result of that or not, it is extremely difficult to say.

The point I would like to bring out in these experiments is, that we did a number of parallel experiments. All animals were injected in pairs, the one with the *Trypanosoma* from the blood and the other with the *Trypanosoma* from the cerebro-spinal fluid, and all the blood *Trypanosomata* were taken from these five cases of what we used to call *Trypanosoma hominis*—the patients who did not show signs of sleeping sickness, although they had *Trypanosoma* in their blood. The two *Trypanosomata* behaved identically in the two sets of animals. They gave rise to similar appearances in the monkeys; behaved similarly in the dogs and the rats; and if the *Trypanosoma* did not appear in the one set of animals, it did not appear in the other. That led us to think we were dealing with one and the same *Trypanosoma*.

Other experiments favoured that view still more. When the *Trypanosoma* had disappeared from the blood in these injected monkeys, I re-injected them with the same *Trypanosoma*, to see whether that *Trypanosoma* would appear again in the blood, but it did not. The animal had apparently become to a certain extent immune. Then I thought one might see what would be the effect of injecting the other *Trypanosoma*. You see, in the first place, one had immunised the monkey with blood, or cerebro-spinal *Trypanosomata*. Then I injected the cerebro-spinal or blood *Trypanosoma;* and when I left the country the second *Trypanosoma* injected had not appeared in the peripheral blood. I think that tends to show that the two *Trypanosomata* are identical.

I come next to the feeding experiments, which have given rise to a certain amount of criticism. The flies which were used were, with very few exceptions, all fresh in from the country, and they were always kept overnight, so as to make them develop an appetite and to make sure that *Trypanosoma* would not be present in them. Then, on the next day, they were fed on an animal specially kept for the purpose: so that every fly brought into the laboratory was kept overnight, and then fed on an animal kept specially for that purpose, which was called a "fresh-fly" monkey or dog with a clean bill of health. Then the flies were kept for twenty-four or forty-eight hours, and finally put into the feeding-boxes for the feeding experiments. It has been said that we might have bred our flies, but that would have been extremely difficult. One could have done it, but seeing that we wanted a large number of flies, and that each female lays only one larva, and that that larva takes six weeks to become a fly, I am afraid that it would have taken too long to get as many as we wanted. I think we did develop about 100, or perhaps 120, young flies, in the whole eight or nine months that I was there.

Dr. Sambon, in his Paper, says that the fresh flies that we put on a monkey took only two or three weeks to give rise to *Trypanosoma* infection; whereas flies which had first fed on *Trypanosoma* patients took six or eight weeks to produce *Trypanosoma* in the monkey. That is true, but there are one or two reasons which I can give you to show why that was the case.

The fresh fly experiments were *pushed;* in other words, we used to get in about 100 flies a day, and, after keeping them overnight, we used to put them all on a monkey, so

as to get the experiments positive as soon as possible. In that way sometimes as many as 40 or 50 flies were put on a monkey, and all being very hungry they always fed very well: that explains why these experiments succeeded rather quickly. Since the hut-tax people have been kept out of Entebbe, the bites of the insects have been less certain of conveying *Trypanosoma*. I have placed as many as 750 flies on one monkey, and yet it has shown no signs of *Trypanosoma*.

Then there is another point. Dr. Sambon says that it took six or eight weeks to infect monkeys by the flies fed on sleeping-sickness patients. That is quite true. The fact is, the patients did not like the flies biting them very much. They often used to put their hands under the blankets and to take off the cages containing the flies, so that quite few flies were fed. Also, it seems that the flies got rather tired of the same patient; after feeding on him a few times, they did not feed nearly so well.

There are one or two other points on which I should like to touch. First, Dr. Sambon asked whether *Trypanosoma* is to be found in other animals. We did find *Trypanosoma* in other animals; but as we have not yet presented our Report to the Royal Society, I am not yet able to give you the details as to this, only that they were different *Trypanosomata*. It has been asked whether *Trypanosoma* has been found in healthy monkeys: but I say "No" most emphatically; we never found *Trypanosoma* in a healthy monkey, that is, a monkey straight from the field. All the monkeys were regularly examined as controls for weeks; but *Trypanosoma* never appeared except as the result of the feeding experiments or of inoculation. I am sure *Trypanosoma* is not a normal parasite in monkeys in Entebbe.

It has been suggested that *Trypanosoma* might be conveyed by some other blood-sucking insect; but the only other blood-sucking fly is the *Stomoxys*, and we did some experiments with them.

As to what Sir Patrick Manson said about the injection of blood from patients suffering from sleeping sickness, I would venture to point out to him that all the blood injections we made were from patients showing no signs of sleeping, and yet having *Trypanosoma* in the blood.

I have brought a few photographs which I think may interest the Society. They were taken by Mr. Stordy, the Government Veterinary Officer. They include a photo-

graph of the Persian patient, and one or two of the natives of Uganda.

