TRYPANOSOMIASIS.

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1.—Definition.

(Synonym: African trypanosomiasis.)

Sleeping sickness is an infection met with in Tropical Africa due to protozoal parasites belonging to the genus *Trypanosoma*, disseminated by various tsetse flies (*Glossina*), and characterized by irregular febrile disturbances, by an erythematous eruption and localized oedemas, by a polyadenitis, tachycardia, and later in the disease by various nervous phenomena; in untreated cases the infection usually terminates in coma and death.

2.—Ætiology.

Protozoology. Two forms of sleeping sickness are commonly recognized, the one due to *Trypanosoma gambiense* and the other due to *Trypanosoma rhodesiense*. Although the identity of these two trypanosomes has been subject of much discussion, and considerable evidence has been accumulated indicating that they are very closely related, if not identical, nevertheless from the clinical point of view it is convenient to regard the parasites, and the diseases which they cause, as separate entities. Their geographical distributions are not the same, the tsetse flies responsible for their dissemination differ, the two infections exhibit certain clinical differences, and finally their reaction to drugs differs.

Trypanosoma gambiense and *T. rhodesiense* are found in the blood, usually in scanty numbers, but sometimes, especially in the case of the latter species, they may be present in large numbers.

Parasites. The trypanosomes can be seen wriggling actively and creating a disturbance amongst the red corpuscles. They occur as fusiform organisms varying from about 10 or 12 μ up to 32 μ in length, and in stained preparations they exhibit the characters shown in the Figure.

Trypanosomes in the blood
(from a stained preparation).

Vectors. The parasites are disseminated from man to man by different species of tsetse flies. *Glossina palpalis*, and to a less extent *G. tachinoides*, are mainly responsible for the spread of that form of sleeping sickness due to *T. gambiense*, and *G. morsitans* and *G. swynnertoni* for that due to *T. rhodesiense*.

Glossina, which for all practical purposes are confined to the tropical and sub-tropical portions of the African continent, are narrow-bodied, elongate, dark brown, blackish, yellowish-brown or yellow flies ranging in size from about 8 to 13 mm., according to the species. They are recognizable when alive and

at rest by their wings being closed flat one over the other like the blades of a pair of scissors, and by the biting proboscis projecting horizontally in front of the head. Both sexes are blood-suckers and they feed during the day-time.

Glossina owes its importance in the dissemination of sleeping sickness to the fact that the trypanosomes undergo a definite and complicated biological development in its digestive system.

It is of importance to note that in comparatively few of the tsetse flies, which feed on an infected man or animal, do the trypanosomes succeed in completing their complicated evolution. The factors determining the proportion of flies which become infected are not, as yet, thoroughly understood.

3.—Pathology.

The trypanosomes frequently multiply in the skin at the site of the infective bite and produce an inflammatory lesion which subsides without suppuration. Within a very short period the parasites invade the blood-stream, where they multiply and give rise to a general septicæmia. Whilst there is good reason to believe that many of the organs of the body, including the minute blood vessels, are damaged by the toxins secreted by the trypanosomes, the chief reactions are to be seen in the lymphatic glands and in the leptomeninges. There is a general adenitis, the lymphatic glands becoming enlarged and elastic. In section they show a hyperplasia of the follicles and a multiplication of the macrophages in the sinuses; around the vessels is an infiltration of leucocytes and plasma cells. Later, the glands become sclerosed, the follicles and glandular tissue being replaced by fibrous tissue.

The most important changes in sleeping sickness are, however, those which occur in the pia-arachnoid. The minute blood vessels in the meninges, in the choroid plexus and in the brain substance itself are damaged by the trypanosomes, which eventually pass through the altered endothelium into the perivascular spaces and give rise to leptomeningitis. This inflammation of the leptomeninges is precocious and progressive, and is responsible for the characteristic clinical manifestations of the disease.

At autopsy the dura mater, in advanced cases, is found to be adherent to the cranium and to the underlying meninges. On incising the dura a considerable amount of clear fluid may escape and the brain is seen to be oedematous and congested. In such cases, owing to the intracranial pressure, the surface of the brain is smooth; the sulci tend to be obliterated, but the convolutions are broad and of normal size. In less pronounced cases, there is little excess of fluid, and the surface of the brain exhibits a normal appearance. The meningitis is predominantly vertical, and according to Caldwell (1937) rarely extends more than half way down the sides of the cerebral hemispheres. Meningeal adhesions at the base of the brain are rare. There is a diffuse generalized leptomeningitis, which is just as marked on the inner surface of the hemispheres as on their lateral aspects. The brain itself is of normal consistency, but here and there it may exhibit softenings at the sites of hæmorrhagic foci. The ventricles are frequently distended, and the choroid plexuses show signs of chronic inflammation.

