AMERICAN TRYPANOSOMIASIS

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Synonyms: South American trypanosomiasis; Brazilian trypanosomiasis; Schizotrypanosomiasis; Enfermedad de Chagas; Chagas’ disease.

Definition.—American trypanosomiasis is an infectious disease of man and lower animals caused by Trypanosoma cruzi. It occurs more or less commonly throughout Central and South America and is transmitted by species of reduviid bugs. Two forms of the disease are generally recognized, the acute and the chronic. The pathological changes are brought about by the invasion of the tissue cells by the parasite, where it develops and eventually brings about their destruction. The acute form of the infection is common in children and is accompanied by fever, edema, myocardial disturbances, adenitis and anemia. The chronic form is as yet not well defined and as a rule is asymptomatic.

HISTORY

In 1907, Carlos Chagas, while examining the intestinal contents of the reduviid bug, Triatoma megista, found that many were infected with an organism resembling the crithidia form of trypanosomes. He sent a number of the infected bugs to Dr. Oswaldo Cruz who fed them on monkeys and succeeded in transferring the infection. Chagas later discovered a trypanosome in a sick child and was able to demonstrate that the form was the same as the one Cruz had found in the monkeys on which the Triatomas had fed. Chagas in 1909 described the trypanosome and called it Trypanosoma cruzi. Since that time, over three decades ago, the disease has been found to occur in practically all of the Central and South American countries and Mexico.

At the present time there is some confusion regarding the nomenclature of this parasite, and as noted above it was orig-

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inantly named *Trypanosoma cruzi* (Chagas, 1909). Chagas later discovered what he thought to be stages of schizogony of this flagellate in the lungs of the mammalian host and renamed it *Schizotrypanum cruzi*. It was finally demonstrated that these stages belonged to a different organism, *Pneumocystis carinii* and Chagas (1911) reverted to the original name *T. cruzi*. The two generic names are used indiscriminately in the literature and it should be pointed out here that *T. cruzi* is the valid one and *S. cruzi* is its synonym.

**GEOGRAPHIC DISTRIBUTION AND PREVALENCE**

American trypanosomiasis is common in the states of Minas Geraes, Goyaz and Sao Paulo in Brazil. In the past few years, owing principally to the work of Mazza and his associates, the number of cases of this disease which has been observed in Argentina is steadily increasing. It has also been reported from Uruguay, Peru, Ecuador, Venezuela, Colombia, Panama, Costa Rica, El Salvador, Guatemala and Mexico. In some of the countries where human infections have not yet been discovered, the presence of infected animals and insect vectors has been established. As a matter of fact, the various insect vectors have a much wider distribution, occurring in the western hemisphere from Argentina in South America to California, Texas, Arizona and Utah in the United States.

Since the discovery of *Trypanosoma cruzi* in 1909, there has been a steady increase in the number of cases reported as well as a widening of its geographical distribution; in view of the wide distribution of the insect vectors this is not a surprising fact. Whether this increase is due to an actual spread of the disease, however, or merely to a more ready recognition of the same, is difficult to say. The number of human beings who have been found to be actually infected with the parasite is still remarkably small. The only localities from which any considerable number of cases have been reported are the State of Minas Geraes in Brazil, certain regions in Argentina and in Panama. In Argentina at the present time some 500 cases have been observed by Mazza and his associates, while in Panama some seventy cases have been diagnosed. Outside of these countries only scattered cases have been
reported. In Peru two cases have been recorded, one by Escomel (1919) and the other by Noguchi (1924). Tejera in 1919 described several cases from Venezuela and since then a number of others have been reported. Crespo discovered a few cases in Ecuador (1940) and his findings have been confirmed by the writer, who had the opportunity of examining material from these cases. In Guatemala three cases were described by Reichenow (1934), and Brumpt and Mazzoti (1939) reported the first two cases from Mexico. No human cases have been reported from the United States, although infected insect vectors occur quite commonly throughout certain areas of California and Texas. Packchanian (1939) found 92 of 100 specimens of Triatoma gerstaeckeri, collected in Texas, infected with T. cruzi.

