RÉSUMÉ OF THE ETIOLOGY AND CLINICAL ASPECTS OF AMERICAN TRYPANOSOMIASIS

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I

DISCOVERY OF THE DISEASE

In regions of the interior of Brazil where we were carrying on an antimalarial campaign we found a large *hemiptero,* commonly called "barbeiro," which infested all the houses of the region and attacked man at night after the lights were extinguished.

As we were dealing with a blood sucker and as we knew the important rôle of such insects in human pathology as transmitters of disease, we examined samples of the *hemiptero* and found a flagellate in the hind gut with the morphology of *crithidia,* which might be an exclusive parasite of the insect or might be a stage in the life cycle of a flagellate of vertebrates.

We collected various samples of the hematophage and sent them to Oswaldo Cruz in Manguinhos that they might there be fed on monkeys in order to verify the hypothesis of transmission to vertebrates of the parasite found. This verification could not be made in the zone where we were working because all the monkeys there (*callithrix pennicilata*) were naturally infected by another species of trypanosome described by me (*trypanosoma minasense*). In the blood of the monkey (*callithrix pennicilata*) that fed the hematophages we found the presence of a trypanosome with very characteristic morphology and called by me *trypanosoma cruzi* in honor of my great master, Oswaldo Cruz.

In subsequent studies we proved that the parasite found in the blood of the little monkey was transmitted to other laboratory animals by the bite of the insect, and we concluded with certainty that we were dealing with a new species of trypanosome, whose intermediate host was a *hemiptero*

heteroptero, of the family *Reduviidae*, of the genus *triatoma*, species *megista*. It remained to find out what was the habitual vertebrate host of the parasite, whether it be a wild or domestic animal or man himself. In the investigations to elucidate this last point we were oriented by two essential points of view: first, by the exclusive domiciliary habitat of the insect, it being found only in human residences and never in the outer world; and secondly by the observation of a large number of patients in the zones infested by the "barbeiro" who presented unusual symptoms that did not permit us to identify the disease with any of those known in the nosologic picture. And, furthermore, we always found in such patients some aspects, such as generalized glandular enlargement, edema and ocular affections, that recalled the usual symptomatology of the trypanosomiases. Being thus oriented we directed our investigations toward the houses of the region, all of which were heavily infested by the insect, and sought to find the parasite in man and also in the domestic animals that live in the houses at night. The first positive finding was accomplished in the blood of a cat that showed the trypanosome in great numbers. The first observations of the blood of chronic patients were negative for reasons that we shall see later; and we were already despairing of getting a positive finding when we had the opportunity of examining a feverish child that presented a swollen face, generalized glandular enlargement, splenomegaly, etc. By fresh examination of the blood of this little patient we there found the presence of the trypanosome that was identified as the species transmitted to the little monkey by the bite of the *triatoma megista*. There was thus proven a new disease, the exact pathogenesis and clinical features of which have been elucidated in later work.

II

HABITS OF THE TRANSMITTING HEMATOPHAGE

We will here relate the most important points of the biology and habits of the transmitting hematophage which are related to the epidemiology of the disease.

4

In the human residences the triatome hides itself in the cracks of the walls where it reproduces intensively and goes out at night to feed on man and the domestic animals. In its function of sucking blood, in the rapidity with which it escapes persecution, in its instinct for self-preservation which leads it to await darkness before leaving its hiding places, in the immense infestation of the houses, and also in the difficulty of eliminating it from the contaminated houses, the "barbeiro" very closely approaches the common bedbug.

The great foci of the insect are formed by the houses of primitive construction whose walls and roof furnish propitious shelter for the hematophage. It is the small cottages or huts of the country, roofed with grass and with imperfect walls, that are the most heavily infested. In the rural cities the well-constructed houses are sheltered from contamination; but the hematophage is always found in abundance in the poor houses that are always situated on the outskirts of these cities. In the infested rural zones all the houses are contaminated by the insect, and this determines the high endemic index of the disease. We can state that not one of the rural habitations escapes infestation in the regions where the "barbeiro" exists. And as on the other hand the great majority of the insects found in the human residences are parasitized, one thus has an idea of the high coefficient of human infection.