On microscopic examination the generalized leptomeningitis is manifested not only by a proliferation of the neuroglia cells in the adjacent nervous substance, but also by a proliferation of the endothelial cell nuclei and by an infiltration of the pia-arachnoid membrane with lymphocytes and plasma cells.

A striking feature of sections of the brain is a universal perivascular infiltration. This consists of a proliferation of the vascular endothelium, and packing of the Virchow-Robin space—the continuation of the subarachnoid space formed by the reflection of the pia-mater along each blood vessel which enters the nervous tissue—with proliferated and enlarged neuroglia cells, and with lymphocytes, plasma cells and morular cells. Morular cells, which were first described by Mott (1906), are large round or oval cells with the nucleus staining deeply and pushed up to one end or pole; the cytoplasm contains a large number of clear spherules staining with eosin and giving the cell a mulberry appearance.

The chronic inflammatory change in the central nervous system is manifested by a proliferation and overgrowth of the neuroglia cells, especially those which are related to the subarachnoid and perivascular spaces. The lesions of the neural elements are, as a rule, slight and not comparable with those met with in general paralysis. In sleeping sickness the morbid change is thus primarily interstitial with some secondary parenchymatous atrophy.

Cerebrospinal Fluid. During the course of sleeping sickness certain very characteristic changes occur in the cerebrospinal fluid. According to Sicé, who has studied the subject with very great care, the alternating multiplication of trypanosomes in the general circulation and their subsequent destruction during the trypanolytic crises, which are a constant feature of the evolution of the disease, occasion vascular changes which are particularly manifest in the region of the terminal ramifications of the blood vessels. The choroid plexuses of the ventricles and the Virchow-Robin spaces surrounding the vessels nourishing the brain substance are particularly involved in these inflammatory processes. The changes seen in the cerebrospinal fluid are as follows:—

Physical changes. The spinal fluid is usually clear; exceptionally when the cellular reaction is very great it may be opalescent, but in such cases it is well to consider the possibility of bacterial infection. As a rule, the pressure is slightly raised—30 to 35 centimetres of water in the sitting position—but sometimes the pressure may reach as much as 100 centimetres of water; subnormal pressure is exceptional.

Cytological changes. An increase in the number of white cells is the earliest change seen. At first there is a simple increase in the lymphocytes, which, instead of being 2 or less, as in the normal state, are found to be 10 or 20 more per c.mm. As the disease progresses the number of lymphocytes increases and other cells, viz., plasma cells, morular cells, large mononuclear cells and occasional eosinophil cells, indicative of more pronounced changes, make their appearance, so that in advanced cases the total cells in the cerebrospinal fluid may number several hundreds and even thousands per cubic millimetre. Trypanosomes are frequently, but by no means invariably, to be found in the centrifuged deposit.

Chemical changes. These relate chiefly to alteration in quantity of protein, chlorides and sugar. Increase in the total protein content is a very important and constant sign; instead of the normal amount of about 0.2 gm. per litre, the value may be anything from 0.3 gm. up to 1.0 gm. or even more. Coincidentally, with increase in protein there is a fall in the chloride and sugar values.

Colloidal reactions. These reactions, particularly the modification of Lange, have been examined repeatedly in human trypanosomiasis. In general, the reaction is of the "tabetic" type; when it exhibits the "general paralysis" type it has a grave prognostic significance.

Generally speaking, it can be said that when the patient exhibits definite nervous symptoms changes can be seen in the cerebrospinal fluid; the reverse, however, is not equally true, because it is now known that the cerebrospinal fluid may exhibit pathological changes in cases which present no clinical signs of nervous lesions. It has gradually become recognized that in human trypanosomiasis the nervous system is involved much earlier in the disease than was formerly thought.

4.—Clinical Picture.