ETIOLOGY

_Trypanosoma cruzi_ is a protozoan parasite that inhabits the blood and tissues of man and lower animals. It seems probable that it is not ordinarily a parasite of man but of lower animals and that the economic and social levels of certain individuals or groups of individuals provide the insect vector with the conditions and opportunity of passing the infection to man. The disease is found mainly in rural groups and is practically never seen in individuals who live in urban areas.

The parasite itself is a short, somewhat curved organism with a pointed posterior end. It has an average length, including the flagellum, of about 20 microns. It has the typical trypanosome morphology, possessing a centrally placed nucleus, a relatively large ovoid or egg-shaped kinetoplast which is situated near the posterior end of the organism, and an undulating membrane which is narrow and only slightly convoluted. There is a free flagellum which represents about one third of the total body's length. The trypanosome form is the only one which is seen in the blood stream and when observed in fresh cover-slip preparation it is actively motile, darting in and out among the cellular elements of the blood. The curved appearance of the short broad body, the large ovoid kinetoplast and the relatively straight undulating membrane gives this stage of _T. cruzi_ a characteristic appearance. Dividing forms do not occur, as a rule, in the blood and
this is a feature which is of some importance in its differentiation from other trypanosomes which occur in man.

When the parasite invades the tissue cells of its host it changes from the trypanosome form, losing its flagellum and undulating membrane, and assumes the leishmania form. In this stage, by repeated binary fission the leishmania forms eventually fill and finally rupture the cell. These organisms when liberated either invade other cells in the surrounding tissue and repeat the developmental cycle, or are engulfed by macrophages and are destroyed.

Although the most common developmental form of the parasite which is usually seen in the intracellular position is the leishmania form, the leptomonad, crithidial and trypanosome form also occur. It is generally supposed, although not proved, that the parasite can be in any of these developmental stages at the time invasion of new cells occurs.

TRANSMISSION

Species of cone-nosed bugs or kissing bugs (Hemiptera; Triatomidae) are the important vectors. At least thirty-five species of six genera have been reported as naturally infected or capable of infection in the laboratory (Wood and Wood, 1941; Lent, 1939), and it is probable that the majority of hematophagous species of this family are susceptible of infection. Bedbugs (Cimex) of several species and several species of Ornithodorus ticks have been shown to be capable of harboring the trypanosomes, the latter as long as five years (Brumpt, 1927) but they are not considered important as vectors in nature.

The extrinsic incubation period in the vector is generally from eight to twenty days, but may be longer, after which the bug may remain infective for as long as twenty months, or probably throughout life. Infection of the vertebrate host occurs by means of the feces of the vector, which contain the metacyclic infective stages of the trypanosome, often in enormous numbers. This material, if it falls upon the feeding puncture made by the bug, or is rubbed into abrasions in the skin, or into the eyes, may cause infection. The infective stages are also believed capable of passing through the unbroken skin.
Although many species of Triatomids are capable of acting as vectors to man, only those species which habitually invade houses are of much importance epidemiologically. In Argentina, *Triatoma infestans* appears to be the commonest house-haunting species, while in Brazil its place is largely taken by *Panstrongylus megistus*. In Venezuela, *Rhodnius prolixus* and *Panstrongylus geniculatus* are perhaps the most important vectors, whereas in Panama *Rhodnius pallescens*, *Triatoma dimidiata* and *Panstrongylus geniculatus* are the common species. Mazzotti (1940) has recorded nine species as found naturally infected in Mexico, one or another of which is dominant in different localities. In the United States Wood (1941) has summarized the information available, and lists five species of *Triatoma* as having been found naturally infected with *Trypanosoma cruzi*. No human cases have as yet appeared in the United States, perhaps due to the low rate of infection, 1.3 per cent, in the only species (*T. rubida*) which is at all commonly found associated with man (Wood, *loc. cit.*).