The hematophage presents four phases in its evolution: egg, larva, nymph and adult insect. It is certain that the infection can be accomplished by any of the three stages, larva, nymph or winged insect; the adult insect, however, plays a preponderating rôle in the epidemiology as it is always infected and as it takes short flights, from the wall to the bed which is placed at a distance from the wall or even from one house to another. When a house is abandoned, as frequently happens, the adult insects always migrate to the neighbouring houses, being taken there by the necessity of food. It is a belief among the natives of the interior of the country that the "barbeiro" is a wild insect that invades the houses at night, being attracted by the light. We carried on prolonged investi-

5

gations in this direction and arrived at the certain conclusion that the "barbeiro" is really exclusively a domiciliary hematophage and is never found in the outer world. The easy feeding in the interior of the houses has determined in the course of time a definite adaptation of the hematophage to domiciliary habits, thus making it a harmful companion for man in his home.

The total evolution of the *triatoma megista* from egg to adult insect lasts approximately 260 days, and the winged insect, when regularly fed, lives many months. Now, knowing that the transmission of the parasite takes place during the three phases, larva, nymph and adult, and also knowing that the contaminating property when once acquired is preserved indefinitely by the insect, the epidemiologic importance of a single triatome becomes very evident.

The *triatoma megista* is the most common species in the interior of Brazil and it was with this that we carried out all of our investigations. We consider it as the most important transmitter of the trypanosome. Aside from this, however, two other species of triatomes are frequent in Brazil, being found simultaneously with the *megista;* they are the *triatoma sordida* and *triatoma infestans*, which also transmit the parasite. The *triatoma infestans* is found almost exclusively in other countries of South America, principally in Argentina, Uruguay, Peru, and Ecuador, being known in these countries under the name of "vinchuca."

III

TRYPANOSOMA CRUZI

Trypanosoma cruzi, the etiologic agent of the new disease, presents well-marked morphology and specific biologic conditions that sharply differentiate it from all the species of the same genus. The most notable morphologic characteristic of this trypanosome consists of the large dimensions of its blepharoplast, which is situated in the posterior extremity of the parasite. As an appreciable morphologic condition it also

presents an evident dimorphism by which is expressed the duality of sexes. In the peripheral blood are seen two forms of the parasite, one of them being threadlike, rich in chromatin, with rapid movements, and with nucleus in the form of a rod (with the grosser stains and fixed after drying), and the other being broader, with ovoid nucleus and slower movements. The first form represents the male organism and the other the female, this interpretation being confirmed by the evolution of the parasite in the organism of the transmitting insect.

In the biology of this trypanosome, we must mention as being abolutely peculiar to the species a phase of exclusive localization in the tissues, or better, even within the anatomic elements. In fact, in man in the first phases of the disease, during from twenty to thirty days, and while there is a febrile reaction, the trypanosome is found with great ease in the peripheral blood; when this period is passed and when the acute signs of infection cease, the most prolonged microscopic searches do not show the parasite, which can only be found at the autopsy within the tissues. Thus then the *trypanosoma cruzi* shows two distinct aspects in the human organism; in one of them the parasite is seen in the circulating blood in the form of a flagellate, and in the other it is found in the tissues in the form of a rounded body furnished with nucleus and blepharoplast, usually without flagellum. The first aspect is to be found in the acute cases of the disease in the first days of the infection, while the acute symptoms, especially the fever, last; the second aspect is observed in the chronic forms in any clinical form of the disease.

How are these two aspects of the parasite in the human organism to be interpreted? We believe that when a certain time of infection has passed the presence of antibodies in the blood prevents the parasite remaining there, and that it goes into the tissues where it multiplies actively and where it dispenses with its flagellar apparatus in virtue of its static condition. Only this relative blood immunity can explain the complete absence of the parasite from the circulating blood in the chronic forms. In laboratory animals the same aspects of the

parasite are found, flagellated in the blood and in the form of rounded, aflagellate bodies in the tissues; here, however, certainly on account of the less resistance of the smaller animals, the parasites are found in greater number and for a longer time in the circulation. It is well to emphasize that in man as well as in animals, from the first days of the infection and while the parasites are still abundant in the blood, we can also find them in the tissues in the static condition referred to; and this fact indicates the essential biologic condition of this parasite, the predilection of which for the tissues justifies us in considering it a histoparasite rather than a blood parasite.