Trypanosomal Chancre. In many patients the first sign of the disease is a local lesion at the site of the infective bite. This primary lesion is a furuncle-like swelling of the skin, which does not produce pus, and which appears within a few days of the bite of an infected *Glossina*. In well-marked cases the trypanosomal chancre, as it is called, consists of a raised, indurated, button-like area, dark red or violet-red in colour and measuring up to 3 or 4 cm. or even more in diameter. The surrounding tissue is oedematous and the lesion is painful and very sensitive to pressure; it may persist for 2 or 3 weeks. That these lesions are due to the trypanosome and not to inflammation resulting from the bite itself, or to secondary infection, is proved by the presence of large numbers of trypanosomes in the tissue fluid, and by the fact that the lesion is quickly cured by trypanocidal drugs.

Seven to fourteen days after the infective bite the infection manifests itself suddenly by a sharp febrile disturbance which is often associated with a definite rigor. The temperature rises quickly and within a day or two may reach 103° F. or 104° F. At this time trypanosomes are usually present in the peripheral blood in sufficient numbers to be discovered by microscopical examination. Frequently after about a week the temperature falls to normal for a few days, and then rises again. The second febrile disturbance is usually less violent than the first and of shorter duration. This fever of invasion as it is called, is characterized by its violence, its tendency to remit and to recur, and its gradual subsidence.

When the initial acute febrile disturbance is over, the patient passes into an afebrile state, or, more commonly, into a state in which the morning temperature is normal and the evening temperature slightly raised to 99° F. or 99.5° F. At irregular periods this condition of comparative afebrile calm is interrupted by acute exacerbations of fever lasting a few days.

Asthenia, which is so characteristic of the disease, appears early and becomes progressively more pronounced. Headache, at first transitory but later permanent, is a constant feature. The patient becomes drowsy during the day, but suffers from insomnia at night. Other important early signs of the disease are a generalized adenitis, tachycardia, erythematous eruptions and localized oedemas.

Enlargement of the lymphatic glands is one of the earliest and most characteristic signs of the disease. The importance of this sign from the point of view of diagnosis was emphasized as long ago as 1906 by Dutton and Todd. The hypertrophied glands are easily felt; they are freely movable and, as a rule, painless; they are elastic and semi-fluctuating, giving the sensation of a ripe damson on palpation. It is in this stage that the glands are characteristic of the disease, and it is from them that the trypanosomes can readily be obtained on puncture. Later, the glands become sclerosed and are hard and shotty. Intermediate stages between these extremes are met with, and sometimes even in the same area glands in all stages can be felt. Whilst all groups of glands are involved, those in the neck are most conveniently examined. It must be borne in mind, however, that the condition

of the scalp of the native is a frequent cause of enlargement of the cervical lymphatic glands; but large, elastic, painless and freely movable glands of the kind mentioned above are very characteristic and merit careful examination for trypanosomes. There is no doubt that the infection causes enlargement of the liver and spleen, but, as sleeping sickness patients have so frequently suffered from malaria and other tropical complaints, little importance can be attached to this as a clinical sign of trypanosomiasis.

Tachycardia is a very constant sign in an early trypanosomal infection. Even in the apyrexial periods the pulse rate is usually over 100 per minute. The arterial pressure is usually low. It is possible that these circulatory phenomena are due to myocardial changes, which Peruzzi (1928) has shown to be common in experimental monkeys.

Erythematous eruptions may appear at any stage of the disease, but they are particularly frequent during its earlier stages. They are usually most prominent on the trunk, but they may extend on to the face and limbs, and are much more easily seen on the light skin of the European than on the black skin of the African. Sometimes they assume the form of large irregular patches, but frequently they are circinate. Usually they are transient, but they may persist for prolonged periods. When the rash fades it leaves no trace, and its disappearance is not accompanied by desquamation.

Localized transient œdemas may be seen as early as the first few weeks of the disease; the parts particularly affected are the lower eyelids and the ankles.

Albuminuria is not a constant sign, but it is found in many cases, not only at the beginning of the infection but throughout its whole course.

Certain patients exhibit quite early signs of gastro-intestinal disturbances, with vomiting and diarrhoea of varying intensity.

