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The Comparative Neuropathology of Trypanosome and Spirochæte Infections, with a Résumé of our Knowledge of Human Trypanosomiasis.

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The study of the diseases produced by spirochæte and trypanosome infection is primarily biological. The contagium vivum is a living organism whose activities, like that of all living organisms, are for self-preservation, and especially the preservation of the species. The chemical toxins which these organisms produce are to enable them to live and multiply. It is generally believed that the spirochætes are organisms whose characters link them to the protozoa rather than to bacteria. The *Spirochæta pallida* contracts, moves, and modifies its structure in a manner different from a bacterium. The appearance of resting forms is totally different and they arise in a different manner to the spores of bacteria. Again, the clinical aspects of affection from a spirochæte invasion differ from that of bacterial diseases and conform especially to certain trypanosome infections. There is a periodicity of the symptoms altogether unknown in bacterial diseases, but what has struck me from my own personal experience and knowledge is the great similarity of the histological lesions of the nervous tissues of chronic trypanosome infection—for example, sleeping sickness and the *mal de coit* of horses—to syphilitic and parasyphilitic lesions. Again, there is similarity in the fact that lymphocytes and plasma cells are found in the cerebrospinal fluid in trypanosome diseases of animals and man—for example, sleeping sickness. Moreover, Levaditi has shown that in point of view of sensibility in respect to hæmolysing poisons, blood corpuscles, spirochætes and protozoa generally constitute a homogeneous group, and the spirochætes correspond in this respect more to the protozoa than the

bacteria. It is probable that the periplasium of these protozoa contains a complex of lipoid substances similar to red-blood corpuscles and animal cells generally. This is an important fact, for it possibly affords an explanation of the action of organic arsenic compounds in the treatment of these diseases; for it may be that such drugs as atoxyl, soamin, "606," &c., have an elective affinity for the lecithin complex entering into the formation of the periplasium. By the periplasium I mean the osmotic membrane which covers the viscid protoplasm constituting the body of the organism. Moreover, we can understand why, when energetically pushed, they may injure the nervous system and produce neuritis by combining with the lecithin of the nervous tissue.

Trypanosomiasis corresponds with syphilis in being a disease characterized by inoculation, a period of incubation, affection of nearest lymphatic glands, followed by generalization in the lymph, then the blood-streams, and afterwards by successive eruptions, due to escape of trypanosomes from the blood-stream into the lymph spaces of the tissues, where they set up a similar tissue reaction. Moreover, in severe trypanosomiasis, as in severe syphilis, there is always, or nearly always, a polyadenitis.[1] In the central nervous system in sleeping sickness there is a chronic lymphangitis affecting the membranes and perivascular spaces, due, no doubt, to the escape of the trypanosomes from the blood-stream into the lymphatics in the same way as they escape into the vessels of the skin; they set up in the perivascular lymphatics a chronic inflammatory, endothelial and connective-tissue cell hyperplasia. Both in syphilis and sleeping sickness the location of the evidence of most severe irritation is in the region of the base of the brain; this fact may be due to a direct extension along the lymphatics of the large vessels and nerves entering the base of the skull, or to the greater amount of cerebrospinal fluid in this region and the relatively larger size of the fluid sheaths of the perforating vessels. There is one striking difference between the effects on the nervous system of infection of *Trypanosoma gambiense* and *Spirochæta pallida*, and that is that, whereas every case of this trypanosome infection leads eventually to invasion of the nervous system, in syphilis not more than 5 per cent. to 10 per cent. even of untreated cases result in invasion of the nervous system. I believe this

[1] While the *Trypanosoma gambiense* is still conveyed to man by a specific fly, the *Glossina palpalis*, it is recognized that the *Trypanosoma equiperdum* owes its power of transmitting dourine, or the *mal de coit*, from horse to horse to the fact that it has acquired the habit of perpetuating its species by multiplying in the mucous fluid found at mucous orifices. Possibly the *Spirochæta pallida* has likewise acquired new habits, and, though now transmitted direct from man to man, was at one time dependent upon a biting insect, just as now is the spirochæte of tick fever.

fact has a biological explanation. Examination of the trypanosomes with the ultra-microscope shows them to be very active, motile organisms, giving one the impression that they could readily penetrate the delicate capillary walls of the nervous system, whereas the spirochætes show a sluggish, screw-like movement. Moreover, whereas in every case of sleeping sickness trypanosomes have been found in the cerebrospinal fluid, spirochætes have never (with one doubtful exception) been demonstrated in the cerebrospinal fluid. It is probable that they only exist in the true lymphatic sheath of Robin contained in the adventitia; here they set up chronic irritation causing a localized or diffuse gummatous condition.

With this brief introduction I propose to pass on to a résumé of our knowledge of trypanosome infection as it affects the human subject in the production of sleeping sickness, and I shall conclude by a comparison of the neuro-pathology of this disease with syphilis and parasyphilis of the nervous system.

Although sleeping sickness had been described by Winterbottom as early as 1803, it was not until the beginning of the twentieth century, when the economic future of the British Protectorate of Uganda was threatened by a devastating epidemic of the disease, that the Colonial Office, inspired by Manson, approached the Royal Society with the view of appointing a commission.

Manson and I had, in 1899, investigated several cases which had come to England from the Congo, and although I have had under personal observation only a few cases of the disease, I have been from this time much interested in studying the histological changes in the nervous system. As a result of the action of Manson, a committee of the Royal Society was appointed and Castellani was sent out to Entebbe to investigate the disease. Castellani discovered the trypanosomes in the cerebrospinal fluid; but, as he had already reported a micrococcus (probably the same as the Portuguese Commission had discovered) as the cause of the disease, he did not attach to the trypanosomes the importance which they deserved; nevertheless he found them in five cases, and it is quite possible, had he continued to work at Entebbe, he would have come to a definite conclusion that the trypanosomes, and not the micrococci, were the cause of the disease.

Bruce, the discoverer of the tsetse-fly disease, was sent out, accompanied by Nabarro and Greig. They placed upon a sure foundation the causal factors of sleeping sickness: (1) By confirming and largely extending the discovery of Castellani of the existence of trypanosomes

in the cerebrospinal fluid and the blood of persons suffering from sleeping sickness; (2) by proving the existence of trypanosomes in a biting fly, the *Glossina palpalis;* (3) by correlating the geographical distribution of the disease with the geographical distribution of this biting fly; (4) by communicating the disease to animals, including monkeys, by inoculation with the cerebrospinal fluid and blood of patients suffering with the disease, or by allowing flies to bite patients having the trypanosomes in their blood, then allowing the same infected flies to feed on animals and thereby communicating the disease to the animals.

The investigations carried on by the Sleeping Sickness Commission of the Royal Society established beyond dispute that a specific organism (the *Trypanosoma gambiense*) and a specific fly (the *Glossina palpalis*), which acted as a carrier, were the essential causes of the epidemic of sleeping sickness in Uganda.

The Trypanosoma gambiense.

This was the name given to the organism by Dutton, and the discovery happened in this way. On May 10, 1901, Forde received under his care at the hospital, Bathurst, Gambia, a European, aged 42, the captain of a steamer on the river Gambia. The man suffered with symptoms which were regarded as malarial. Examination of the blood did not reveal malarial parasites but *worm-like bodies* concerning the nature of which Forde was undecided. A little later the patient was seen by Dutton in conjunction with Forde, and the former recognized that these *worm-like* bodies were trypanosomes. Dutton gave an excellent description of this organism, which he called *Trypanosoma gambiense.* The patient died on January 1, 1903. Dutton and Todd, in their first report of the trypanosomiasis expedition to Senegambia, 1902, described further cases of human trypanosomiasis. Of 1,000 cases examined in Gambia, six natives and one quadroon showed trypanosomes in their blood. It subsequently was shown that this trypanosome found in Gambia was identical with that found in Uganda. Dutton, Todd, and Christy, in their report upon trypanosomiasis upon the Congo, state that the organisms in the blood of individuals (whether showing signs of sleeping sickness or not) are identical, and there is no reason to suppose that the trypanosome observed on the Congo differs from the *Trypanosoma gambiense.* Moreover, the pathogenic action upon animals is the same. Thomas and Linton have made a comparative study of the human trypanosomes derived from different sources: (1) Trypanosomes brought from Gambia by Dutton and Todd;

(2) trypanosomes sent by Bruce and Nabarro from Uganda; (3) trypanosomes of Dutton Todd, and Christy from the Congo (from the cerebro-spinal fluid of sleeping-sickness patients and from the blood of patients showing no signs of this disease). Thomas and Linton inoculated the trypanosomes from these various sources into a large number of animals, and they found that the pathogenicity was almost the same in all cases. (Nabarro). Laveran has confirmed these researches by experiments upon animals with three different strains of the human trypanosome.

Plimmer concluded from certain experiments which he made upon rats that *Trypanosoma gambiense* and *Trypanosoma ugandense* are quite distinct and separate, but Thomas and Breinl (of the Liverpool Tropical School) made experiments on a large number of rats using several strains of human trypanosomes, including the two strains used by Plimmer, and they obtained results similar to those of Thomas and Linton and Laveran. Consequently it may be affirmed that the *Trypanosoma gambiense*, originally discovered and described by Dutton, is the specific organism of sleeping sickness, whether it be acquired in the Congo State, Senegambia, Uganda, or Portuguese West Africa. In the early stages of infection the lethargy characteristic of the disease does not occur, and the case recorded by Manson, of a European lady missionary, at first exhibited only the symptoms of trypanosomiasis and was described as a typical case of infection by *Trypanosoma gambiense;* subsequently, and for a few months prior to death, she developed the characteristic lethargy. Low and I examined the tissues of this patient and found the characteristic lesions which I had previously described. This case and many others which have died since show that the name "negro lethargy" had to be entirely abandoned, for Europeans, and in fact any human being, may be infected and die of sleeping sickness; and there is no racial immunity against sleeping sickness. It may be mentioned that in the "Bulletin of the Sleeping Sickness Bureau" just published there is a synopsis of fifty European cases; of these, one lived three and a quarter years and one case six years.

But the name "sleeping sickness" also should be abandoned for that of "human trypanosomiasis." There are at present in England three cases being treated for infection by *Trypanosoma gambiense;*[1] two of these I have recently seen, and neither shows any lethargy although trypanosomes are present in the blood and the patients are subject to irregular paroxysms of fever. One case, owing to the high fever and sweating that followed, was thought (as in the original case of Forde) to

[1] I am indebted to Dr. Daniels, of the Tropical School, for his courtesy in allowing me to see these cases.

be suffering with malaria, until examination of the blood revealed the true cause. It would be better therefore to follow the convenient classification of the French Sleeping Sickness Commission. They distinguish *cas en bon état*, persons who have no symptoms whatever of trypanosome infection; *cas suspect*, persons who have symptoms which lead to further investigation; and *cas cliniques*, cases which can be diagnosed from the symptoms alone. A more accurate division, which they make when it is possible, depends on the result of lumbar puncture (Bagshawe). If invasion of the subarachnoid space has taken place, it is regarded as evidence of the patient having passed into the second or third stage; if not, he is in the first. But I shall have occasion to refer to this matter more fully later.