The natural hosts of most species of these bugs are probably small mammals, in whose burrows and nests many species have been found. When found in human habitations, they hide during the day in cracks in the walls, floors and furniture, much as does the common bedbug, coming out to feed at night. The immature insects are wingless, but the adults of most species fly actively, and at times are attracted to lights.

The actual method of the transmission of *T. cruzi* has been hotly disputed. Chagas (1927) contended that transmission occurred as a result of the bite of the insect vector, while others, particularly Brumpt (1927), believed that infection occurred as a result of the contamination of the mucous membrane or of the wound of the bite by the infective fecal material deposited during the act of feeding.

Recently Dias (1934) has published the results of a very carefully controlled series of experiments; he found that in all instances in which contamination of the skin by the fecal material from the bugs could be ruled out, no infection occurred. On the other hand, when contamination was permitted to take place infection nearly always resulted.
The essential lesion produced by *Trypanosoma cruzi* is a parenchymatous degeneration of the affected tissue with a concomitant inflammatory reaction of the interstitial structures. The lesion is initiated by invasion and subsequent rupture of the tissue cells by the parasite, and the reparative process consists merely in fibrosis of the damaged areas.

*Trypanosoma cruzi* has been seen in almost every organ and tissue of the body but the outstanding lesions are always found in the heart and brain, and in the fatal cases so far described in the literature, death has been the result of irreparable damage to one or the other of these organs. Goiter is very common in the area of Brazil where Chagas discovered the first cases of American trypanosomiasis, and he and his colleagues believed that *T. cruzi* was responsible for this condition. They described it as parasite thyroiditis. It has, however, been definitely established that there is no relationship between *T. cruzi* infections and goiter and that Chagas was actually dealing with endemic goiter with a superimposed trypanosomal infection.

As mentioned above, the principal and most extensive pathologic changes are found in the heart. This organ is usually enlarged and frequently shows a yellowish mottling of the myocardium. The pericardial sac contains an excess of fluid, in some cases as much as 400 cc. (Lundeberg, 1938). Microscopically, one sees an extensive parenchymatous myocarditis with a concomitant infiltration of the interstitial tissues by lymphocytes, plasmocytes and macrophages. The muscle fibers are thin and stringy and widely separated from one another. Some of the cardiac cells show a loss of striations and an increased affinity for eosin stain, appearing more or less like the cardiac cells undergoing degeneration in such toxic infections as diphtheria. As long as the cells containing the parasites remain intact there is no cellular reaction around them. The rupture of the cell with the liberation of the parasites and accompanying toxic products, however, calls forth an intense inflammatory reaction. The epicardium and endocardium may likewise be involved and show in places nests of parasites and inflammatory reaction.
The brain when involved is edematous and congested. The edema of the meninges may be so pronounced that this membrane has the appearance of a gelatinous cap covering the brain (Johnson and De Rivas, 1936). Examination of the fluid which is usually present will often show the presence of motile trypanosomes. Sections from all parts of the brain show congestion and a moderate amount of perivascular round cell infiltration. The most prominent lesion is a focal inflammation which is easily seen with low power magnification. These lesions consist of collections of mesoglia cells mixed with mononuclear cells. In many instances necrosis of these areas is present. These foci have no relation to the blood vessels and have been found in all parts of the brain. The parasites are found in these inflammatory areas or lying free among the nerve fibers, in mesoglia cells and astrocytes.

The liver is usually enlarged and histological examination shows parenchymatous degeneration and fatty changes. Parasites are not commonly found in this organ. The spleen, also, is very frequently enlarged to some extent, but parasites are practically never seen in this tissue.

Pathological changes in the lymph glands have been described and consist of enlargement and congestion, with lymphoid hyperplasia, mononuclear cell production and phagocytosis.

Parasites have been found in the thyroid, suprarenals, ovaries, testicles and prostate. Their occurrence in these locations is by no means a regular finding and their presence is usually not associated with any extensive damage.