As the disease progresses the patient becomes more and more emaciated and asthenic, the slightest effort fatigues him and he becomes apathetic. He is drowsy during the day-time and frequently falls asleep, but insomnia at night is the rule. Neuralgic pains, muscular cramps, and rheumatic pains in the joints are commonly met with. Many patients complain of a sense of tingling of the face, the palms of the hands, the fingers and the soles of the feet. Hyperæsthesia is often noticed quite early in the disease; deep pressure, such as that which occurs in the palm of the hand when turning a large key in a stiff lock, is followed, after a short interval, by a degree of discomfort amounting to actual pain (Kérandel's sign). Paresis of one or more muscular groups, particularly of the facial muscles, is not uncommonly seen in the early stages. Coincidentally with these symptoms psychical disturbances develop; the patient becomes irritable, melancholic, emotional or depressed. Memory fails, there is intellectual degeneration and the character changes.

As the meningo-encephalitic changes progress the patients may exhibit multitudinous nervous signs, such as paresis or paralysis of various muscles or groups of muscles, hemiplegia or paraplegia with incontinence, incoordination of movement, alteration in muscle sense, rigidities, various contractures, epileptiform convulsions, delirium, severe headache, pronounced somnolence, and profound psychical disturbances; finally they sink into a state of coma, and death results. Although no part of the central nervous system escapes, different portions of it seem to be predominantly involved in different cases, with the result that clinically a whole series of nervous types of the disease have been described, viz., medullary, cerebellar, cerebral, psychical, etc.

With the development of the nervous manifestations the earlier symptoms tend to become modified. The fever does not entirely disappear but becomes much less pronounced, and there may be long apyrexial periods interrupted now and again by rises of temperature which begin suddenly and end as quickly. The tachycardia characteristic of the early stages often becomes less pronounced, but the cardiac manifestations, e.g., bruits, arrhythmia, hypertrophy or dilatation, develop, and are possibly related to the myocarditis to which reference has already been made. The erythematata may sometimes persist until the later stages of the disease. Attacks of diarrhoea or dysentery often continue, but the appetite remains unchanged until the final coma. Albuminuria associated with chronic nephritis may persist. The liver and spleen may remain enlarged until death or they may return to their normal size. The lymphatic glands tend to become atrophied and sclerosed, but some of typical character may be found. The general condition rapidly deteriorates and the emaciation progresses until the patient is reduced to skin and bone.

Although impotence develops early in the man, menstruation, as a rule, persists unchanged for a long time in the woman. Aubert (1935) and others, however, have drawn attention to the frequency with which women suffering from sleeping sickness abort or give birth prematurely to dead children.

Visual disturbances. Ocular troubles are not uncommon in trypanosomiasis; one or both eyes may be involved. Cyclitis, interstitial keratitis and iritis, which are fairly frequently encountered in the earlier stages of the disease, are due to the localization of trypanosomes in the interstitial spaces of the parts involved; the conditions are, as a rule, benign and they disappear rapidly.

There may be also lesions in the depth of the eye involving the retina and the optic nerve. Two kinds of lesions may be exhibited by the optic nerve: the disc may be oedematous as the result of meningeal invasion by the trypanosome or of hypertension of the cerebrospinal fluid; or there may be signs of optic atrophy with pallor and narrowing of the vessels of the disc. These changes may occur in the absence of any arsenical treatment, but, as will be mentioned later, optic atrophy with defective vision or even complete blindness is the chief danger resulting from the treatment of sleeping sickness by the aromatic compounds of arsenic.

Types of the Disease. As a general rule, the disease produced by *T. rhodesiense* is more violent and runs a more rapidly fatal course in untreated patients than does that produced by *T. gambiense*. It was formerly thought that these differences were sufficient to distinguish the two infections clinically, but it is now recognized that *T. rhodesiense* may produce a very chronic and insidious disease, and that *T. gambiense* may produce a virulent and rapidly fatal disease.

5.—Treatment.

The history of the treatment of sleeping sickness constitutes one of the most remarkable chapters of modern medicine. What was, before 1905, an almost invariably fatal disease can now, if recognized early, be cured with a great degree of certainty. Of the long series of synthetic compounds which have been prepared for the treatment of sleeping sickness four have stood the test of time, and it is on them that we now rely. These are the aromatic arsenical compounds—atoxyl, orsanine, tryparsamide, and the urea substitution compound, germanin.

Atoxyl (tryproxyl) is the monosodium salt of p. aminophenyl-arsinic acid. This drug, which is now almost entirely superseded by the more active and less toxic

orsanine, is given in 10 per cent. solution in sterile distilled water, either subcutaneously, intramuscularly or intravenously. The dose is 10—15 mgm. per kilo. of body weight (0.5—0.75 gm. for an adult), and the injections are given once weekly for about 6 to 12 weeks.