The principal seats of localization of the *trypanosoma cruzi* in the tissues are the cardiac muscle, the central nervous system and the striated muscular system. In the heart the protozoon is found within the cell proper in the form of large parasitic agglomerations. In this case the cellular substance is sometimes totally destroyed and only the membrane and the nucleus are spared, the nucleus being adherent at a point on the inner side of the membrane. Thus many cells of the myocardium are transformed into true parasitic cysts which are found in all parts of the organ, and it is not rare that the continuity of neighbouring cysts by the destruction of the Weissmann segments can be seen. As a result of this localization of the parasite there are seen intense phenomena of inflammatory reaction of the myocardium, an acute or chronic myocarditis being a constant lesion in the disease. This notable localization of the protozoon, in which the parasitic agent hides itself in the interior of the proper functional element of the organ, causing its destruction, is reflected, as we shall see, in the clinical expression of the disease, and expresses one of its most interesting chapters.

In the central nervous system the parasite is found in agglomerations in all zones of the neuraxis, in the cerebral cortex, the protuberance, the cerebellum, the central white matter, in the gray nuclei, in the bulb and in the spinal cord. The neuroglia cell, in the interior of which the protozoon multiplies in the rounded form, constitutes the initial seat of localization in this

organic system. In whatever zone of the brain or spinal cord it localizes, the parasite determines numerous foci of leucocytic infiltration, forms of the protozoon being found in the recent foci and disappearing from the old ones.

The striated muscle constitutes another constant seat of the parasite, it being localized in the interior of the striated fiber itself, at times occupying its whole extent and destroying the sarcolemma.

Aside from the organic systems referred to, which are almost constantly parasitized, the protozoon has been found in the testicles, suprarenals, liver, spleen, thyroid gland, and also in other organs, in man as well as in laboratory animals.

It must be emphasized that, contrary to what happens with other species of the same genus, the *trypanosoma cruzi* never presents binary fission in the peripheral blood. The numeric increase of this parasite in the organism of the vertebrate is accomplished by multiplication of the aflagellate bodies within the tissues, bodies in which is seen the formation of the locomotor apparatus, the parasites, now flagellated, passing into the circulation. And when a condition of relative immunity does not exist in the blood, the flagellates there progressively increase in number, as happens in man in the acute phase of the disease; however, in the chronic forms, because the blood becomes unfavorable to their life, they are soon destroyed.

A result of this localization of the *trypanosoma cruzi* within the tissues is the great difficulty in the parasitologic diagnosis in the chronic forms of the disease. In these cases protracted search of the blood, including cultivation and inoculation into susceptible animals, never succeeds in revealing the presence of the parasite, which only the autopsy demonstrates. On this point we possess a large number of observations of patients of the chronic form, in whom we never succeeded in showing the parasite during life, while the autopsy showed it in its usual localizations in the tissues.

THE PROTOZOON IN THE ORGANISM OF THE
TRANSMITTING INSECT

The great majority of *triatoma megista* collected in the human residences are infected by *trypanosoma cruzi*. In them the parasite is observed in large number in the hind gut and is also found in the feces naturally passed by the insect. In the intestine of the triatome the crithidial forms of the protozoon predominate, in which the blepharoplast is found in front of the principal nucleus in relation to the free flagellum; however, typical trypanosomes with a blepharoplast behind the principal nucleus are also observed here, and these show a plasm narrower than the forms of the peripheral blood of the vertebrates.

The finding of the parasite in the salivary glands of the insect offers great difficulty and has only been successfully accomplished in rare cases. Here among the glandular elements are found the elements inoculated by the bite of the insect.

When we feed on parasitized animals triatomes reared in the laboratory and free from infection, we can follow all the changes undergone by the parasite in the digestive tube of the transmitter. In the impossibility of describing here with all the details the cytologic phenomena of this evolution, I shall limit myself to referring to them in general outlines. In the mid gut of the insect the trypanosome undergoes its first changes, the blepharoplast approaching the principal nucleus with which it fuses, the parasite losing its flagellum and undulating membrane and becoming rounded. In the forms that are thus changed there are seen successive processes of binary or multiple division, and there result from them the crithidia forms which do not remain in the mid gut of the insect but pass to the hind gut with the digested blood. From the hind gut the parasites probably pass to the general cavity of the insect and localize themselves in the salivary glands. It has not yet been possible to find the parasite in the general cavity of the triatome nor to verify with certainty the last changes undergone by it in the