The evidence therefore points to the important fact that the changes found in the central nervous system—which I shall describe fully later—are due to the infection of the subarachnoid space by the parasites. It would be interesting to know if other forms of trypanosomes enter the subarachnoid space or whether it is only the *Trypanosoma gambiense*, because I have never found any lesions like those of sleeping sickness in any other form of trypanosomiasis, although sections of the brain may show swarms of trypanosomes in the blood vessels. I am inclined to think that it is the invasion of the subarachnoid space by the *Trypanosoma gambiense* which renders it so incurable. Bruce doubts whether a case is ever cured (but *vide* p. 17). The various drugs—e.g., atoxyl, soamin, mercury, trypanroth, and antimony—certainly cause the trypanosomes to disappear from the blood, but whether they will attack the organism when once it has infected the cerebrospinal fluid is the important question to be ascertained. I should doubt it, for these drugs do not pass from the blood into the cerebrospinal fluid. Seeing that the organism can easily penetrate the walls of the delicate capillaries of the central nervous system, once the subarachnoid space is invaded, there is always a reservoir for reinfection of the blood and lymph streams. Although the cerebrospinal fluid is not (owing to the absence of proteid) a suitable medium for development, yet by the production of inflammation of the meninges the fluid acquires proteid substances, and the organism obtains thereby a nutrient medium; moreover, the reaction engendered by their presence is lymphocytic, and not polymorphonuclear phagocytic.

The question arises whether the reappearance of trypanosomes in the blood may not be due to latent endocellular forms. It will be remembered that Schaudinn affirmed that trypanosomes may pass through states of endoglobular development. Since then there has been

a good deal of discussion upon the relations which exist between intracellular parasites and trypanosomes, notably concerning Leishman-Donovan bodies. Carini, in a recent paper from the laboratory of Mesnil in the Pasteur Institute, describes and figures trypanosomes undergoing endoglobular development in the blood of Leptodactylus. In the examination of the tissues of a large number of cases of sleeping sickness, dourine, and other trypanosome infections, I have found and described cells which presented appearances *suggesting* the possibility that there were endocellular forms; and Salvin Moore and Breinl described what seemed to be somewhat similar cell forms as occurring in the spleen, lungs, and bone marrow of rats inoculated with *Trypanosoma gambiense;* these forms they regarded as a resistant form of the trypanosome.

I will now pass on to the part played by the fly, the carrier of the disease.

The Glossina palpalis.

Since the publication of the Report of the Sleeping Sickness Commission in 1903, it was known that *Glossina palpalis* was the transmitter of the disease, but only recently, owing to the researches of Kleine, published in March, 1909, have we learnt that the fly after the ingestion of trypanosomes *(Trypanosoma brucei)* remains non-infective for eighteen to twenty days, but after that period it is able to infect susceptible animals. This important observation regarding the *Trypanosoma brucei* was confirmed by Bruce for the *Trypanosoma gambiense*, and the researches of Bruce and his colleagues make it highly probable that some flies may remain infective for the rest of their lives. Bruce and his colleagues made the following interesting experiment: They inoculated a monkey subcutaneously with a small droplet of fluid obtained from the gut of a fly that seventy-five days previously had been fed on an animal infected with *Trypanosoma gambiense.* The droplet of fluid prior to injection was found on examination to be swarming with trypanosomes. When the blood of the monkey was examined eight days after, trypanosomes were found, showing that it had been infected (*vide* fig. 1).

Kleine has also investigated the existence of *Trypanosoma gambiense* in the alimentary canal of flies reared from the pupa which were first fed on animals infected with that parasite, and subsequently on healthy animals. Kleine's figures exhibit a marked difference in form. The slender, red-coloured flagellates, poor in plasma, with dark nucleus he considered to be male forms. The plump, blue-stained, possessing one,

two, three, or more nuclei, he considers to be female forms. He asserts, with reason, that a sexual increase may occur even in the resting stage. Kleine, moreover, found parasites in the salivary glands, but he regards their presence as accidental, and not as playing an important part in the transmission of the disease. He found no evidence of hereditary or germinal transmissions, as Leishman has shown to occur with the spirillum of tick fever. A most important step forward has been made by these researches of Kleine, confirmed by Bruce, for we now know that some kind of development of the trypanosomes takes place in the fly after ingestion; but whether a sexual process occurs, as Kleine shows, or whether there is merely such a multiplication as occurs in cultures is not at present decided with certainty.

It was previously believed that the fly only retained its infectivity for forty-eight hours, consequently it was thought that it would be possible to stamp out the disease in an island by one day clearing out its infective population, and a few days later re-stocking it with healthy natives. Bruce remarks that it is known by experiment that the fly can retain its infectivity up to eighty days; indeed, it is probable that after a fly has become infected it will harbour the trypanosomes for the rest of its life, but what the duration of this is under natural conditions is unknown. Further experimental investigations by Bruce and his colleagues are of interest, although they by no means afford a positive solution of the question. The lake shore was cleared of the native populations in December, 1907, and had been deserted for nearly one year when the experiments began. Flies in this district were caught and allowed to feed upon monkeys, with positive results; it was therefore concluded that the *Glossina palpalis* on the uninhabited shores of Victoria Nyanza can retain its infectivity for a period of at least two years after the native population had been removed. The practical importance of this continued infectivity of the flies is undeniably great, but what the cause is, and how it can be prevented, is another matter. The experiment does not, in my judgment, prove that the flies live two years, or that there is germinal transmission. From a conversation I have had with several Europeans now in England suffering with infection of *Trypanosoma gambiense*—notably Mr. Grimes, an elephant hunter—it is impossible to control the movements of the native, and numerous means of re-infection of the flies of the district are possible; in fact, Bruce himself points out the possibility of the flies having fed on natives who frequent the lake shore in spite of prohibition; or it might be explained by the fact that the natives who were employed in

collecting the flies were the subjects of trypanosomiasis, but Bruce asserts that it cannot be by infection of the flies by natives, because precautions were taken in respect to fly-boys and canoe-men employed by the committee; or, lastly, it is possible that the mammals and birds along the lake shore have been infected, and so act as a reservoir of disease. It will be remembered that Koch thought the crocodile might be a host for the sleeping-sickness parasite.

Bruce sums up: "There remain then the two theories—long duration of life of the fly, and a local reservoir. The former at present cannot be answered, and there is no experimental proof of the

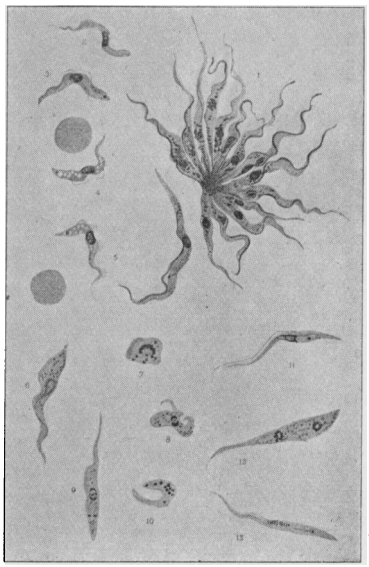


FIG. 1.

(1) Rosette form from the mid-gut (× 1,000). (2-5) *Trypanosoma gambiense* from the blood of the monkey into which a tiny drop of the contents of the mid-gut of fly had been injected (× 1,000). (6-13) Trypanosomes from the fore-gut of fly stained by Giemsa (× 1,000).—Report 10, Sleeping Sickness Commission.

latter, since the injection of the blood of the lake-shore birds and mammals into susceptible animals has always up to the present given negative results." It appears to me that the main difficulty in accepting Bruce's conclusions is the fact that the natives may, and probably do, frequent the lake shore in spite of the prohibition.

It may certainly now be assumed that there is a period of time in which the fly does not transmit the disease after biting an infected

person; and experiments appear to show that there is a period in which it more certainly transmits the disease, and this is correlative to the finding of large numbers of trypanosomes in the alimentary tract; and, as Todd suggests, this is an indirect support of the sexual stage, which Kleine's observations so clearly indicate. Kleine found that of 410 flies which had fed on animals infected with *Trypanosoma gambiense*, 22 became infected (5 per cent.). It seems therefore necessary that both males and females should be ingested in order that the flies may become infective. Bruce was formerly of the opinion that mechanical transmission played an important part, but recent experiments published in the *Proceedings of the Royal Society*, August, 1910, led him to the conclusion that mechanical transmission plays a much smaller part (if any) in the spread of sleeping sickness than has been supposed. The researches of Bruce and his colleagues show that "cattle may act as a reservoir of the virus of sleeping sickness, and that healthy animals may be infected from them by means of *Glossina palpalis*. It has also been proved that cattle in the fly area do naturally harbour *Trypanosoma gambiense*. It is therefore possible that the cattle and antelopes living in the fly area may act as a reservoir, and so keep up the infectivity of the *Glossina palpalis* for an indefinite period." [1] The fact that the geographical distribution of sleeping sickness corresponds with that of the geographical distribution of this particular fly *a priori* is against another source of transmission, although this does not necessarily follow, for the two modes may be coincident. *Glossina morsitans*, the fly that carries the *Trypanosoma brucei*, has not as yet been shown to act as a carrier to the *Trypanosoma gambiense*.

We may next inquire what other possible means there are of the transmission of the infective organism. Seeing that a scratch in making an examination of an infected rat probably led to Lieut. Tulloch being infected with *Trypanosoma gambiense*, and his death six months later, it is conceivable that sporadic cases of infection may arise from other causes than the bite of the specific fly, and the members of the Sleeping Sickness Commission in the French Congo bring forward evidence in favour of the transmission of the disease by biting insects other than glossina; they think that mosquitoes and other biting insects are important auxiliaries conveying infection in each hut from person to person during the night. They say that in regions where the natives nurse their sick in their own houses the disease spreads with much greater rapidity than in those where they drive

[1] *Proc. Roy. Soc.*, B., 1910, lxxxii, p. 484.

them away. They give instances of one member of a family after another becoming infected, and quote instances in which a native was saved from infection, in their belief, by the use of a mosquito net. They found sleeping sickness extremely prevalent in marshy districts where mansonia abounded, and the Commission attributes to this method of infection, in some instances, the annihilation of whole villages.

Bagshawe, having thus stated the French Commission's observations, remarks that in nearly all cases there was a palpalis area near at hand or within a few miles. Moreover, why is not sleeping sickness endemic in the southern negro states of America and the West Indies, and why have there been no epidemics there? Certainly in the old slave days numbers of infected negroes must have been conveyed there. Again, the disease is endemic or epidemic only on the shores of the palpalis-haunted lakes and rivers. In Uganda, inland from the Victoria Nyanza and out of the reach of tsetse flies, no instance of infection from a sporadic case has come to light. I am informed by Dr. Grimes that sleeping sickness occurs nowhere in Rhodesia except on the borders of Lake Tanganyiki and the Loupopo River flowing from it. He also informed me that six cases of human trypanosomiasis existed at Broken Hill, and one European had died of sleeping sickness. No cases, however, had occurred in southern or north-western Rhodesia, and in those regions there is no *Glossina palpalis*.