Orsanine is the monosodium salt of 2.oxy-4.acetyl-amino-phenyl arsinic acid. It is given in 20 per cent. solution in sterile distilled water, either subcutaneously, intramuscularly or intravenously. The dose is 20—35 mgm. per kilo. (up to 2 gm. for an adult), and the injections are given at weekly intervals for 10 or 12 weeks.

Tryparsamide (tryponarsyl) is the monosodium salt of p. glycinamino-phenyl arsinic acid. This compound, which is very soluble, is given in 20—40 per cent. solution; it is administered intravenously, and solutions should be made in sterile distilled water immediately before use. Whilst tryparsamide is less active as a trypanocidal substance than orsanine, it has the great advantage of acting in the later stages of the disease when the meninges are involved. It is usually given in doses of 20—40 mgm. per kilo. of body weight (2—3 gm. for an adult); the doses are given at weekly intervals until a total of about 30 gm. has been administered, after which the drug should be stopped for a period of a month or so.

If lumbar puncture shows that the cerebrospinal fluid has not become normal after a course of tryparsamide, the treatment must be repeated. The condition of the cerebrospinal fluid is the essential guide to treatment in the later stages of sleeping sickness, and one is not justified in concluding that a cure has been obtained until the cerebrospinal fluid has returned to normal and has remained so for at least six months.

Germanin (Bayer 205, moranyl, atrypol) is a complex urea substitution compound containing no heavy metal. It is a slow-acting, but exceedingly valuable trypanocidal substance. The compound is usually given intravenously in 10 per cent. solution in sterile distilled water. The customary dose is about 1 gm. for an adult, but doses as large as 1.5 gm. or even 2.0 gm. have been employed. The doses are usually repeated at intervals of two or three days until a total of 10 gm. has been administered.

It has already been pointed out at the beginning of this article that *gambiense* and *rhodesiense* infections differ in their response to drugs. Generally speaking, *gambiense* infections are sensitive to the aromatic arsenicals and to germanin, whereas *rhodesiense* infections, although sensitive to germanin, are relatively resistant to the aromatic arsenicals. Another point to be borne in mind is that the disease is much more easily cured in its early stage than later on when there are pronounced nervous lesions. In fact, before the advent of tryparsamide the great majority of advanced cases ran their course to the inevitable termination; in all cases exhibiting pathological changes in the cerebrospinal fluid tryparsamide should be used.

Bearing these facts in mind we are able to lay down the following rules for treatment:—

Gambiense infections. Early cases with normal cerebrospinal fluid should be treated with orsanine or germanin; later cases with pathological cerebrospinal fluid should, after a few preliminary doses with orsanine or germanin to produce peripheral sterilization, be treated with tryparsamide.

Rhodesiense infections. Early cases should be treated with germanin. Owing to the relative resistance of these infections to arsenicals, the treatment

of later cases of *rhodesiense* infections, with pathological cerebrospinal fluids, is much less satisfactory than is the treatment of corresponding cases of *gambiense* infections. The best results are obtained from a combined treatment with germanin and tryparsamide.

It is important to remember that both the pentavalent aromatic arsenicals (atoxyl, orsanine and tryparsamide) and germanin may produce toxic signs, and consequently must be used with care. Occasionally the aromatic arsenicals produce gastro-intestinal symptoms, with vomiting and acute diarrhoea, but these are generally transient and cease when the drug is stopped; other rare toxic effects are disturbances of hepatic function and dermatitis. The most serious accident resulting from the arsenicals is damage to the optic nerve. Disturbance of vision may develop gradually or suddenly, and it is always necessary to inquire carefully regarding the sight of the patient when administering a course of treatment with one of the arsenical compounds. The first signs of damage to the optic nerve are dimness in the acuity and narrowing of the fields of vision; the patient may also complain of mists and sometimes of flickerings. Scotoma, either central or peripheral, indicates a more advanced stage of damage. As a rule, if the condition is recognized early and the drug immediately stopped, the sight is restored, but, unfortunately, the damage is sometimes progressive and continues until the sight is completely lost. It is important to note that in the early stages the ophthalmoscope may fail to reveal any change, and it is only after the sight is permanently damaged or completely destroyed that the appearances of optic atrophy manifest themselves. The precise cause of this catastrophe is still obscure, but there seems no doubt that there are two factors at work, viz., the meningeal lesions produced by the disease, and the drug. Patients with considerable meningeal involvement are more likely to develop disturbances of vision when treated by an arsenical than are early cases, and consequently the greatest care is necessary when treating advanced cases of the disease.