The type and the extent of the lesions which occur in the nonfatal and chronic cases are not well known. Recently Mazza and others (1934, 1935 and 1939) have shown that in such cases the myocardial lesions are focal rather than diffuse, with accompanying hyperplasias of connective tissue and fibrosis. Parasites were usually not found. This is in agreement with the observations of Johnson (1938) on experimental infections in dogs, who found that the lesions present were of the focal inflammatory type, composed of the usual collection of round cells and cellular debris. Scattered throughout the myocardium of the animals there were small scarred areas representing healed focal inflammatory lesions. Parasites were
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not found even after long searches. Ev. Chagas (1935) states that in the hearts of patients with chronic cardiac involvement there is hyperplasia of connective tissue and fibrosis with parenchymatous degeneration. The parasites tend to migrate to neighboring regions, so that next to fibrotic areas acute lesions characterized by an inflammatory cellular exudate with degenerating muscle fibers may be found.

Diagnosis

A definite diagnosis of American trypanosomiasis cannot be made except by the demonstration of Trypanosoma cruzi or upon obtaining satisfactory evidence of its presence. In the acute stage of the disease the etiological agent can, as a rule, be found by direct microscopic examination of the blood or by inoculation of suspected blood into susceptible animals. However, after the acute febrile period is passed and the parasites are confined to the tissues it is often very difficult to demonstrate their presence and one usually has to rely upon the complement fixation reaction for diagnosis.

A method of demonstrating the presence of T. cruzi in the peripheral blood when the usual thick film and animal inoculation methods fail is that to which Brumpt (1914) gave the name xenodiagnosis. This consists in allowing known clean insect vectors to feed on the patient with the suspected disease and examining the bugs for developmental phases of the parasite after a suitable incubation period. A source of vectors known to be uninfected is of course essential, necessitating the maintenance of a laboratory colony. Dias (1936) is of the opinion that this method is of great diagnostic value, but it is time-consuming and a diagnosis cannot be made in less than six to twenty days, the time usually given as required for the developmental cycle in the bugs.

The most efficient and accurate method for the diagnosis of this infection, when blood smears and animal inoculation give negative results, is the complement fixation reaction. Guerreiro and Machado (1913) introduced this test, using an antigen prepared from tissues, heart and spleen, of heavily infected animals. While this test appeared to constitute a distinct advantage over the older methods, considerable difficulty was experienced in the preparation of a uniformly satisfactory
antigen. Kelser (1936) described a modification of the original test and showed that a satisfactory antigen could be easily prepared from cultures of *T. cruzi* and that it was apparently trustworthy in identifying the disease in man. In a survey of over 1200 individuals in Panama, Johnson and Kelser (1937) found the test a valuable and dependable one in the detection of infection of the human host with the parasite. More recently Romaña and Dias (1942) have reported a further modification of the test consisting in the use of an alcoholic antigen prepared from the cultural forms, instead of the glycerine saline antigen of Kelser. As this alcoholic antigen can be preserved for much longer periods, it is considered a more practical one for common use than the glycerine saline antigen of Kelser. Briefly, the antigen is prepared as follows: The organisms obtained from culture are washed three times with normal saline and mixed with pure acetone (ten times the volume of parasites) and left to stand for twenty-four hours with frequent shaking; the acetone is then removed by centrifugation and the parasite mass dried at 37° C. The stock antigen is made by extracting 1 gm. of these dried parasites in 1 cc. of absolute alcohol at a temperature of 37° C for twenty days; for use the alcoholic extract is further diluted with normal saline solution.