Another possible means which had been put forward is coitus. We know that a trypanosome disease affecting equines (especially in mule-producing countries) is the *mal de coit* or dourine. In this disease a trypanosome has probably acquired the habit of direct transmission from one individual to another by multiplying in the mucous discharges of the sexual organs, and thus has arisen a new means of perpetuating the species. Koch and Kudicke put forward the hypothesis that sexual coitus explained the occurrence of the disease in women who lived in a palpalis-free area and who said they had never left it.

Kudicke's experiments support this hypothesis, likewise those of Manteuffel. The former introduced into the vagina of an uninfected monkey, taking care to avoid any injury, the blood of another monkey infected with *Trypanosoma gambiense*, and thereby infected it. The latter showed that blood containing trypanosomes placed upon a small patch of unshaven sound skin, allowed to dry and then covered with collodion, was followed in the greater number of animals by infection. These observations certainly suggest the possibility of infection by coitus. But as regards the explanation of the forty-four female patients

treated by Kudicke, Hodges offers the following suggestions: "When the epidemic first swept through the lake-shore district the men, whose employment naturally carried them into the greatest danger, usually suffered first. As the men weakened, their occupations, such as canoeing, were in part taken up by the women, who then ran greater risks and more often contracted the disease, while many of their husbands by this time had either died from it or showed obvious symptoms of its presence."

If sporadic infection does occur by one or other of the "auxiliaries" described it must be unusual; for if we are sure of one thing in the ætiology and geographical distribution of this disease in Uganda, it is coincidence with the habitat of the *Glossina palpalis*. All the facts therefore point to the conclusion that something more than mere mechanical transmission of infection is necessary—viz., an intermediate host—and we owe to Kleine's investigations the proof of this, which the following experience in Uganda practically substantiates. In the progress report of the sleeping-sickness camps in Uganda, 1909, it is stated that "hundreds of sick have for long periods been collected in places in which *Glossina palpalis* is absent, and the disease has in no case spread either to the attendants or in the neighbourhood. This has materially assisted to impress on the natives—a task at first so difficult—the truth of that which they have been taught concerning the connexion between the fly and the spread of the disease."

I have endeavoured to give a résumé of our knowledge of the ætiology of this remarkable disease—a disease not only of great interest to the medical profession, but also to the general public.

Clinical Study of Human Trypanosomiasis.

My experience clinically is limited to several negroes, including the three in which I first described in 1899 the changes in the central nervous system which accounted for the principal clinical phenomena observed during life; also of several Europeans, including the first case, whose nervous system was examined post mortem. But besides these cases of negroes which have been brought to England and the Europeans who have returned from Africa and died in England, I have had forwarded to me the material from twenty-two cases that have died in Uganda, as well as material from monkeys and other animals which have been inoculated experimentally. An account of the pathological findings in this material formed the subject of the seventh report of the Sleeping Sickness Commission.

Description of the Disease.

The following account of the clinical symptoms is based upon my own experience, the notes of the cases of which I have examined the nervous system and which died in Uganda, together with knowledge acquired by reading the admirable reports of the Portuguese Commission and French Commission, the account given by Nabarro in his valuable translation of Laveran, and Mesnil's work on trypanosomiasis, as well as a recent important progress report on the Uganda sleeping-sickness camps by Hodges:—

First Stage: Local Infection followed by Generalized Blood and Lymph Infection.—A history obtained from Europeans shows that there is a period of incubation extending from the time of infection by the bite of the fly to the time that the parasite becomes generalized in the blood. At the point of inoculation a painful red papule, which may develop into a furuncle, appears; the nearest glands may become enlarged and painful. Twelve days may pass before the constitutional symptoms manifest themselves in the form of fever and sweating. This may be accompanied by swelling of glands, but not necessarily; there is always fever, irregular, intermittent, sometimes high fever and sweating, which occur at the end of the rise of temperature. The patient usually thinks he has contracted malaria; quinine, however, affords no relief, and examination of the blood, instead of showing malarial parasites, reveals the trypanosomes. This is often associated with nervous excitation, insomnia, headache as well as prostration, weakness, and emaciation. The respiration and pulse-rates are accelerated apart from the febrile attacks. Localized œdemas, especially of the face and ankles, puffiness of the eyelids, and evanescent, congested, or erythematous patches on various parts of the body, make their appearance. These symptoms may considerably improve and even end by completely disappearing at the commencement of the second period, which marks the invasion of the subarachnoid space and the presence of trypanosomes in the cerebro-spinal fluid.

In negroes the above-mentioned symptoms are usually unobserved or even absent; consequently the diagnosis could only formerly be made by the examination of the blood. The parasites, however, are often very scanty and difficult to discover in the blood. Having been struck with the frequency of glandular enlargement, I suggested to Greig and Gray that they should examine the fresh juice of enlarged glands obtained by excision or puncture. This method for diagnosis was

performed by them, and found most useful when the organisms could not be seen in the blood. Moreover, it shows that possibly the lymphatic glands may harbour the parasites and lead to reinfection of the blood-stream and the infection of the subarachnoid space when the paravertebral glands are infected. Recent work confirms the observations of Dutton and Todd that the larger the glands the more likely are trypanosomes to be found in them. These observers, in a comprehensive investigation, have found that cervical gland enlargement without obvious cause in a native who has been exposed to the risk of infection is almost certainly due to trypanosomiasis, and should be regarded as such until the contrary is proved. Nabarro remarks: "The observations of Dutton and Todd in Gambia, and of Bruce, Nabarro and Greig in Uganda, show that in negroes this first stage is accompanied as a rule by no obvious signs of disease except the glandular enlargement above referred to." The French Commission, however, found that whereas under treatment some glands diminished in size, others did not; they concluded that the enlargement of these, though they often contained trypanosomes, was due to other causes. There are, moreover, cases in which the swelling of the glands is never very great. This was notably so in the case of a Persian who died of sleeping sickness, and whose tissues I examined. Heckenroth mentions the case of a boy who had slight suborbital œdema, and in whose blood trypanosomes were found. Not until a year later did any glands become puncturable. Heckenroth considers œdema as valuable an early sign as gland enlargement. The French Commission point out that the catamenia ceases in women and sexual desire is lost in men.

Second Stage: Sleeping Sickness, Lethargy.—The chief symptoms are fever and nervous manifestations. There is a pronounced expression of hebetude, which, once it has been seen, can immediately be recognized. The patient is indifferent to his surroundings, there is apathy and tendency to sleep or drowsiness, from which, however, he can be aroused to answer questions and for a brief period of time take an interest in what is said; but fatigue readily occurs, and, as a rule, answers are only obtained in monosyllables. He is paretic and unsteady, shuffling or oscillating in his gait. There is unsteadiness on standing, which increases on closing the eyes; there is nearly always tremor of the tongue and later of the hands when they are held out, and sometimes even when this measure is not resorted to; but there is no intention tremor. The knee-jerks are increased, and neither ankle clonus nor Babinski's sign can as a rule be obtained. The speech is slow, and sooner or later

only monosyllables are uttered; but there is no slurring or elision of syllables, as in general paralysis, although there is some intellectual deficiency, as shown by weakness of memory, will power, and attention. Questions are comprehended as a rule, and the answers given are rational. There is no grandiose delirium, and hallucinations are but seldom noticed. There is no tendency to grandiose delusions, and the autocritical faculty is not wanting, for they keenly realize their hopeless condition. There is no optic neuritis or changes in the fundus, and the Argyll-Robertson pupil is invariably absent. The patient may remain in this condition, gradually getting more lethargic and feeble for three to six months, and then the terminal period commences in which there is profound lethargy, intense tremors and muscular weakness, loss of control over sphincters, and tendency to bed sores.

The resistance to microbial invasion is so lowered by the trypanosomiasis that the patients readily fall victims to pneumococcal and streptococcal infections resulting in bronchopneumonia and septicæmia; it is not surprising, therefore, that pneumococcal or streptococcal meningitis complicates the clinical picture in the terminal stages of the disease, and hastens its fatal termination. In the majority of the cases of which I have examined the tissues, I have found diplococcal or streptococcal infection either of the lymphatic glands or of the central nervous system, generally both.

In the excellent clinical study published in the French report, attention is drawn to the fact that "since our arrival in the Congo the cerebral form of the disease has attracted our attention, and we have observed numerous cases of insanity and hallucinations. This acute form of the disease is known to the natives." From their observations on twenty-four whites who were patients at the Pasteur Institute, the members of the Commission conclude that there is a cerebral and medullary form. The former they divide into diffuse and circumscribed. The diffuse is manifested by mental and meningeal symptoms of a subacute character, accompanied by loss of the intellectual faculties. The circumscribed form is characterized by localized cortical irritation and destruction, causing epileptiform convulsions and paralysis. The medullary forms are manifested by paraplegia, with some sensory troubles and bladder affection. The cerebral forms are incurable; the spinal progress slowly and respond to treatment. The French report also states that the mental complications of trypanosomiasis belong to the category of organic mental alienation, and are characterized before all by intellectual decadence. It may happen that the intellectual

decadence is preceded by a period of slight exaltation. Mental confusion is more or less profound, and is characterized by stupor, confusion of ideas, amnesia, and disorientation, to which may be added visual and auditory hallucinations and non-systematized delusions. The evolution of these symptoms is always rapid, in some weeks the intellectual decadence becomes very profound, and the stupor appears. These symptoms remind one rather of Korsakow's psychosis, and it may be asked whether the treatment by arsenic may not have had something to do with them. Slight optic neuritis was mentioned. Possibly owing to the patients being kept alive longer by the treatment, a deeper affection of the nervous system may have taken place. Against this, however, I may state that I found the most profound change throughout the whole central nervous system in four of the cases that died in England. The most profound changes were found in an uncomplicated case that was under Dr. Stephen Mackenzie in the London Hospital in 1890; the patient lived six months after admission, and the only symptoms noted up to a few days of death were progressive lethargy, paresis, and tremors. Three days before death he could be aroused, and could answer when spoken to in monosyllables or simple phrases, such as "Good morning"; the same occurred in the two other cases which were under my care in the Charing Cross Hospital.

Again, on looking through the notes of the twenty-one cases of which post-mortem material was forwarded to me for examination, I can find no mention of paralysis or epileptiform convulsions; in fact, the main symptoms recorded pointing to the affection of the central nervous system were progressive paresis, tremors, and lethargy. Many of them, although in an advanced stage of the disease when admitted to the hospital, were able to tell where they came from, and give an account of their previous life. Most of these cases showed an advanced meningo-encephalitis.