hind gut before reaching the general cavity and the salivary glands. These changes that have been referred to are always found when the hematophage is fed on animals with flagellated forms in the peripheral blood; aside from these, however, another developmental phenomenon has been discovered by me in the mid gut of the insect and doubtless represents the first phase of the sexual cycle of the trypanosome. In insects that had fed several hours before on infected animals in which the two forms of the parasite were appreciable in the peripheral blood, we found appearances that we interpret as the fecundation of the protozoon. One of the forms of the trypanosome, the broader, becomes rounded and there becomes adherent to it the thin form which I consider as the male organism, the nucleus of which penetrates posteriorly into the plasma of the broad form, fusing with its nucleus. The adhesion of the thin form to the broad form is accomplished by the flagellar extremity, and the fusion of the two forms occurs a few hours after the insect has ingested the blood. We have all reasons for affirming that this is a phenomenon of fecundation, for in another flagellate, the *prowazekia cruzi*, we found a phenomenon absolutely comparable with this.

Thus then we may admit that the trypanosome in the organism of the triatome presents two distinct developmental forms: in one of them there occurs the simple multiplication of the flagellate, comparable to what occurs in artificial culture media, and the final form of which is the crithidia of the hind gut of the insect. The other developmental form is initiated by the fecundation between the two forms of the parasite in the mid gut of the hematophage and after a change which is not yet determined this evolution terminates in the organisms with the morphology of trypanosomes observed in the salivary glands of the insect. It is in this way that we today look at the evolution of the trypanosome in the organism of the *triatoma megista*, however, we are still carrying on some investigations on the subject which may elucidate some of the points that are still obscure.

CLINICAL ASPECT OF TRYPANOSOMIASIS

American trypanosomiasis is observed under two essential aspects: an acute infection and a chronic one. In the acute infection there are included the cases in the first phase of the disease when they present the initial symptomatology, in which the febrile reaction predominates. This condition of the disease is principally characterized by the presence of flagellates in the peripheral blood. The chronic infection includes the infected ones who have escaped death in the first phase of the disease and in whom there are observed clinical syndromes, predominating on the side of certain apparatus or organic systems, according to the localizations of the parasite and to the lesions occasioned by them.

Let us treat of the acute infection in general outline. This is observed almost always in children during their first months or, at most, within the first years of existence. The reason why the acute infections occur almost exclusively in infants is perfectly understood from the domiciliary condition of the disease and by the high infecting index of the hematophages in the human residences.

The child as soon as born becomes subject to the bites of the triatome and consequently to inoculation with the parasite; for this reason it becomes quickly infected. Does hereditary transmission of the parasite occur? As yet we are not in a position to give a definite solution to this point, which is of great importance in the epidemiology of the disease; we believe, however, that the transmission of the disease by intrauterine contagion often occurs, in spite of the fact that we have not yet succeeded in obtaining unquestionable evidence of it. We think thus because otherwise many facts of common observation would be inexplicable, in which individuals present evident symptoms of the disease without having recognized any former acute attacks. Aside from the fact that trypanosomiasis in its pathogenesis presents an appreciable similarity to syphilis, it is not to be wondered at that in this point they also bear resemblances.

The duration of the course of the acute cases has varied in our observations between ten and thirty days. One of two events may then occur: either these cases terminate in death within a few days or they pass to the chronic form, with a course which is sometimes long, so that the infected individual may reach an advanced age, although with appreciable anomalies in some parts of his organic system.

In the acute form there is always a complex of pathognomonic symptoms that are absolutely constant and not confusable with other disease. The general symptomatology of these cases is the following: continuous fever persisting while flagellates exist in the peripheral blood, reaching a temperature in the more serious cases of 40°, with slight morning remissions; spleen and liver always enlarged in volume, general glandular enlargement, the glands of the neck being appreciable in large numbers and those of all the peripheral plexuses being enlarged. Finally, as a more characteristic sign we must refer to the swollen face, so that the patient appears bloated; and so peculiar to trypanosomiasis is this appearance that it constitutes one of the most certain symptoms for the diagnosis of the acute forms, raising the suspicion as to the nature of the infection even at a distance. This last sign, on which we must insist, is one of the most peculiar in trypanosomiasis; some days after the appearance of the febrile reaction and after the child presents itself as a patient, the parents note the appearance of this tumefaction, which is most marked in the face and other regions of the body, this as a rule being the sign of disease that attracts most attention and leads them to seek the physician.