**SYMPTOMATOLOGY**

American trypanosomiasis has been reported as presenting many clinical manifestations, and Chagas (1916) and others have endeavored to group cases according to principal symptoms. Considerable doubt, however, has been raised as to whether many of the symptoms which have been noted are in any way the result of infection with *Trypanosoma cruzi*. It is now generally conceded that cardiac disturbances, fever, edema, adenitis, anemia and nervous symptoms may occur singly or in combination in the acute and chronic forms and that such manifestations as goiter, cretinism and paralysis have no connection except as superimposed pathological conditions. In children, particularly very young children and infants, the disease is a serious one and very often terminates fatally. In older children and adults the infection is much less severe
and milder symptoms are exhibited, with recovery the rule. Many individuals in whose blood trypanosomes have been found never exhibit signs of the disease or give any history of illness. This has been true of the great majority of cases seen in Panama (Johnson and Kelser, 1937).

The acute disease is usually seen in infants and young children and commences as a rule with febrile disturbances. Swelling of the face and extremities may occur but usually subsides when the temperature returns to normal. A very common early manifestation, which has been designated as Romaña's sign, is unilateral ophthalmia, characterized by swelling of the lids and conjunctiva of one eye. This is usually sudden in onset. There is painless edema and a reddish-violet discoloration of the lids with hyperemia and edema of the conjunctiva. The cornea is not affected and conjunctival secretion is scanty. The swelling is slow to subside and is almost always associated with fever. Adenitis may or may not be present. The pre-auricular, submaxillary and cervical glands are most frequently involved, usually as a result of the ophthalmia.

Cardiac symptoms resulting from the invasion of the myocardium by the trypanosomes are indefinite and variable. The heart is usually enlarged and alterations in rhythm are, as a rule, not pronounced. Arrhythmias when encountered are usually seen in those cases which terminate fatally. The principal properties of the cardiac muscle which are usually affected are those of excitability and conductibility as evidenced by the occurrence of extrasystoles and varying degrees of heart block. The extrasystoles are usually ventricular in origin.

Enlargement of the liver occurs and the degree of enlargement is dependent upon the degree of myocardial involvement and circulatory disturbance.

In acute cases which terminate fatally, progressively severe dypsnea, vomiting and anuria have been reported (De Coursey, 1935).

Patients who survive the acute stage usually become symptom-free and remain so. Chagas, Mazza and others feel that spontaneous cure does not occur and that those who survive the acute stage pass on into a so-called chronic stage, the
symptoms of which are due to the multiplication of the parasite in the internal organs. Yorke (1937) states that, “there is fairly clear evidence that myocardial degeneration and subsequent heart failure is a very common cause of death in many places in South America where infected bugs and cases of human infection with *Trypanosoma cruzi* are known to occur. The evidence that the myocardial degeneration is to be associated with previous or actual infection with *T. cruzi* is, however, by no means satisfactory.”

The extent of the damage to the heart musculature or other organs in nonfatal cases is not definitely known and the pathology which exists in the so-called chronic cases is equally obscure. There is good reason to suppose, based on recent postmortem observations and experimental studies on animals, that American trypanosomiasis may be responsible for a good deal of the chronic heart disease which is fairly common in Brazil, Argentina and elsewhere and the cause of many sudden deaths.

**PREVENTION AND TREATMENT**

**Prevention.**—It has been mentioned in a previous section that *Trypanosoma cruzi* is normally a parasite of lower animals, particularly armadillos, oppossums and rodents in whose nests and burrows the insect vector is commonly found. The human infection occurs almost entirely in rural areas where insect vector, animal host and the individual are in close proximity. The type of dwellings which are used in these areas—cane and adobe huts with thatched roofs—affords the vectors ideal hiding places, and where once established they are exceedingly difficult to eradicate. Thus prevention and control depend on the destruction of animal hosts and eradication of the insect vector. In cases where control of the vectors is difficult the use of mosquito nets at night will afford some protection.

**Treatment.**—There is no specific treatment for this disease. The drugs which are commonly used in other forms of trypanosomiasis are of no value in American trypanosomiasis. Recently Mazza (1940) has reported that a preparation (Bayer 7602) seems to have specific therapeutic properties, but this has not been confirmed.
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