Hodges, whose experience is based upon 5,081 cases received at the four sleeping-sickness camps at Uganda, thus comments on the effects of modern treatment:—

"Speaking generally of the effects of treatment, it must be said that atoxyl and its allies—though possessing a marked, if transitory, trypanocidal action—have not proved to be suitable for routine administration to all classes of cases, and that no considerable number of cures can be expected to result from their administration by the methods in use. *But it cannot fail to be noticed, by those who have been familiar with the natural course of sleeping sickness before the use of modern*

remedies, that this course is, if not cut short, at any rate considerably modified by the administration of the organic compounds of arsenic."

Paralysis, paresis, and epileptiform convulsions, which among untreated cases occurred in a small percentage, are now commonly met with and are often the precursors of sudden death, which itself was very exceptional before the use of organic arsenic. Sudden or rapid death, in fact, generally preceded by cerebral symptoms, would appear now to be almost the rule among such cases as have received full courses of organic arsenic, while the prolonged lethargic stage which almost invariably marked the end of untreated cases is either scarcely noticeable or absent. It would seem probable therefore that, owing to the prolongation of the course of the disease by treatment, the nervous lesions are afforded time to become more pronounced and eventually to kill the patient, and that this may happen even though all trypanosomes may have been eliminated from the system.

If this be so, and these nervous lesions are in no way due to the treatment itself, it of course follows that, when once the disease has reached a certain stage, the lesions then existing are likely to be progressive, apart from the toxins produced by trypanosomes, and that treatment by trypanocidal drugs during or after that stage will probably be useless. When this stage actually occurs is not known, and it is doubtful whether there would be any clinical symptoms by which it could be recognized, though it has long been agreed that it is necessary to begin treatment at as early a stage as possible.

I have recently examined the tissues of the central nervous system of a case of human trypanosomiasis who was treated so energetically with atoxyl that, owing to neuritis and mental confusion and dullness, the administration of the drug could not be continued. It had been given intermittently for eighteen months, and apparently it effected a cure, for the man lived for three and a half years after treatment had been suspended, and trypanosomes, which had, early in the disease, been found in the glands and blood, could no longer be found. Death from pneumonia occurred, the man for several years having been in excellent health. I could find no evidence of the characteristic perivascular infiltration of lymphocytes and plasma cells in the brain. It is probable that the trypanosomes had never entered the subarachnoid space. A full account of the case will be published shortly in the *Proceedings of the Royal Society*. I have seen a well-marked perivascular infiltration of the subcortical tissues in a case that died nine months after infection.

Before describing fully the changes in the central nervous system in sleeping sickness, it will be advisable to consider the changes in the lymphatic glands. We shall then be in a position to compare the same with those found in the central nervous system and elsewhere.

The occurrence of irregular remittent pyrexia, in cases of infection by *Trypanosoma gambiense*, with erythematous urticarial eruptions, suggests association with paroxysmal elaboration of a poison or the multiplication of the parasite. The great frequency with which the lymphatic glands become enlarged may be associated with the paroxysms of fever and the presence of the protozoa in the glands. It has been shown that this enlargement is not due to microbial infection; it must therefore be due either to trypanosomes or a toxin engendered by them irritating the gland and causing proliferative hyperplasia of the cell elements. It is a matter of speculation whether the degenerative changes occurring in the neoplastic formation produce cytotoxins or not; probably by analogy they do not.

Histological Changes in the Lymphatic Glands.

A lymphatic gland in the first stage of swelling shows the following changes: Active proliferation of the lymphocytes in the germ-centres so that they are very densely packed together. In the lymph-cords and sinuses a very active cell-proliferation can also be observed. The oval staining nuclei of the endothelial cells lining the lymph-channels can be seen greatly increased in numbers and proliferating. Numbers of large mononuclear cells can be seen; these are round, with a deeply-stained round nucleus. They differ from the small mononuclears by the more abundant cytoplasm. Others are plasma cells of Marscholko containing a nucleus with a wheel-like arrangement of chromatin, and all stages can be traced up to the formation of a typical plasma cell and its final granular degeneration. The origin of these different types of plasma cells has always been a matter of dispute. Moreover, it is a question whether the nuclei seen in the body of branching retiform cells belong to endothelial plates, or are nuclei of branched connective-tissue cells. There is no doubt that these nuclei, when subjected to irritation, are excited to hyper-nutritive activity and proliferate, and produce mononuclear cells. There is increased vascularity of the gland, and not infrequently hæmorrhages; in fact it presents the appearance of chronic inflammation, and we must suppose that the cell proliferation is a defensive reaction to a noxious agent. The cell proliferation goes on

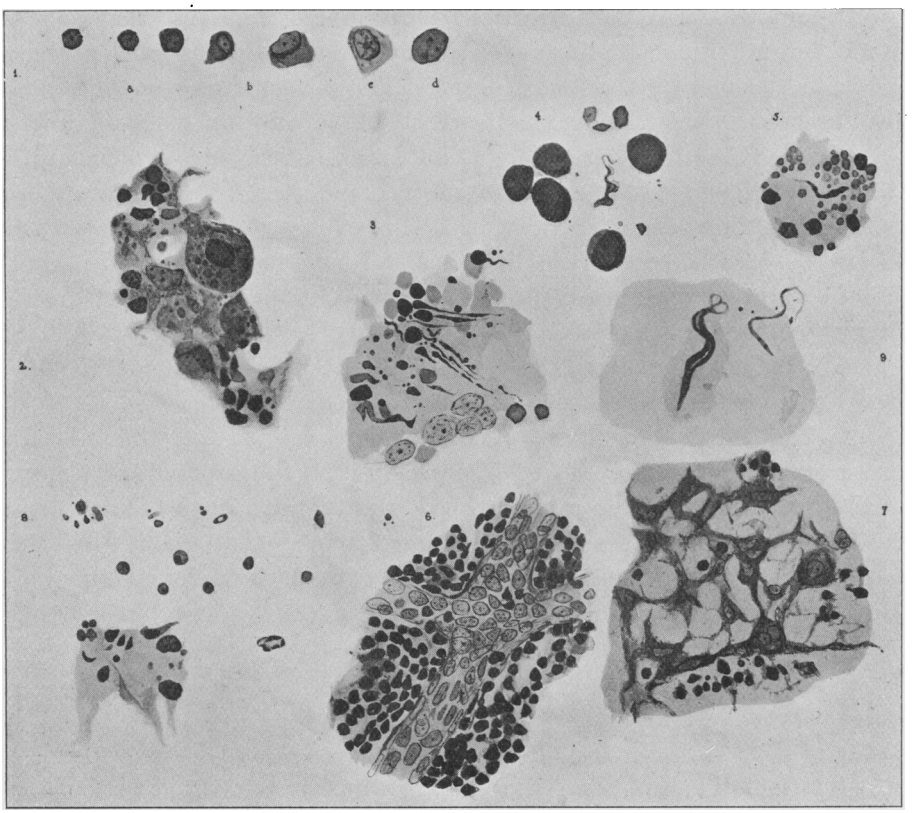


PLATE I.

CHANGES IN THE LYMPHATIC GLANDS.

FIG. 1.—Lymphocytes in all stages of transition to plasma cells.

FIG. 2.—Lymphocytes, plasma cells, and endothelial cells in all stages of granulo-aqueous degeneration. (× 375.)

FIG. 3.—Thread-like bodies and granules, deeply stained, seen in section of lymphatic gland. (× 750.)

FIG. 4.—Trypanosome in smear of fresh lymphatic-gland juice. Several lymphocytes and micronuclei. (× 750.)

FIG. 5.—Trypanosome in a section of lymphatic gland amidst disintegrated cell products.

FIG. 6.—Section of lymphatic gland from a fatal case of sleeping sickness. The glands in this case were not much enlarged. There is marked proliferation of the endothelial nuclei of the lymph channel. (× 375.)

FIG. 7.—Proliferation of the connective-tissue cells of the reticulum of a lymph sinus. Marked proliferation of the nuclei of the endothelial cells seen. This change closely accords with the change observed in the perivascular lymph spaces of the central nervous system. (× 375.)

FIG. 8.—Various granules and products of cell and (trypanosome?) degeneration seen in the perivascular cell infiltration of the central nervous system. (× 375.)

The preparations were stained with Leishman or Giemsa stain, and the glands used for preparation of specimens illustrated by figs. 1 to 5, inclusive, were removed during life in the first stage of the disease, before the invasion of the central nervous system had occurred.

until, automatically, an increase in numbers deprives the cells of sufficient nutrition, or they are destroyed by the virus and granulo-aqueous degenerative changes occur. These necrobiotic changes may be observed in the glands which are sterile by cultural tests for micro-organisms. In this stage there is only very occasionally evidence to be found in sections of the existence of trypanosomes. I have rarely in a very large number of sections seen any evidence of trypanosomes or their degenerated remains. Occasionally I have found the dead parasite in the form of attenuated thread-like forms, or macronuclei or micronuclei. According to Greig they can always be discovered in the fresh juice of the enlarged glands, but Thomas and Anton Breinl consider that they are not more numerous in the glands than in the blood.

In the third stage of very chronic cases, a few of which I have examined (one removed during life and sterile), the products of degeneration had been in great part absorbed, and the gland had become dense and fibrous. This is the final sclerous change that occurs in other chronic neoplastic formations, the fibrous conjunctival elements preponderating over the cellular elements. As a rule, in sleeping-sickness cases, death occurs before this can take place.

Morbid Changes in Lymphatic Structures.

All the observers from the earliest times have noticed the enlargement of the lymphatic glands; and Greig, at my suggestion, punctured the glands and examined the fresh juice. He is of opinion from his observations that this is an easier and more reliable mode of determining the existence of *Trypanosoma gambiense* than examination of the blood or cerebrospinal fluid. Dutton and Todd came to the same conclusion working in the Congo State. Many natives in Uganda and the Congo State have, however, enlarged glands, and yet are not the subjects of sleeping sickness. They may be, however, and probably in nearly all cases are, candidates for the disease.

Do the trypanosomes get into the glands and multiply there, setting up a chronic inflammatory process which terminates in fibrosis? The glands may be inflamed and enlarged and yet be sterile as regards micro-organisms. It is probable that trypanosomes infect the lymphatic glands by escaping from the ruptured capillaries, or they may have become infected by the cerebrospinal fluid when this secretion contains trypanosomes. Similarly by capillary hæmorrhage the trypanosomes may infect the cerebrospinal fluid and the lymphatic structures of the

central nervous system. If the trypanosomes can set up chronic inflammatory changes in the lymphatic glands (as there is no doubt they do), and microscopic examination of sections reveals but occasional and scanty evidence of their presence, it is quite reasonable to suppose that they can similarly produce chronic inflammatory changes in the lymphatic structures of the central nervous system. We do not know if the trypanosomes produce this chronic irritation by their mere mechanical presence, which seems unlikely, seeing that vessels may be crammed with trypanosomes in nagana and surra without causing lymphangitis. There is, according to Plimmer, Thomas, and Anton Breinl, however, no experimental evidence that trypanosomes produce a chemical toxin; although that would seem the most probable cause of the chronic inflammatory change. The numbers of trypanosomes found in the cerebrospinal fluid are in no way proportional to the changes found in the central nervous system. Yet there is considerable evidence (*vide* Sleeping Sickness Reports, Royal Society) to show that not until trypanosomes are found in the cerebrospinal fluid does the chronic inflammatory change take place. If they existed in abundance instead of sparsely, we might consider that this fluid afforded a suitable medium for their propagation, and the absence, normally, of lymphocytes in this fluid might be counted a cause. On the other hand, the small quantity of proteids which the cerebrospinal fluid contains would not admit of suitable nutrition.