Dr. F. W. MOTT said that his experience was pathological, not epidemiological. At present there were two theories for the epidemiology: (1) *Trypanosoma*, (2) *Diplococcus*; and Dr. Castellani had latterly adopted both, the micro-organisms being of the nature of a secondary infection. With regard to the morbid histology of the central nervous system, Dr. Mott had little or nothing to add to his original description, which was published in the *Transactions* of the Pathological Society. Examination of a number of cases from Uganda, and the European case of Sir Patrick Manson, had only shown the correctness of his presumption that the chronic inflammation of the membranes and nervous substance of the whole brain and spinal cord existed as exhibited by an extraordinary accumulation of *Lymphocytes* in the subarachnoid space, and in all the rivers, rivulets and streams of the cerebro-spinal fluid which surround the blood-vessels (the so-called Perivascular lymphatics)—channels which carry the special nutrifying fluid of the brain, and serve not only for the special metabolic processes of nutrition and the gaseous exchanges, but also to wash out the waste products. Such accumulation of *Lymphocytes* would interfere mechanically with the circulation of the fluid, and biochemically by the *Lymphocytes* taking up the oxygen which was normally intended for the nervous structures; hence a condition would arise not unlike that which he had seen in internal hydrocephalus, where ventricular accumulation of fluid produced lethargy and stupor, paresis, tremor, fits, etc. At first there was functional depression rather than destruction of the cells and fibres, later a true degeneration occurred. He might say that he had observed in several cases which he had examined, including the European case, a chemical change in the myelin sheaths without actual Wallerian degeneration, and he had observed the same appearance in certain chronic infectious processes. In the two cases which were in Charing Cross Hospital, a striking feature was the universally-enlarged lymphatic glands; and he found, on looking through Colonel Bruce's report, that in every case, with one exception, the glands were enlarged: the exception being a case of cerebral tumour and not sleeping sickness. A missionary who attended the meeting of the Pathological Society four years ago, stated that enlarged glands constituted a well-recognised symptom. They

had, then, three definite pathological facts: (1) excess of *Lymphocytes* in the blood contained in the vessels of the brain; (2) accumulation of *Lymphocytes* in the perivascular lymphatics and the subarachnoid space; and (3) enlarged lymphatic glands. In two of the cases recorded by Colonel Bruce, the glands were suppurating. Admitting that the glands of the groin and other superficial glands were very liable to enlargement in the Negro, owing to sores, etc., and admitting that syphilis was very prevalent among Negroes, still the fact remained that those causes would not account for practically nearly all cases having glandular enlargement, or for the special pathognomonic change in what constituted the special lymph canalicular system of the nervous system. Was this due to *Trypanosomiasis?* that parasite being really a blood parasite. Or was it due to an organism such as the Portuguese described, the *Diplococcus?* which, as far as he could see, was the same as Dr. Castellani had discovered, and to which in his first report he pinned his faith as the cause of the disease. Or did this organism, as he subsequently held (after his observation of the *Trypanosoma* in the cerebro-spinal fluid), act as an important subsidiary cause in a secondary infectious process? He stated in his report to the Royal Society that he had grown it with absolute certainty (and always pure) from eight out of ten *post-mortem* examinations from the cerebro-spinal fluid and blood of the heart taken with aseptic precautions. *In vita* he (Dr. Castellani) had found it only once in the blood, but he had grown it in two cases out of three from the cerebro-spinal fluid removed by lumbar puncture. In the *Journal of Tropical Medicine*, of June 1st, 1903, he had given further observations showing that that organism was present in the blood of the heart in 32 out of 39, and in 30 out of 39 in the cerebro-spinal fluid. In connection with those observations, Dr. Mott remarked that that infection would account for the lymphatic gland enlargement, and for the appearances which the cerebro-spinal, sub-arachnoid, and canalicular systems manifested in every genuine case of sleeping sickness. He had only had the opportunity of examining the lymphatic glands in two cases: one was that of the European patient of Sir Patrick Manson, and the other was an enlarged gland which he had not previously examined from one of his old cases. In both of them he found the *Diplococcus*. In the case of the former, every section of the gland showed numerous clumps of those organisms lying in the lymph channels of the gland, which were filled with cells and fibrin like the

appearances presented by the *Alveoli* in croupous pneumonia. It might be said that *Diplococcus* or *Streptococcus* infection was due to bed-sores and lung disease. He did not think so, for the following reason:—Dr. Eyre and himself had withdrawn cerebro-spinal fluid *post-mortem* from 21 cases of insane patients who had died mostly with lung disease, and many with bed-sores; and after careful examination, in not one did Dr. Eyre find *Diplococci*, and in one only *Streptococci*, and that was a case of suppurative *parotitis*. *Staphylococcus aureus* and *albus* were occasionally found, and sometimes *Bacillus coli*. He had been unable to find *Trypanosoma* in the blood-vessels or sub-arachnoid spaces of sections of the central nervous system, although he had looked at hundreds of sections. It might be urged that they could not be seen in sections, only in smears; but his assistant, Dr. George Watson, and he himself, had found that sections of the brain of a rabbit dying from Surra showed enormous numbers of the *Trypanosoma*, enough to produce mechanically the profound changes observed in the nervous system. But against the fact that they could not be seen in the vessels, it might be said that they took on a different form, or were hidden in the tissues in sleeping sickness. He did not regard the experiments on animals as conclusive. The strong arguments in favour of the *Trypanosoma* being the cause of that remarkable disease, to his mind, was the admirable research as regarded the distribution of the fly, the distribution of the disease, and its correlation with the existence of the fly and the existence of the *Trypanosoma* in the blood of the natives by Colonel Bruce and his assistants. The case under Sir Patrick Manson's care was of great importance in showing the chronic nature of the disease. That was of exceptional interest, because they found that the patient for a long time exhibited the *Trypanosoma* in the blood, and then died with the diplococcal infection, which in this instance might therefore be assumed to be related to the onset of the symptoms.

Mr. James Cantlie: I should like to ask Dr. Nabarro a question about this spreading of the disease. Has this spreading of the disease ceased? Is it limited to the districts marked on the map, or does it spread in all directions? I should like to ask whether or not Dr. Nabarro has gathered that the disease is stationary, or whether it has only reached a certain stage?