There is some evidence that visual disturbance following the administration of an aromatic arsenical may be benefited by a course of sodium thiosulphate; 10 cc. of a 20 per cent. solution is given intravenously on alternate days. Remarkable success is claimed by Raingeard (1934) who treated in this way a series of 26 patients suffering from recent or old-standing ocular troubles (12 were actually blind) following the administration of atoxyl or tryparsamide.

The most common and serious toxic effect of germanin is damage to the renal epithelium. A considerable proportion of cases treated with this drug develop albuminuria after the administration of a number of doses. As a rule, it is transient, and is not accompanied by any concomitant symptoms; sometimes, however, the condition is more severe, and on centrifuging the urine there may be a deposit containing red cells and granular casts. Cessation of treatment generally causes these signs to disappear or diminish, but they may reappear when the treatment is renewed. Occasionally, very severe renal damage occurs, with uræmia, anuria and death. Another, but very much rarer, toxic effect of germanin is dermatitis.

Drug-Resistance. It was shown many years ago in Ehrlich's laboratory that the repeated administration of a subcurative dose of atoxyl resulted in the production of a strain of trypanosomes resistant to the drug. The phenomenon of drug-resistance has been the subject of much work during the last ten years, and it is now known that a strain of trypanosomes which has become resistant to any one of the aromatic compounds of arsenic is also resistant to all the other aromatic arsenical compounds. Resistance to the aromatic compounds of arsenic is quickly acquired, whereas resistance to germanin develops very slowly. Resistance to the

aromatic arsenicals when once acquired persists indefinitely. It is not lost by changing the species of vertebrate hosts or after repeated cyclical transmission through *Glossina*.

To what extent arsenic-resistance results from treatment of human trypanosomiasis is at present uncertain, and the subject is one which urgently requires more investigation.

6.—Diagnosis.

The diagnosis of trypanosomiasis depends, in the early stages at least, upon the discovery of the trypanosomes. In order to discover the trypanosomes, the following procedures should be adopted:—

- (1) *Trypanosomal chancre*. If the patient presents a lesion resembling a trypanosomal chancre, it should be punctured with a hypodermic syringe and the drop of fluid obtained examined microscopically, either in the form of a coverslip preparation or as a stained smear. As trypanosomes are readily found in considerable numbers this is a valuable method of making a very early diagnosis.
- (2) *Blood examination*. This can be carried out on fresh coverslip preparations or on stained thin or thick films.
- (3) *Gland puncture*. If the patient exhibits typical enlarged semi-fluctuating glands, one of the easiest methods of discovering the trypanosomes is by the puncture of such glands. The minute drop of fluid removed by means of a hypodermic syringe is examined either as a fresh coverslip preparation or as a stained thick or thin film.
- (4) *Triple centrifugation of a large volume of blood*. About 5 cc. of blood are withdrawn from a vein into 1 cc. of a 1 per cent. solution of sodium citrate, and centrifuged at low speed until most of the erythrocytes are thrown down. The supernatant fluid is then removed and again centrifuged at low speed until the remaining erythrocytes and most of the leucocytes are deposited. The supernatant fluid is again removed and centrifuged at high speed, the deposit being examined microscopically for trypanosomes, in fresh preparations or in stained films.
- (5) *Lumbar puncture*. In old-standing cases of sleeping sickness where trypanosomes are frequently difficult to discover in the blood, and where the lymphatic glands are sclerosed and atrophied, lumbar puncture is an invaluable aid in reaching a diagnosis. Although trypanosomes are by no means always found in the centrifuged deposit of such cases, the typical pathological changes—cellular and protein—exhibited by the fluid are sufficient to warrant a diagnosis in a suspicious case coming from an endemic region.

7.—Prognosis.

This varies materially, according to the stage of the disease at which treatment is commenced. If the diagnosis is made early, the outlook with proper treatment is remarkably good in both *gambiense* and *rhodesiense* infections. Even well-advanced cases of *gambiense* infection showing pronounced changes in the cerebrospinal fluid are often cured by adequate treatment. In advanced cases of *rhodesiense* infection the prognosis is not nearly so hopeful.

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