The posterior spinal ganglia always show some chronic changes, proliferation of the endothelium of the lymphatic capsules of the ganglion cells, together with interstitial lymphocyte accumulation, and these chronic changes may be due to the absorption of toxins from the neighbouring infected paravertebral glands.

In practically all cases of sleeping sickness the cervical glands are enlarged, and the most chronic change is found about the base of the brain. Hence a possibility that the chronic inflammation of the lymphatics spreads along the nerves, spinal ganglia and roots to the central nervous system, and especially along the lymphatics of the nerves and vessels entering the base of the skull. Examination of other tissues—e.g., the heart, pericardium, liver, alimentary canal, and testicles—shows, though generally speaking in far less degree, an infiltration and accumulation of lymphocytes in the lymphatics, suggesting a chronic inflammatory reaction of the lymphatics.

The Histological Changes in the Central Nervous System.

Observations of Bruce and his colleagues show that it is the invasion of the subarachnoid space by the organisms which cause this change, and my observations and experience show that there is a parallelism between the depth of the lethargy and the diffuseness and intensity of the lymphatic perivascular infiltration.

In the seventh report of the Sleeping Sickness Commission of the Royal Society I stated, as the result of an examination of a large number of sections stained by polychrome and eosin, Mallory and Heidenhain-eosin methods, that the meningeal-cell infiltration was the result of an irritative process affecting the pia-arachnoid serous membrane, which was manifested not only by a proliferation of the neuroglia cells but also by a proliferation of the endothelial-cell nuclei and an infiltration of the pia-arachnoid membrane with lymphocytes, which may become transformed into plasma cells. But sections do not show the mode of origin of these cells in such a clear and demonstrative manner as the following methods which I adopted. The pia-arachnoid membrane was stripped off small portions of brain from a number of cases of chronic sleeping sickness, including the European case under Dr. Bradford, which was of unusual value, because there was no terminal or secondary microbial infection, and because there was *no noticeable enlargement of the lymphatic glands*. Small portions of the stripped-off membrane were divided by tearing rather than cutting, so that the thin frayed edges could be examined under a high power of the microscope. They were stained by hæmotoxylin and eosin, Leishman's stain, polychrome and eosin, and Eisath's modified Mallory stain, and mounted in Canada balsam. Several interesting facts were observed. *The fibres forming the interlacing network were coarser than natural and much increased.* Many of the vessels were gorged with blood and there were *many capillary hæmorrhages*. A variable number in different cases of large cells containing blood-corpuscles or altered blood-corpuscles were seen, similar to those seen in sections. These cells were usually oval, sometimes round, with the oval or round nucleus pushed up to one end. Sometimes the cytoplasm contained discrete corpuscles, sometimes this *endothelial macrophage* had digested the corpuscles and the cytoplasm had assumed in consequence a uniform orange stain. Some of these cells containing blood-pigment had undergone nuclear proliferation; four or five deeply-stained, round nuclei could be seen in one cell. The adventitial sheath of the arteries can be

distinctly seen, and there is often evidence of endothelial-cell proliferation shown by an increase in the number of large, pale oval nuclei, many of which could be seen undergoing mitosis and proliferation; they resembled the endothelial nuclei seen in the lymph sinus of the lymphatic glands, but the great mass of cell infiltration is in the meshwork of the pial trabeculæ of the subarachnoid space and its prolongation as a sleeve around the vessels entering the grey matter.

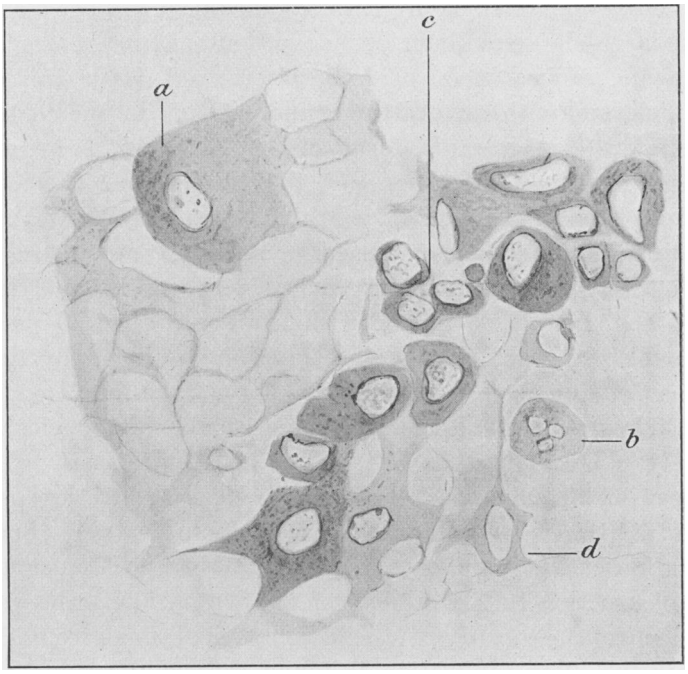


FIG. 2.

Small portion of pial-arachnoid tissue stained by Eisath's modified Mallory method mounted on the flat. (× 500.)

Preparations stained by logwood and eosin and Van Gieson's fluid exhibit two kinds of nuclei—viz., (1) large, pale, oval, less often roundish nuclei, with a delicate nuclear membrane and very fine intranuclear network, similar in all respects to the oval nuclei of a lymph sinus; (2) smaller round or irregularly shaped more deeply-stained nuclei with a narrow investing cytoplasm, also large cells containing similar deeply-stained nuclei, and not infrequently some cells, two or more, even as many as six, round nuclei, which are sometimes unequal in size

and always uniformly, diffusely, and deep stained throughout. These cells are endothelial cells undergoing endogenous nuclear proliferation.

The endothelial cells of the lymphatic sheath of Robin and the endothelial plates lying upon the trabeculæ of the subarachnoid space and the pial sleeve of the vessels, as the result of the chronic irritation produced by the presence of the trypanosomes in the cerebrospinal fluid, undergo a progressive formative hyperplasia similar to that of the lymphatic glands.

In preparations stained by Eisath's modified Mallory stain, I have observed large flat endothelial cells without any processes exhibiting the following appearances of hyperplasia: (*a*) With the cytoplasm stained pink, and with an oval or round nucleus in the centre stained light yellow; (*b*) the same form of cell can be seen undergoing endogenous nuclear proliferation; (*c*) the same form of cell dividing or divided into small mononuclears in which there is only a relatively small surrounding pink-stained cytoplasm. Besides, we find cells which morphologically resemble the branched retiform cells of connective tissue of the lymphatic gland, with a large oval unstained nucleus. These nuclei appear to undergo division to form hyaline mononuclear cells which are seen proliferating in the inflamed lymphatic glands. The increase of the large and small mononuclear lymphocytes in the blood may be due to this cell hyperplasia in lymphatic structures. The meningeal and perivascular infiltration is due not only to active endothelial-cell proliferation *in situ*, but also to accumulation of the lymphocytes by conjunctival proliferation and consequent obstruction to the outflow of the lymph along the vessels, also obstruction to the escape of the cerebrospinal fluid from the craniospinal cavity. The infiltration is found especially around the vessels having a lymphatic and pial sheath; this sheath disappears on the smallest vessels, therefore we can easily understand why it is that the smallest vessels and capillaries show little or no investing sheath of cell infiltration. However, in chronic cases, lymphocytes, and especially plasma cells, can be seen closely applied to them. Do the branching processes of the *neuroglia cells* form a meshwork around the larger vessels and cause obstruction, or is the meshwork in which the mononuclear cells lie merely the thickened and proliferated trabeculæ of the connective-tissue cells of the lymphatic and pial sheath? My answer is that the infiltration around the large vessels and in the membranes entirely corresponds in appearance with the infiltration which I have described in patches around the vessels of the visceral layer of the

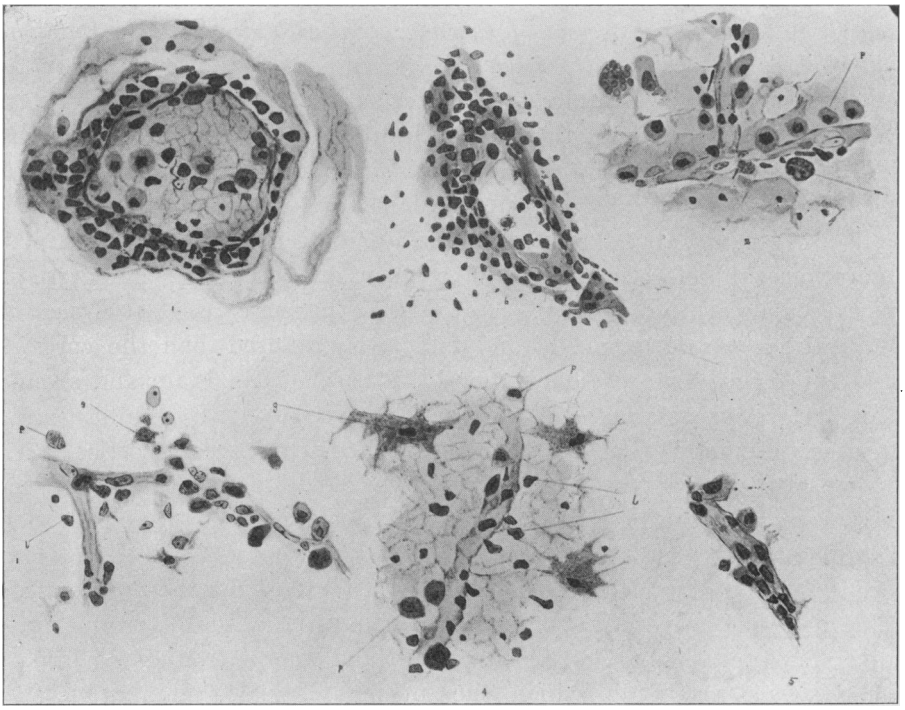


PLATE II.

CHANGES IN THE PERIVASCULAR LYMPHATICS OF THE CENTRAL NERVOUS SYSTEM, &c.