Dr. H. T. Bulstrode: So far as I understand the disease, its medium of conveyance is the *Glossina palpalis;* and if this view is wholly true, the danger of contracting the disease must be limited to the areas already inhabited by the fly, or areas to which it may be carried. We have heard about the distribution of the fly in Uganda, but not in Senegambia or Angola. I should like to know whether the areas of the disease and of the fly correspond there. In his Paper, Dr. Sambon drew a terrible picture of the possible spread of the disease up the Nile, across the Suez Canal, and along the coast to India. I fail to see how that could happen. So far as I gather, the disease is not directly communicable from person to person, but only through *Glossina palpalis,* and therefore in the area of the distribution of that fly. Dr. Nabarro has spoken of the depopulation of an island by sleeping sickness. This fact suggests that the distribution of the fly has extended, or that the *Trypanosoma* may have other agencies of spread than *Glossina palpalis.* Otherwise, it is difficult to understand how the island in question became peopled in the first instance. It appears to me that if the distribution of *Glossina palpalis* is not altering, there should be little danger to the residents of fly-free areas in the importation of infected human beings, as the disease is not directly communicable. Probably, however, we are only in possession of part of the whole story.

Mr. E. E. Austen, of the Natural History Museum, South Kensington, in writing to express his inability to be present at the adjourned discussion, asked permission to state that his interpretation of the "exact facts" was at variance with that of Dr. Sambon. Mr. Austen adds: "The point is a small one, but it should, I think, be cleared up. According to Dr. Sambon, Dr. Brumpt and himself were "the first to publish a definite opinion" as to the agency by which sleeping sickness was carried, and Dr. Sambon had stated that his views had been expressed "in a lecture on Sleeping Sickness delivered at the Livingstone College, and subsequently published in the *Journal of Tropical Medicine* of July 1st, 1903;" and Dr. Sambon adds: "Dr. Brumpt's observations were published on July 2nd . . . . . Brumpt incriminated *Glossina morsitans;* I suggested a West African species, and more especially the widely-distributed *Glossina palpalis.*" Now it is true that in the reprint of his former lecture, to which Dr. Sambon refers, he gives a figure of *Glossina palpalis* (copied, *without acknowledge-*

ment, from my *Monograph of the Tsetse-Flies*), but the illustration appears merely as Fig. 3, without any name or description whatever! Moreover, in the text, after indicating reasons for supposing that "a fly of the genus *Glossina*" is the carrier of the disease, and stating that "the genus *Glossina* comprises several species, some of which have a wide distribution in West Africa," Dr. Sambon simply adds: "The carrier of sleeping sickness should be sought amongst the latter." *Nowhere in the reprint of this former lecture does Dr. Sambon suggest that especial suspicion attaches to Glossina palpalis;* and, moreover, the only occasion on which he mentions this species by name is in connection with remarks on the occurrence of tsetse-flies in general in the vicinity of water, when he refers to my observations on the habits of *Glossina palpalis* in the neighbourhood of Freetown, Sierra Leone.

In his Preface to my *Monograph of the Tsetse Flies*, after alluding to my determination of ten specimens of *Glossina palpalis* among a small box of biting flies just received from Entebbe, Uganda, and sent home by Colonel Bruce, Prof. Ray Lankester wrote as follows: "This particular species of tsetse-fly is essentalliy a West African species, known from the Gambia to the Congo. It certainly suggests the need for an inquiry into the possible connection between this fly and the sleeping sickness, when we remember that that disease has been established for years on the West Coast of Africa, but was unknown in Uganda until two years ago. Sir Henry Stanley met with "tsetse-fly" for a long distance on the Upper Congo; and it is suggested by Mr. Austen that *Glossina palpalis* reaches Uganda by way of the valleys of the Congo and the Aruwimi."

Whether *Glossina palpalis* is, like sleeping sickness itself, a recent importation into Uganda, or whether—as seems more probable—the fly has been established there from time immemorial, the foregoing quotation is, I think, sufficient to dispose of Dr. Sambon's contention that he was the first to suggest a connection between *Glossina palpalis* and sleeping sickness. Professor Lankester's Preface was written on May 15th, 1903, and my *Monograph*, in which it appears, was published before the end of the following month. Dr. Sambon's lecture, in which, as I have shown, there is no reference whatever to *Glossina palpalis* in connection with sleeping sickness, only appeared in print in the number of the *Journal of Tropical Medicine*, dated July 1st, 1903.

DR. NABARRO: In reply to Dr. Cantlie, I think I may say the disease is spreading along both shores of the lake. It is spreading on the western shore of the lake, and also on the eastern shore; I understand, in both cases, approaching German territory. The Germans are becoming rather anxious about it, and they sent one of their colonial surgeons over to Entebbe, to study the disease and learn something about it. We showed him many things, and gave him a good deal of information; and he went back quite satisfied with our statements, and ready to deal with the disease, if it should spread into their territory. It is certainly spreading on the Kavirondo side, on the north-eastern shores of the lake.

With regard to how the disease is spread, that, I must own, is a difficult question, because the *Trypanosoma* is very scanty in the blood of the patients. I personally think, from what I have seen, that they are more numerous in the blood in the early stages of the disease than they are in the later stages. I have thought that possibly the fly gets a larger number of *Trypanosoma* in him in the early stages of the disease than later on. Then the period of incubation may extend over years, in all probability. There are cases on record in which the latent period extended over several years.

Again, I think the fly has been in the country for a long time, but that the *Trypanosoma* has only recently been introduced into the country; and I know for a fact that the Albert Nyanza, situated to the north-west of Victoria Nyanza, has the fly all round its shores, but there is no sleeping sickness there. That we ascertained only shortly before I came away. One of the collectors in the Uganda Service was sent there, and he found a number of flies, but there was no sleeping sickness; and one fears that if infected patients should get there, they might spread the disease. When infected patients get into the interior of Uganda the disease dies out with them, just as malaria would if there were no mosquitoes. People have gone from the shores to the interior, but the disease has never spread from them to other inhabitants of the house or other people in the village. All the *Trypanosomata* we found in animals seemed to be different from the *Trypanosomata* in sleeping sickness. I would like to remind you that the work of investigation is still going on, and that further experiments have yet to be made. There is no doubt, however, about the ravages of the disease. I believe, in Usoga itself, nearly 50,000 people died last year. It

is a perfect abode of the dead: all the villages are depopulated.

Dr. C. F. Harford: Mr. President and Gentlemen,—I really have no right to say anything in this matter, since I have not had an opportunity of making any recent observations of sleeping sickness; but as I had a case under somewhat prolonged observation now some fourteen years ago, I may say a word or two with regard to the subject. My attention was drawn to the case by the natives, who seemed to have a great knowledge of the disease, although it was in a part of Africa where only sporadic cases occur—on the Upper Niger, at the confluence of the Upper Niger with the Benue. It seems curious that they should have so close an acquaintance with the disease, seeing that so few cases occurred, and those not as an epidemic.

One point which always impressed itself upon the natives—that is, the intelligent natives—whom I spoke to, was the occurrence of these enlarged glands. I think that is a matter of considerable importance: the natives there had distinctly the idea that if the lymphatic glands were removed, the disease would be cured: they told me that they had performed the operation, with the result that the disease was cured. My idea of that suggestion was that they probably regarded all cases of enlarged glands as sleeping sickness,; and that when they had scratched out the glands, and sleeping sickness did not develop, they thought they had cured the disease.

I was very much interested in this case, and I made certain inquiries from educated natives; and one fact to which they drew my attention was, that it only attacked the natives of tropical countries: in other words, they regarded it as a disease of the negro race.

I am interested in the subject also from the practical point of view. I have at my college students—missionaries—who have had a great deal to do with the disease, both on the Congo and in Uganda, and seen a good deal of it there. Also, in my position as Physician to the Church Missionary Society, I hear a good deal of it from missionaries who have come there, and from my friends, Drs. A. R. & J. H. Cook, who, I am sure, have contributed something to the elucidation of this problem. Although these gentlemen have not now much opportunity for scientific research, owing to their arduous medical missionary labours, still they have done a good deal, as you may have

seen from Dr. Cook's paper in *Journal of Tropical Medicine* some time ago. Naturally, he makes no mention of *Trypanosoma;* his investigations being devoted to the inquiry with regard to *Filaria perstans.*

I think we owe a great deal to Dr. Sambon for having read to us such a careful Paper, and such a large amount of evidence with regard to this important disease: and I hope that we may express the desire that some practical steps shall be taken to deal with this subject. It seems to me that whatever may be the possible conclusion to this subject, there cannot be much question that the tsetse fly is an insect which is a terrible scourge, not only to men but to animals, and that every effort ought to be made to see what can be done to deal with the tsetse fly in its haunts. I am not in any way a naturalist; but I do hope that something may be done to thoroughly go into this question.

Perhaps I may mention one practical step that has been taken in Uganda: that is, the authorities of the Uganda Industrial Mission have felt so strongly the danger of having their establishment in a fly zone, that they have actually taken the step of abandoning most valuable premises in order to get away from that district. That shows that there is a good deal of belief in the importance of this discovery. I think we ought to take steps, in order to make practical use of it.

Sir Patrick Manson, K.C.B., F.R.S.: I should like to make one or two suggestions for further inquiry. Dr. Harford spoke about sporadic cases of sleeping sickness. There is no question about the existence of these cases, for you get them in many places—on the West Coast of Africa, on the Gambia, in Sierra Leone, up the Niger—in all these districts you get occasional cases of sleeping sickness, and yet you do not get it in epidemic form. It would be interesting to know the relation these cases bear to the presence of *Trypanosoma* in the general population of these particular places.

A good many years ago I was asked to see a patient in consultation at St. Thomas' Home: a missionary who had come from German East Africa. He presented a curious combination of symptoms, and I confess I could not understand them. He had a peculiar enlargement of the glands, great prostration, and half a dozen other symptoms, which now I know must have belonged to *Trypanosomiasis.* This missionary, I believe, had never left German East Africa. If there be one case of *Trypanosoma* disease in German

East Africa, why not many? He must have been infected in some manner. If there was sleeping sickness in German East Africa, I think it is quite possible that you may have sleeping sickness in many other places; but the disease has not been recognised. This remark is borne out by what we now know about a similar disease: it has been ascertained only within the last few weeks as regards this disease that it belongs to the same category as *Trypanosomiasis*—I allude to the pest known in India as "Kala-azar," which is now known probably to be attributable to a *Trypanosoma*-like parasite inhabiting the spleen, liver, and bone marrow. It was at one time supposed that this disease was confined to one part of the country; but of late it has been found all over the country, and has depopulated some of the places through which it passed. It now appears that a similar disease exists in China. Only lately a German pathologist has recorded a case in the person of an individual who came from Pekin. I myself saw a similar case in a gentleman from South Africa; and I am fairly certain I have seen a similar case in a soldier from Aden. And this *Trypanosoma*-like disease has the same distribution characteristics that are now fairly recognised as belonging to *Trypanosoma* disease. You get places where it becomes epidemic, and places in which it is sporadic. It would be interesting to find out the exact conditions which determine the epidemicity, and (to coin a word) the sporadicity of the disease.