FIG. 1.—Transverse section of a small vessel of the medulla oblongata, showing perivascular infiltration with lymphocytes. Many of these have a hyaline appearance. The lumen of the vessel contains blood corpuscles, large and small mononuclear leucocytes, and a trypanosome is seen in the centre. This was the appearance presented by the vessels throughout the cortical and subcortical structures. The preparation was obtained from a very chronic case. (× 375.)

FIG. 2.—Small vessel with plasma cells (*p*) and morular cells (*m*). (× 375.)

FIG. 3.—Small vessel dividing into two capillaries, showing nuclear proliferation of the endothelial cells. In the neighbourhood are plasma cells (*p*), lymphocytes (*l*), and glia cells (*g*). (× 375.)

FIG. 4.—Three large neuroglia cells (*g*), their branches ending in a network around and upon a small vessel. In the meshes are lymphocytes (*l*) and plasma cells (*p*). (× 375.)

FIG. 5.—Small vessel with proliferation of endothelial nuclei and two plasma cells (*p*).

FIG. 6.—A transverse section of a vessel in a very chronic case of sleeping sickness in a European, showing marked perivascular infiltration with lymphocytes. (× 187·5.)

pericardium in the lymphatic spaces of the heart muscle and the perivascular lymphatics of the liver and the testis. Moreover, *I am unable to trace the processes of the neuroglia cells any farther than the outer sheath of the infiltration.* Again, no place shows the perivascular and meningeal infiltration better than the lymphatic and pial sheaths of the vessels in the soft membranes covering the cerebellum and their extensions between the folia, *yet there are no neuroglia cells seen in the adjacent cortex of the cerebellum*, although the neuroglia cells are seen in abundance in the white matter. The neuroglia proliferation is therefore not essential for the production of this characteristic perivascular cell infiltration. As a rule, the subcortical perivascular infiltrations are more marked and extensively diffused than the cortical, and this is especially evident about the base of the brain and around the perforating arteries; this corresponds in a way with syphilitic brain disease. Sometimes when there is but little evidence of cortical perivascularitis, there may be found very marked infiltration around the vessels of the base of the brain and the perforating arteries and their ramifications.

It is often difficult to distinguish lymphocytes from the proliferating nuclei of glia cells. We may distinguish three kinds of lymphocytes in transverse sections of blood-vessels and the surrounding tissues: (1) Hyaline forms, in which the nucleus is pale, staining poorly, irregular in outline or lobulated, and with a small amount of cytoplasm. (2) Small mononuclear cells in which the nucleus is irregular in outline or round, staining either deeply throughout, or the chromatin is arranged in the form of a wheel, with a central nucleolus, from which straight spokes pass out to a nuclear membrane ending in little knobs; there is hardly any surrounding cytoplasm. (3) Large mononuclears possessing phagocytic functions, the main difference from the smaller variety being the much larger amount of surrounding cytoplasm; they form the so-called plasma cells, and are developed from the proliferating endothelial plates, the same as the smaller lymphocytes; the latter can develop into them (*vide* Plate I, fig. 1). Whether an endothelial plate will form small or large mononuclear cells apparently depends largely upon the number of nuclei the original nucleus divides into.

In sections of vessels cut obliquely so that the outermost structure of the wall is shown—that is, the part in contact with sleeve of cerebrospinal fluid—I have seen endothelial cells lying like scales on the bark of a fir tree, or a tesselated pavement, and presenting all the appearances of the typical plasma cells of Marscholko. It appears to me a mere

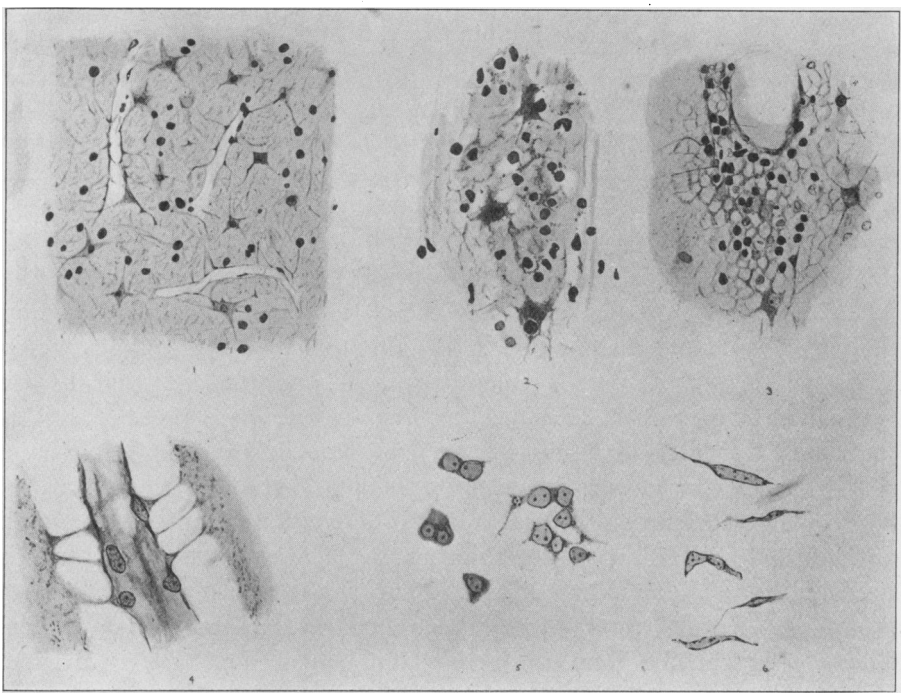


PLATE III.

NEUROGLIA, HYPERPLASIA, AND PROLIFERATION, &c.

FIG. 1.—Section of subcortical white matter of the brain of a monkey that died after infection by trypanosomes, caused by the bites of infected flies. There is little or no perivascular infiltration, but a considerable increase in size and number of the perivascular glia cells. The animal lived only eight months. (× 320.)

FIG. 2.—Section of subcortical white matter of a monkey that died eighteen months after infection, and showed the characteristic perivascular infiltration, with lymphocytes and plasma cells. The neuroglia proliferation is well shown, and in the meshwork of the branching fibres, which form a reticulum around a small vessel in longitudinal section, are numerous lymphocytes. (× 450.)

FIG. 3.—Transverse section of a blood vessel, with the pia-arachnoid and lymph-sheath much increased by proliferating cell elements. The lymphocytes are pale and unstained, and fill the connective-tissue meshwork. The neuroglia cells are seen externally, sending their processes inwards to join the connective-tissue reticulum of the pial sheath. (× 375.)

FIG. 4.—Small vessels of brain of a monkey in which experimental anæmia had been produced by ligature of all four arteries. This is to show the perivascular space filled with cerebrospinal fluid. The supporting trabeculæ are well seen passing across from the nervous matter to the wall of the vessel. It is easily to be understood that if this sheath is filled with cells entrapped in a thickened and proliferated network, the circulation of the lymph and cerebrospinal fluid will be interfered with. (× 750.)

FIG. 5.—Young neuroglia cells undergoing proliferation. (× 375.)

FIG. 6.—Red cells (Stäbchenzellen of Alzheimer), rarely met with, although occasionally appearances like this are seen. (× 450.)

quibble whether plasma cells are developed from lymphocytes or endothelial cells, since, in my opinion, there is sufficient evidence to show that both plasma cells and lymphocytes in chronic inflammatory conditions develop from endothelial cells of serous membranes and perivascular lymph structures, and from endothelial plates of the connective tissues.

The Neuroglia.

It is often a matter of some difficulty to distinguish young neuroglia cells from hyaline lymphocytes. By use of the modified Heidenhain and the polychrome and eosin stains, I was able to see all the changes which Watson described in juvenile general paralysis, and just as in that disease neuroglia-cell overgrowth is a leading histological characteristic, so it is of sleeping sickness and chronic trypanosome infections. The young neuroglia cells may be recognized by their pale-staining round or oval nuclei with a delicate intranuclear network containing one or two small nucleoli and a definite nuclear membrane. The chromatin substance is stained blue; surrounding the nucleus is a well-defined zone of protoplasm stained pink, of irregular quadrate or polygonal outline. These cells can be seen in groups and undergoing active division, especially in the neighbourhood of the ganglion cells. The various phases in the development of the neuroglia cells can be seen, viz.: (1) The nucleus, surrounded with an indefinite amount of cytoplasm, polygonal or irregularly quadrilateral in shape; (2) the protoplasm tending to form short spike-like processes, sometimes giving it a star-like appearance; (3) increase of cytoplasm around the nucleus and commencing formation and differentiation of the *darkly-stained* Weigert stiff fibrils; (4) further development of the Weigert fibrils and extension of one on to the wall of a vessel, there ending in a foot-like expansion; (5) further increase of development of the Weigert fibrils and differentiation from the pink-stained protoplasm on which they appear to lie; (6) the protoplasm is almost entirely differentiated into fibrils, and the nucleus is shrunken and stains deeply like the fibrils, so that the whole glia cell is stained a deep blue-black.

Distribution of the Glia Proliferation.

The distribution varies in different cases; it is almost entirely a primary interstitial overgrowth and not secondary to neural degeneration. It exists in a marked degree in cases which during life presented

no very marked symptoms pointing to destruction of nervous elements. In some very chronic cases in which there have been many epileptiform seizures, there may have occurred sufficient degeneration in the pyramidal tracts to give rise to a secondary sclerosis, but this is exceptional.

The glia proliferation, which is not visible to the naked eye in sections of the spinal cord, becomes very manifest when examined with a low power, and there is a diffuse glia proliferation, as I first pointed out in the two cases which I first investigated. This diffuse subpial glial proliferation affects the periphery of the cord and spreads inwards along the septa; it is not only met with in the white matter, but is evident also in the grey matter. The situations in the brain where glia proliferation is most obvious in general paralysis are the situations in which it is most obvious in sleeping sickness. Thus it is well advanced in the most superficial layers of the cortex, where large branching cells with deeply-stained Weigert fibrils can be seen forming a subpial felt-work. The large branching cells with Weigert processes extending on to the small vessel walls cannot be seen so well amidst the columns of cells as in the subjacent white matter. From the examination of the brains of two monkeys that died of sleeping sickness after experimental inoculation, the glia-cell overgrowth and extension of processes on to the vessels appeared to be more marked than the perivascular mononuclear infiltration, as if this tissue was the first to respond to the irritation of the noxious agent (*vide* Plate III, fig. 1). However, examination of a case—Mrs. S.—in whom symptoms only existed for two months, did not show a glia proliferation in excess of the mononuclear infiltration; nor could I find any neuroglia proliferation or perivascular infiltration in a chronic case of infection by *Trypanosoma gambiense*, a native of Uganda, who died of pneumonia and pneumococcic meningitis after an illness of ten days, but who, prior to this illness, had displayed no symptoms of nervous affection.

The meningeal and perivascular infiltration with lymphocytes and *plasma* cells was regarded by Nissl as pathognomonic of general paralysis; but I pointed out that plasma cells as well as lymphocytes occurred in the perivascular infiltrations of sleeping sickness, and I figured the same on p. 289, vol. ii, *Archives of Neurology*, 1903. I mention this because an Italian observer claims to have first described plasma cells in sleeping sickness.

Changes in the Central Canal of the Spinal Cord.

Not only is there evidence of a chronic irritative action of the cerebrospinal fluid by the cell proliferation in the meningeal and perivascular lymphatics, but in all chronic cases the central canal of the spinal cord is filled up owing to a proliferation of the cells of the ependyma. I found that this had occurred in quite juvenile subjects. It was so in the little Congo negro boy who died in Charing Cross Hospital in 1898, and I was of opinion then that this fact afforded evidence of a very chronic nervous affection caused by some irritating agent. Such change denotes, then, a chronic process of considerable duration. Examined under a high power, the nuclei of the cells lining the spinal canal may often be seen undergoing active proliferation, and specimens stained with polychrome and Heidendain-eosin method exhibit large pale nuclei with a thin membrane and chromatin granules stained blue, surrounded by a pink cytoplasm, often with numerous processes. In some very chronic cases the glia proliferation had led to the formation of abundant Weigert fibrils. In the grey matter around the central canal numerous glia cells having a similar appearance can be seen.

I deem it of little importance whether the glia proliferation precedes mononuclear cell infiltration, or whether by its doing so it obstructs the flow of the lymph and entangles the mononuclear cells; nor do I regard it of much importance whether we speak of this formative cell hyperplasia as a chronic inflammatory process or not. The important fact to recognize is that this meningeal and perivascular infiltration is a hyperplastic reaction of fixed tissue elements to a noxious agent—*Trypanosoma gambiense*. So far we are on certain ground. It is, however, a matter of speculation whether this tissue reaction is due to (*a*) the relatively few trypanosomes which can be demonstrated in the fluid; (*b*) the elaboration of a toxin by them; (*c*) a transition to some hitherto undiscovered modified forms.

Changes in the Small Vessels and Capillaries.

The capillaries in the pia and in the brain tissue show the following changes, but these are not nearly so marked as in general paralysis of the insane.

The nuclei of the endothelial cells may undergo proliferation, and in the neighbourhood of the capillaries and small vessels there are often numerous lymphocytes, plasma cells, and glia cells sending a process on

to the wall of a vessel; but I fail to find evidence of sprouting new capillaries as seen in general paralysis, nor can I but very rarely find any evidence of the Stäbchenzellen or rod-cells described by Alzheimer in general paralysis (*vide* Plate III, fig. 6).

The marked proliferation of the vascular endothelium with hyaline degenerative changes of the small vessels so frequently met with in general paralysis is hardly ever seen in even the most chronic case of sleeping sickness, nor can I find any evidence of endarteritis so generally met with in all cases of syphilitic brain disease. There may be a granulo-aqueous degeneration of the lymphocytes and plasma cells in the perivascular spaces, but I have never seen caseation nor have I seen tumour formation. This looks as if the trypanosome when it was surrounded by cells in the perivascular space did not undergo division and multiply because it requires a fluid medium, but was walled in by cells and killed unless it had escaped into the free cerebrospinal fluid. Whereas the growth starting in the meninges and spreading inwards along the pial sheaths as well as superficially suggests that the spirochæte multiplies at the expense of the cells, resulting from the chronic irritation of the endothelial and connective-tissue cells spreading thereby and setting up fresh cell hyperplasia with the formation of lymphocytes and plasma cells; but inasmuch as the walls of the arteries participate in this cell hyperplasia, endarteritis occurs, and this, in conjunction with the rapid neoplastic formation, leads to necrobiosis of the older central portions of the tumour.

Vascular (usually capillary) hæmorrhages are met with in all forms of trypanosome disease, and probably are the result of obstruction by the organism. Hæmorrhages may occur in syphilis, but these are due to arterial degeneration, as a rule, with thrombosis or rupture of the vessel.

Changes in the Neural Elements.

Although the meninges are in many cases obviously thickened and the convolutions flattened (indications of some intracranial pressure), yet there is no naked-eye wasting of the brain. The depth of the grey matter of the cerebral cortex is not appreciably diminished, although the vessels both in the grey and white matter may appear somewhat congested.

I have not observed granulation of the ependyma of the ventricles, so characteristic of the meningo-encephalitis of general paralysis of the insane. Moreover, the marked wasting of the grey matter of the

cerebral cortex, so characteristic of the disease, is not met with in sleeping sickness. The convolutions are broad and of normal size, and the sulci tend to be obliterated in sleeping sickness, whereas in general paralysis the convolutions are shrunken from atrophy of the neural elements, cells and fibres, and the sulci are consequently broad and deep. In both diseases there is thickening of the leptomeninges and septal and perivascular changes, but here, it seems to me, the similarity ends. But this statement becomes more apparent and convincing when the microscopic changes are described. Moreover, a comparison of the size of the remaining structures of the central nervous system shows that in general paralysis there is a primary neuronic atrophy which does not occur in sleeping sickness. Thus to the naked eye the spinal cord in the latter disease may appear normal as regards amount of grey and white matter, whereas in general paralysis the cord is often much reduced in size and there is very obvious neuronic atrophy.

The naked-eye appearances therefore point especially to a primary parenchymatous degeneration in general paralysis with chronic interstitial and meningeal inflammation, whereas in sleeping sickness the morbid change is primarily interstitial and with some secondary parenchymatous atrophy (*vide* figs. 3, 4, 5).

Microscopic Examination of the Nerve Cells and Fibres.

In uncomplicated cases that have died within six months of the onset of the lethargy untreated by organic arsenical preparations, I have found a widespread diffuse infiltration of the meningeal and perivascular lymphatics, especially of the subcortical structures, with comparatively little distortion of Meynert's column or atrophy of cells. In a European who was treated and lived one year, having epileptiform seizures for weeks prior to death, there was a considerable atrophy and destruction of cell elements; but the perivascular and glia change, as compared with general paralysis, was out of all proportion to the neuronic atrophy.

Cells.—The changes in the ganglion cells may be considered as due (1) to the primary lymphangitis, and (2) to secondary microbial toxæmia. It is difficult to differentiate the cells which are affected by the one cause from the other. I consider, however, that the chronic change is indicated in those cells in which (1) there are appearances of atrophy of the dendrons, the protoplasmic processes being either attenuated or broken off; (2) there is a perinuclear chromatolysis, the cytoplasm still exhibiting some remnants of a pattern of Nissl granules in the circum-

ference of the cell and on the dendrons; (3) the nucleus is large and clear, and often eccentric. Sometimes a dead ganglion cell may be seen being devoured by phagocytes. The cells of the spinal cord usually show much less change than the cells of the medulla oblongata and the cerebral cortex. The cells of the posterior spinal ganglion usually show chromatolysis, but not destruction (*vide* Plate IV). The appearance of the cells in acutely fatal trypanosome affections—e.g., surra and jinga in animals—could be accounted for by the anæmia caused by the blood change and the obstruction of the small vessels by the trypanosomes. In the brain of a rabbit dying of surra one month after inoculation, the ganglion cells all showed a shrinking of the cytoplasm, a marked chromatolysis and disappearance of the Nissl granules and swelling of the nucleus, and a change not unlike that observed in some forms of experimental anæmia.

Fibres.—In cases uncomplicated by terminal microbial infection, there is a certain amount of fibre atrophy proportional to the cell atrophy described. This atrophy is most obvious in the tangential layer of the cortex cerebri, where the fibres in places are greatly diminished, or even absent. There may also be some diminution of the fibres in the super-radial and inter-radial systems, especially in chronic cases. There is, however, in the brain as in the spinal cord, no definite system tract sclerosis, the result of atrophy of a neuronic system. Generally in the lateral columns corresponding to the pyramidal systems some degenerated fibres can be seen by the Marchi method, but the glia proliferation tends to follow the distribution of the septa rather than to accord with any definite atrophy of a system of nerve fibres. By the Marchi method, the cerebrum, cerebellum, spinal cord, and spinal ganglia were examined in a number of cases. In most instances the results were unsatisfactory, owing to a generally diffuse blackening of the myelin sheaths and the deposition of black granules. I consider that this change was probably the result of acute changes in the myelin, brought about by terminal microbial toxæmia, fever, &c. Some few of the cases, however, did not show this generalized change in the myelin, and a certain number of fibres showing Wallerian degeneration were found. These changes we may regard as definite, and indicative of neuronic decay.

Examination of Nervous Tissues of Animals Experimentally Infected by Trypanosomes.

Experimental Evidence.—Animals inoculated with *Trypanosoma gambiense* usually die before the characteristic lesions of the nervous system can occur. I have examined the tissues of nine animals (monkeys) which were inoculated at Entebbe in one way or another with *Trypanosoma gambiense.* They were all said to have exhibited the characteristic lethargy, but it is very difficult to differentiate (according to my experience) between a monkey that sits moping when profoundly ill and an animal which exhibits a lethargy on account of the brain lesion.

The tissues of the brains of all the animals sent to me, with the exception of two, showed no characteristic change. The vessels of the brain were empty and there was no meningeal or perivascular infiltration. Several of these animals had survived the infection (as proved by the existence of trypanosomes in the blood) one year. One was subsequently infected with diplo-streptococci from a case of sleeping sickness; yet there was no sign of the meningo-encephalitis met with in every case of human sleeping sickness. This was the experience, apparently, of Ayres Kopke.

The tissues of two monkeys inoculated with *Trypanosoma gambiense* showed, however, the characteristic lesion of human sleeping sickness. I have examined portions of the tissues, and find that there is a very marked neuroglia proliferation of the perivascular lymphatics, endothelial cell proliferation and lymphocyte accumulation, and a few plasma cells around the vessels of the brain in all the situations examined. In fact, the lesion in no respect differs essentially from that of human sleeping sickness.