As Dr. Mott has suggested, I think there is probably a combination of causes in sleeping sickness, viz.: *Diplococcus* and *Trypanosoma*; and I think the experiment which he suggests, that a monkey which has *Trypanosoma* should be inoculated with *Diplococcus*, in order to see whether the double infection would produce the disease, would be a very useful one. I strongly advocate that the Commissioners now in Uganda should follow out Dr. Mott's suggestion.

I would like to make another observation in connection with the suggestion that the presence of *Trypanosoma* in the cerebro-spinal fluid was the determining cause of the symptoms of sleeping sickness. I do not hold with that idea: I think it is a little far-fetched. I think the *Trypanosoma* is the cause of the sleeping sickness; but to dogmatise as to the processes, or as to the manner in which it causes it, is going a little beyond the facts. When a patient is afflicted with inflammation of the central nervous system, naturally the parts are congested; the vessels are

congested and prone to rupture, and there is an escape of blood undoubtedly into the cerebro-spinal fluid; and one would naturally expect that any organism such as *Trypanosoma*, which is capable of defending itself against the *Phagocytes*, would remain in the cerebro-spinal fluid for some time.

I think it is necessary to be cautious in interpreting a condition of this sort. There is a certain phenomenon which occurs in connection with *Filaria*. You sometimes get rupture of the lymphatic vessels, and effusion of lymph into the tunica vaginalis, and the production of the disease which used to be known as Chylocele. If you examine the fluid in these cases you will find millions of living *Filariae*, much more abundantly than in the blood even; the reason for that being this: the ruptured vessel permits the lymph to escape and the *Filaria* with it; but the *Filaria*, not being able to find their way back, are imprisoned as fish in a net. I believe exactly the same thing happens in the case of *Trypanosoma:* that a rupture of the vessels allows them to escape. Moreover, the red-blood corpuscles would tend to settle down, whereas *Trypanosoma*, being endowed with powers of motion, would be likely to move about and become diffused. I think we should not attach too much importance to the appearance of *Trypanosoma* in the cerebro-spinal fluid, as being part of the pathology of the disease.

One word in conclusion. I think the profession has been a little unjust—I don't want to say disagreeable things, but I think the profession has been a little unjust, in the way in which it has ignored the work of the early investigators into this Uganda disease. When Dr. Low, Dr. Castellani, and Dr. Christy were sent out by the Royal Society, they got specific instructions to investigate on certain lines: more especially they were asked to determine whether *Filaria perstans* was the cause of sleeping sickness; and the plan by which they were to set about it was to see whether the areas of the parasite and the disease corresponded. That piece of work they carried out thoroughly, and they got no credit. Also, they were to find out, or endeavour to find out, any micro-organism that might possibly be considered as the cause of the disease. That they certainly did, for Castellani, in the first place, determined the presence of this *Diplococcus* which, as Dr. Mott says, is often found in such cases, and in the second place, he (Castellani) demonstrated the presence, in a large proportion of cases, of *Trypanosoma* in the blood.

Also, Dr. Christy has shown that the range of *Filaria perstans* and of sleeping sickness do not correspond. I think those early investigators have done their work thoroughly, and I think they should receive due credit for what they have done.

Dr. Frederick Mott: I should just like to say that I have only found this *Diplococcus* in this case of Sir Patrick Manson's, and I think he perhaps misunderstood me. I was referring to the work of Dr. Castellani and Colonel Bruce.

Major McCulloch: There is one point on which I should like to ask a question. Dr. Sambon says that "a fly disturbed while sucking a *Trypanosoma*-infected animal *may* convey the disease to a healthy animal by means of its blood-soiled proboscis, just as malaria may be conveyed by a needle soiled with malaria-infected blood." But I think Dr. Nabarro examined the probosces of a considerable number of flies, and actually found *Trypanosomata* in them. There is also one little inaccuracy, I think, and that is the conveying of malaria-infected blood. Of course, he can scarcely mean that malaria-infected blood can convey malaria to the human body.

The President: Before calling upon Dr. Sambon to reply, I should like to tender to him our grateful thanks for his very interesting Paper, which has led to so instructive and valuable a discussion. This proposal was warmly seconded by acclamation.

Dr. Sambon: Before replying to the various criticisms, I must thank you for the kind way in which you have listened to my Paper. I am very pleased that Dr. Nabarro is here to-night; and although I take objection to some of his experiments, and especially to the conclusions he draws from them, I feel great regard for the work he has so actively carried out, together with Colonel Bruce and Captain Craig, in Uganda.

Dr. Nabarro admits the correctness of my remarks as to the time elapsing before the appearance of trypanosomes in the blood of monkeys submitted to the bite of tsetse flies; he owns that a much longer period elapsed when the flies were previously fed on cases of sleeping sickness than when they were made to bite the monkeys directly and immediately after being caught; but he endeavours to explain thi fact by stating that the experiments made with flies

not previously fed on cases of sleeping sickness were *pushed:* that is to say, that in these experiments a much larger number of flies were used in order to obtain a positive result as soon as possible; whilst in the other set of experiments not only *fewer flies were used*, but many of them were *not properly infected*, partly because the patients on which they were placed prevented them biting, and partly because the flies got tired of the same patient after feeding on him a few times. These statements now made by Dr. Nabarro are at variance with those published in the "Further Report."

The data published in the Report are as follows:—

First Set of Experiments.

Five monkeys (Exp. 114, 115, 99, 97, and 116) were submitted to the bite of flies fed previously on cases of sleeping sickness.

Exp. 114.—880 flies were employed. Of these, 522 actually fed on the patient, and were placed on a monkey after a fast of 8 hours. The monkey showed trypanosomes in its blood 65 days after first bite.

Exp. 115.—881 flies used; 509 fed, and were allowed to bite monkey after a fast of 8 hours. Trypanosomes appeared after 75 days.

Exp. 99.—582 flies used; 508 fed, and were placed on monkey after a fast of 24 hours. Trypanosomes appeared after 70 days.

Exp. 97.—294 flies used; 255 fed, and were allowed to bite monkey after a fast of 48 hours. Trypanosomes appeared after 48 days.

Exp. 116.—354 flies used; 277 fed, and were allowed to bite monkey after a fast of 48 hours. Trypanosomes appeared after 65 days.

Second Set of Experiments.

Three monkeys (Exp. 94, 130, and 131) were submitted to the bite of flies freshly caught, and not previously fed on patients suffering from sleeping sickness.

Exp. 94.—186 flies used. Trypanosomes appeared after 14 days.

Exp. 130.—1,034 flies used. Trypanosomes appeared after 29 days.

Exp. 131.—757 flies used. Trypanosomes appeared after 23 days.

In the face of these data, Dr. Nabarro's explanations are inadmissible. Indeed, you will notice that in Exp. 94, when fewest freshly-caught flies were used (186), a positive result was obtained in the shortest time (fourteen days); and that in Exp. 115, when as many as 881 flies were

used eight hours after feeding on a sleeping sickness patient, it took the longest time (seventy-five days) to obtain a positive result.

Dr. Nabarro's remarks as to the number of flies which did actually bite the sleeping sickness patients are likewise contradicted by the following statement in the "Further Report," p. 56, Section 12:—

"The sleeping sickness patients did not seem to feel the bites of the flies, as they made no complaint or other signs of inconvenience. There was, as a rule, about thirty flies in each cage, *but only those which filled themselves were reckoned as having fed.*"

My criticism of the experiments made by Colonel Bruce, Dr. Nabarro, and Captain Craig, is based on the facts published by these gentlemen in their "Further Report." I never thought of doubting their accuracy, but unfortunately Dr. Nabarro's statements to-night do not tally with those published in the Report.

Dr. Nabarro remarked that the rearing of flies for the experiments would have involved too much time. Certainly, it would have taken more time, and would have needed more care; but the results of the experiments would have been of a more definite and valuable kind. Dr. Nabarro says: "I think we did develop about 100, or perhaps 120, young flies." It is a great pity he did not use these flies. It is likewise to be regretted that Dr. Nabarro and his collaborators did not try experiments with *Stomoxys*, because some observers believe that these flies are capable of conveying the trypanosomes of nagana. Most of all I regret that—knowing that tsetse flies were to be found on one bank of the Nile and not on the other—Dr. Nabarro did not thoroughly investigate this all-important point.

Dr. Bulstrode has asked whether the distributional areas of *Glossina palpalis* and of sleeping sickness correspond in Senegambia or Angola. As to Senegambia and Angola, the available information is rather scanty, but so far as it goes it is certainly in favour of correspondence. On the Congo, Dr. Brumpt has made very careful investigations, and he has shown that there is a very close connection between tsetse flies and sleeping sickness. Dr. Brumpt noticed that where the men remained inland for agricultural work, the disease attacked the women who went to the river to get water. In other cases, where the men went to fish, they contracted the disease, while the women who remained in their villages were spared. The Trappist Fathers have a

mission at Banamia, about twenty minutes from the Congo. A few years ago, some 3,000 Lolo fishermen lived on the river bank; now this number has fallen below 300. The others have been destroyed by the sleeping sickness. Close to the mission is a village of cultivators; the latter rarely go to the river and drink the water of local springs. The disease is almost unknown to them.

Dr. Bulstrode seems to think that I have drawn a very terrible picture of the possible spread of the disease up the Nile, and by means of the coast to India. He says he fails to see how that could happen. Well, a few years ago, no one would have believed that sleeping sickness might spread from its old endemic centres on the Congo to the Victoria Nyanza; now it is rapidly encircling the lake. As to the Nile, already some doubtful cases have been described from Korosko; and we know that *Glossina palpalis* and other tsetse flies are to be found on its banks. The spread of the disease does not depend only on the distribution of its insect host, but on a number of other œcological conditions as yet unknown to us. Wherever sleeping sickness and tsetse flies coexist, their topographical distribution is the same, but geographically their distributional areas do not overlap. There are plenty of places in Africa abounding with *Glossina palpalis* and other tsetse flies, but without sleeping sickness; just as there are many places in Europe abounding with *Anopheles maculipennis* and other anophelina, but without malaria. However, in a general way, it is quite reasonable to surmise that sleeping sickness may invade any region inhabited by its necessary carrier.

Major McCulloch remarked that I was inaccurate in stating that malaria might exceptionally be conveyed from one man to another by means of a needle soiled with malaria-infested blood. But I will mention a very striking case which happened in the Hospital of St. Spirito, in Rome. While examining a slide of blood from a case of sub-tertian fever, Dr. Pinachi broke the slide and cut his finger. He washed the wound very carefully, and thought no more about it. However, after a short period of incubation, Dr. Pinachi suffered from a severe attack of sub-tertian fever; and, notwithstanding a prompt and plentiful administration of quinine, came very near losing his life.