A correlation of the clinical notes of thirty cases of sleeping sickness before the treatment by organic arsenical preparations was introduced, with a microscopic investigation of the changes in the central nervous system, shows that there is a parallelism between the intensity of the chief nervous symptoms—viz., drowsy lethargy, mental enfeebleness and fatigue, paresis and tremors—and the generalized chronic diffuse meningo-encephalitis. The general intense perivascular infiltration with lymphocytes and plasma cells must interfere with the circulation of the ambient fluid of the neurons, whereby they suffer from an insufficiency of oxygen. The fluid which circulates in the perivascular lymphatics is the ambient fluid that takes oxygen from the blood to hand it over to the nerve

cells. This progressive, universal, and intensely inflammatory state of the perivascular lymphatics would interfere with its flow and lead to deficient oxygen supply. There is an interference with the outflow of the cerebrospinal fluid, but not sufficient to produce a choked disk, so that, although this may tend to produce cerebral anæmia, it cannot be so important a cause of the functional defect of the neurones, and yet it may take part in the production of the symptoms. The principal cause of

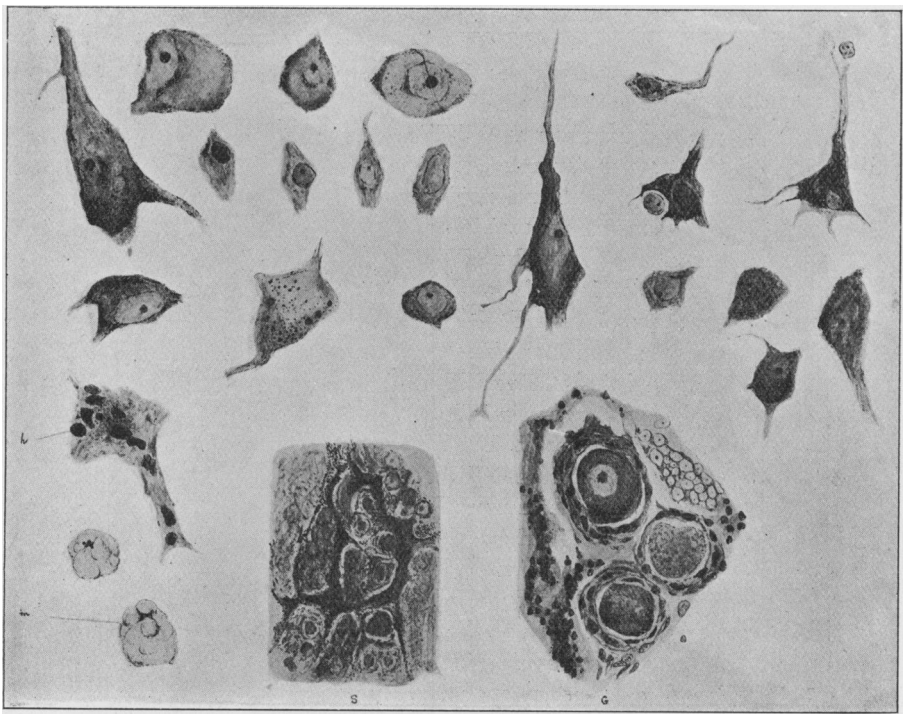


PLATE IV.

CHANGES IN THE CELLS OF THE CENTRAL NERVOUS SYSTEM.

Appearance of various large and small pyramidal cells of the cerebral cortex in advanced cases of sleeping sickness, showing various degrees of chromatolysis, eccentric position of the nucleus, breaking off and disappearance of the processes.

The cell (*h*) is obviously dead and being devoured by phagocytes. Below this are two granule cells (Körnchenzellen). (× 375.)

FIG. *S* is a section of a posterior spinal ganglion, showing an intense interstitial lymphatic-cell infiltration with lymphocytes. (× 90.)

FIG. *G* shows a portion of the section of the same more highly magnified. Not only can the interstitial lymphatic-cell infiltration be observed, but there is a proliferation of the endothelial cells of the capsule. (× 375.)

the lethargy, in my judgment, is the perivascularitis. Moreover, a vicious circle is established, for the more these lymphatics become obstructed by the actively growing young cells, the more the oxygen that may be in the fluid will be snapped up by them and the less will be at the disposal of the neurones. Consequently, the oxygen supply necessary for functional activity of the nerve cells becomes progressively less and the drowsy stupor deepens proportionally. The experiments of Verworn prove the importance of oxygen storage by the nerve cells and

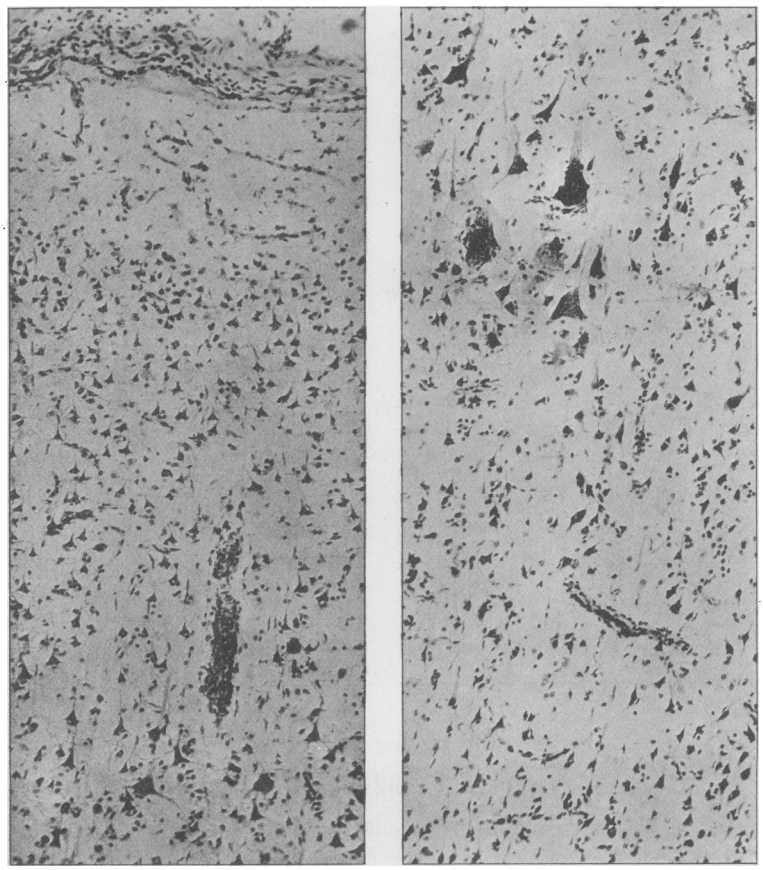
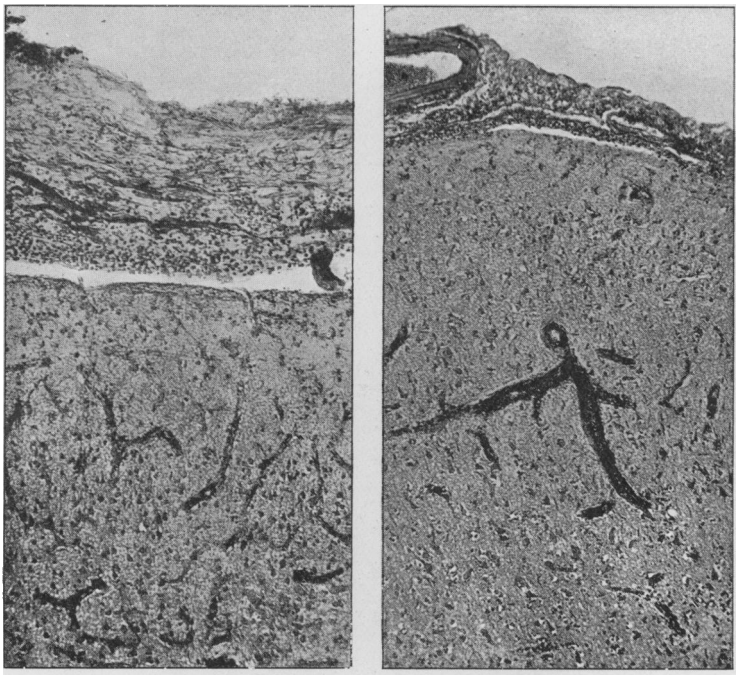


FIG. 3.

Photomicrograph of the cortex from a case of uncomplicated very chronic sleeping sickness. The pyramidal cells are not destroyed; there is not any increased vascularity; there is some perivascular and meningeal infiltration, not nearly so marked as in the subcortical tissue. The columns of Meynert are not disorganized; this accords with the fact that the main symptoms were paresis, tremors, drowsy lethargy, but no epileptiform seizures or mental disturbance beyond enfeeblement. (× 150.)

the necessity of its supply for functional activity. In widespread generalized syphilitic meningitis and perivascularitis a drowsy stupor is a frequent symptom ; in general paralysis the perivascularitis may be very intense in the cortex, but never so diffuse and intense in all the subcortical structures as in sleeping sickness. The progressive dementia which is the characteristic of the former disease is proportional to the atrophy and wasting of the cortical substance—a condition which is not usually met with in sleeping sickness. In juvenile general paralysis the primary parenchymatous change is more manifest because convulsive



a FIG. 4. *b*

Two sections of the cortex in general paralysis ; thickening and infiltration of membranes, perivascular infiltration, formation of new vessels and marked atrophy of cortical substance, especially in *b*, the frontal region ; *a* is the post-central region. (× *a*, 120 ; *b*, 75.)

seizures are less frequently met with. I have observed two forms of change in the cells in general paralysis—viz., an atrophic change and an acute swelling accompanied by chromatolysis similar to that observed in experimental anæmia. This change is doubtless due to vascular stasis and accounts for the fact that after prolonged unilateral convulsive

seizures one hemisphere will be found to weigh very much less than the other, and microscopic examination will exhibit acute destruction of nervous elements in the hemisphere opposite to the seizures. If we regard the parasyphilitic affections, tabes and general paralysis, as being due to premature decay of neurones, it is not to be expected that drugs which benefit by killing the organisms will be of any service. Seeing

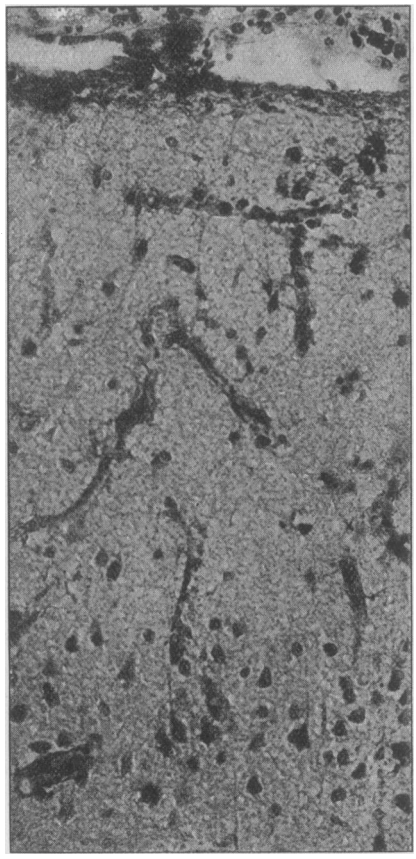


FIG. 5.

Section of the brain of a case of advanced general paralysis, showing the absence of cells in the superficial layer of the cortex. Numbers of vessels are seen to which many glia cells are attached. There is a complete absence of fibres and destruction of the superficial cortical cells (stained by van Gieson method). (× 262.)

that the spirochæte has never been demonstrated either in the tissues or cerebrospinal fluid in these affections, whereas it has in gummatous meningitis, we can understand why mercury, antimony, and arsenic

compounds will, by killing the organism, cure syphilis of the nervous system and will not cure general paralysis or tabes. But why do these drugs have no influence in sleeping sickness? In syphilis the organism has not escaped into the free fluid, for it has never been demonstrated there. To rid the nervous system of the syphilitic organism it is therefore probably not necessary for the drug to get into the cerebrospinal fluid.

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