Professor Lankester suggested that I should correct a statement in my Paper with reference to the number of cases examined by Dr. Castellani, and as to the interpretation given by the latter to the presence of trypanosomes in

these cases. I am well aware that Professor Lankester contends that Dr. Castellani did not understand that the trypanosomes found in the cerebro-spinal fluid of sleeping-sickness cases could have anything to do with the disease, until Colonel Bruce pointed it out to him. I know also that numerous articles have appeared, both in medical and in non-medical papers, expanding on Dr. Castellani's discovery of a *Streptococcus* in sleeping sickness, and even going the length of reproducing a factitious illustration of the bacterium, in order to disconnect his name from the discovery of the trypanosome; but all this is very unjust. I have nothing to correct; indeed, my statement is couched the very words employed by Colonel Bruce in his progress Report:—

"Dr. Castellani informed us of the work he had done: one especially interesting observation being that he had discovered trypanosomes in the cerebro-spinal fluid in 5 out of 15 cases of sleeping sickness. Dr. Castellani remained in Entebbe for three weeks after the arrival of the new commission, and during this time *he examined* 29 *further cases for trypanosomes, with the result that* 70 *per cent. were found to contain these parasites. Dr. Castellani, we presume, has already published these results.* After his departure, the commission continued to pursue this line of work."

In his "Further Report," Colonel Bruce says: "At the time of the arrival of the commission, Castellani did not consider that this *Trypanosoma* had any causal relationship to the disease, but thought that it was an accidental concomitant, like *Filaria perstans.*"

However, he adds: "This most interesting discovery of Dr. Castellani's, which was due to his introduction of the method of centrifugeing the cerebro-spinal fluid in his search for his *Streptococcus,* has been of the utmost possible value to the present commission. It put them at once on the right track, and led to the rapid and easy elucidation of the etiology of this hitherto mysterious disease. Without a knowledge of his observation, they might have worked for months in the dark; and, in truth, they might even have returned to England still ignorant as to the true cause of the disease."

Let us place ourselves for a moment in Dr. Castellani's position. When he first discovered *Trypanosoma* in the cerebro-spinal fluid of a patient suffering from sleeping sickness, should we have jumped at once to the conclusion that the *Trypanosoma* found in this single case was un-

doubtedly the cause of the disease? Later, when Dr. Castellani found the *Trypanosoma* in 5 out of 15 cases, would it have been reasonable to incriminate this parasite, when it was known that *Trypanosoma* fever—then believed to be a distinct disease—was present in Uganda? But when the *Trypanosoma* was found in over 70 per cent. of sleeping-sickness cases, and not in the cerebro-spinal fluid of *Trypanosoma*-fever cases, and never in healthy persons, was it necessary for anyone to point out that *there might be a connection between the Trypanosoma and sleeping sickness?*

Professor Lankester then made some disparaging remarks with reference to my own researches concerning the transmission of sleeping sickness. He said there was nothing in them. The suggestion that a tsetse fly might be the carrier would occur to anybody. The real interest in the matter is, that Colonel Bruce found *Glossina palpalis* where it was not previously known. I have fully explained in my Paper the reasons which led me to incriminate a West African tsetse fly, and more especially the widely-distributed *Glossina palpalis*. I will not go over the same ground twice. I know full well that the suggestion of a tsetse fly occurred to many: it occurred to Professor Blanchard, to Professor Laveran, to Dr. Mesnil, to Dr. Brumpt, to Colonel Bruce, to Professor Lankester, and to many others; but, as Dr. Brumpt remarked, in the course of the discussion, there is some difference between a mere suggestion, based on analogy, and the deduction from carefully-observed facts. As to the discovery of tsetse flies in Uganda, surely it should not be my place to inform Professor Lankester that tsetse flies have been known to occur in Uganda many years before their "discovery" by Colonel Bruce. Sir Harry Johnston, in his admirable book on the Uganda Protectorate, says: "Flies of the genus *Glossina* exist in the Uganda Protectorate. They have been caught there by Mr. Jackson and myself, not to mention many other collectors." Professor Lankester's generosity towards Colonel Bruce is unbounded. In the preface to Mr. Austen's *Monograph of the Tsetse Flies*, he states that the discovery by Colonel Bruce of a *Trypanosoma* in nagana led to the discovery of a similar parasite in surra. Professor Lankester should correct this statement, because the *Trypanosoma* which gives rise to surra was discovered by Griffith Evans fifteen years previously; and, indeed, it was this discovery which led to the elucidation of nagana, a disease very probably identical with surra.

Professor Lankester's remarks have been followed up by a letter by Mr. Austen, also, of the Natural History Museum, in which the priority in suggesting that *Glossina palpalis* is the carrier of sleeping sickness is attributed to Professor Lankester. Evidently, the matter of priority is not so unimportant as Professor Lankester stated when discussing my claims. According to Mr. Austen, the priority is due to Professor Lankester, because the latter made the suggestion in a preface dated May 15th, 1903, but not published until the end of June. My Paper appeared in the *Journal of Tropical Medicine* on July 1st, 1903, but was read at the Livingstone College at the end of May. This as regards dates. But let us examine the reasons which led Professor Lankester to suggest a possible connection between *Glossina palpalis* and sleeping sickness. On the 15th of May, 1903, Professor Lankester received a small box from Entebbe, containing some biting flies sent home by Colonel Bruce for determination. Mr. Austen examined these insects, and found amongst them ten specimens of *Glossina palpalis*. As this particular species had not been hitherto described from East Africa, Mr. Austen surmised that it might be a recent importation into Uganda, and that it reached the Protectorate by way of the valleys of the Congo and the Aruwimi.

It is entirely on this assumption that Professor Lankester bases his suggestion. He says: "This particular species of tsetse fly is essentially a West African species, known from the Gambia to the Congo, It certainly suggests the need for an inquiry into the possible connection between this fly and the sleeping sickness, when we remember that that disease has been established for years on the West Coast of Africa, but was unknown in Uganda until two years ago." Unfortunately, Mr. Austen's assumption is erroneous. *Glossina palpalis* is not of recent introduction into Uganda. Although widely spread in West Africa, it is by no means limited to that part of the Continent. Sir John Kirk found it on the Zambesi in 1860, and Dr. Brumpt found it on the River Omo; on the Nile, in the vicinity of Nimulé; and all along the Congo, from the sources of the Welle to Matadi. However, apart from this, Professor Lankester's suggestion is very vague, and does not differ from that made previously by Professor Blanchard and others, with the exception that it limits to *Glossina palpalis* a *rôle* which is probably played by other tsetse flies.

Mr. Austen endeavours to prove that I did not suggest that especial suspicion attaches to *Glossina palpalis*. He says: "Now it is true that in the reprint of his former

lecture, to which Dr. Sambon refers, he gives a figure of *Glossina palpalis*, but the illustration appears merely as Fig. 3, without any name or description whatever!" The fact that I gave a figure of *Glossina palpalis* should be sufficient evidence that I did especially incriminate this species. At the same time, I did not wish to exclude all other species. This can be done only by means of appropriate experiments; and that is why I did not mention only *Glossina palpalis*, but said that the carrier of sleeping sickness should be sought amongst those species of the genus *Glossina* which have a wide distribution in West Africa.

Professor Lankester incriminated *Glossina palpalis* simply because he received a box of flies from Entebbe containing specimens of this species. I incriminated *Glossina palpalis* on account of other reasons already stated, and without knowing for certain that this species was to be found in Uganda. Recent information shows, I think, that I was working on sound lines. The omission of the descriptions under the figures was an oversight in the printing. It was corrected soon after in the reprints of my Paper.

Colonel Bruce and Dr. Nabarro did not determine the flies they used in their experiments; they merely tell us that they noticed two varieties of tsetse flies, one darker than the other. Therefore, even admitting that they succeeded in transmitting Castellani's *Trypanosoma* from sleeping-sickness patients to monkeys, it would be impossible to say quite definitely whether *Glossina palpalis* is a carrier, and whether it is the only carrier, of sleeping sickness.

Professor Lankester finally attacked my contention that the tsetse fly does not carry the trypanosomes in a passive way, as maintained by Colonel Bruce, but that it acts the part of a true alternative host. He says: "It is no use claiming priority for a thing of that kind; the thing is to show that a change occurs." Well, I think that I have produced a certain amount of evidence. I have stated that we find various forms of trypanosomes in the blood, and that some of these forms, such as the large, stumpy forms, with short flagellum and numerous dark-staining granules in their plasma, are undoubtedly sexual forms which must go through further development; but even if the trypanosomes underwent no change within the body of the fly, comparable to that of the malaria parasites, still I think we should have enough evidence to prove that the tsetse fly does not act merely as a passive carrier but as a true

and necessary host. Finally, the results obtained by Colonel Bruce and Dr. Nabarro in their experiments greatly strengthen my belief that the trypanosomes can be transmitted by the tsetse fly to its progeny; and that, therefore, some tsetse flies may be able to transmit the infection on issuing from their puparium.

Dr. Mott's remarks concerning the *Streptococcus* are very interesting, and tend to support Castellani's theory that both the *Trypanosoma* and the *Streptococcus* may be concerned in the causation of sleeping sickness. The bacterium might possibly be the cause of the terminal nervous symptoms, and the trypanosome its carrier from one anatomical region to another: just as *Dysenteriae amœba* may be the carrier of *Streptococci* into the liver. This association would explain the very variable length of time elapsing in different cases between the moment of infection and the onset of nervous symptoms. At one time it was generally believed that only one disease at a time could develop in man, and that only one disease at a time could prevail in a place. Now, we are beginning to understand that the morbid state may be the resultant of several disease agents; and, indeed, amongst pathogenetic organisms there may be a kind of *metabiosis* similar to that which brings about the fermentation of wines and the so-called "ripening" of cheeses.

Sir Patrick Manson expressed a doubt that the *Trypanosoma* might not have any connection with sleeping sickness. Considering that Sir Patrick Manson has himself contributed the most convincing evidence in favour of a causal connection between the *Trypanosoma* and the disease, I believe his doubt is more figurative than otherwise. The analogy between the symptoms of sleeping sickness and those peculiar to nagana, surra, and other *Trypanosoma* diseases of horses, dogs, and cattle, the constant presence of trypanosomes in patients suffering from the disease, the appearance of nervous symptoms in concomitance with the invasion of the central nervous system by the parasite, the development of sleeping sickness in people far and long removed from the endemic centres of the disease, the demonstration here in England of trypanosomes in the blood of Sir Patrick Manson's case long before the manifestation of nervous symptoms, and the striking experiments mentioned by Dr. Brumpt, show that there can be no further doubt as to a causal connexion between Castellani's trypanosome and sleeping sickness.