By clinical investigation it is easy to prove that this is not a case of renal edema but rather one of myxedematous infiltration, of generalized myxedema, and this is confirmed by the histologic examination of the subcutaneous cellular tissue in which the reactions of mucin are appreciable. Thus in the acute forms of trypanosomiasis one of the elements of myxedema is observed with extreme frequence, this being a fact which indicates a functional alteration of the thyroid gland in this initial phase of the infection. And the autopsies in cases of this

nature, by showing the presence of the parasite and histo-pathologic processes in this gland, give a foundation for this symptom and make evident the attack of the parasite on the thyroid gland.

From the point of view of prognosis the cases of acute infection are divided into two groups: in one of them there are symptoms pointing to involvement of the nervous system and the patients present appreciable signs of acute meningitis; and in the other such signs are not observed. In the first group of clinical cases the gravity is much greater and termination by death within a short time is the rule; and at autopsy marked lesions are found in the brain and meninges with localization of the parasite in the brain substance. The anatomo-pathologic signs are those of an acute meningo-encephalitis and the parasitic foci may be observed in any part of the brain. In these clinical cases the greater abundance of the parasites in the peripheral blood should also be noted. On the other hand, in the acute cases without meningo-encephalic symptoms death is rarely observed, the patients usually passing to the chronic state.

Let us proceed to consider the principal aspects of the chronic infection. The predominance of some syndromes on account of the localization of the parasite in certain organs justifies us in admitting some principal clinical forms in the chronic infection; but we must state that between these forms there are no sharp limits, because in all there are some symptoms which are constantly present and constitute the essential characteristic of the disease. In some cases, however, the symptomatology is more accentuated in reference to certain organic systems and this gives a basis for the systematization of the disease into some clinical groups in which there predominate certain functional changes. We shall study the principal of these clinical aspects in a general way, it not being possible here to enter into minute descriptions.

CARDIAC FORM OF THE DISEASE

Among the most notable facts in the pathology of this disease are the localizations of the parasite in the cardiac

14

muscle of man and laboratory animals, within the proper fiber of the myocardium. This being so, it can be understood that in the clinical expression of trypanosomiasis cardiac symptoms at times figure in a predominating way. The heart changes in this disease form one of its most curious aspects, and in them we find a great mass of facts that are of value in elucidating the points that are still obscure in cardiac pathology. This is true because, by the side of the functional change which is appreciable by clinical methods, it is not difficult to verify the etiology and pathogenesis which are represented by the parasite in the myocardial cell and by the lesions determined by it in the whole muscle.

From the beginning of our clinical studies of the disease, our attention was attracted by the cardiac arhythmia in young individuals without any sign of generalized sclerosis, and without symptoms of any inflammatory process in the kidneys. And the cases of this nature that came under our observation in a relatively short space of time and in a diffuse population were numerous. Certainly outside of the epidemiologic conditions of the regions in which we were studying, alterations of cardiac rhythm were never observed in so high a number in young people. In such patients there are always found other symptoms of infection; here, however, the changes in the circulatory apparatus predominate.

The first autopsies of the disease soon explained this fact of constant observation by demonstrating the parasite in the myocardium and the lesions there caused by it in acute and chronic cases of trypanosomiasis. And in laboratory animals numerous experiments also indicated the predilection of the parasite for the cardiac fiber. Those properties of the cardiac muscle fiber that become principally affected are those of excitability and conductibility, according to numerous observations that we now have.

The alterations of excitability include extrasystoles which occur here with extreme frequency and under the most variable forms. There are seen very characteristic extrasystoles of auricular origin and others of ventricular origin. From the

15

point of view of frequence of the extrasystole there are also seen the most varied appearances, as they occur either infrequently interspersed between the normal systoles, or repeated in each cardiac cycle, giving to the pulse the classic aspect of bigeminism. And many other aspects are here observed in which all the variations of cardiac rhythm may be characterized.

It is worthy of note that these alterations of rhythm are observed at any age, even in children of six and eight years; and it should also be noted that, in spite of the abundance of parasites in the myocardium in the acute cases, in these there do not occur alterations of rhythm but rather a great insufficiency of the organ. We believe that such alterations depend upon processes of diffuse myocarditis with interstitial sclerosis of the organ, an anatomic condition which is still absent in the early stages of the disease and only found in the chronic forms.

Next to the arhythmia from extrasystoles attributable to disturbance of excitability come in order of frequency the alterations in the conductibility of the myocardium. Here are observed all grades of disturbances of the function, from its initial decline to complete elimination in which the ventricular rhythm is independent of the rhythm of the auricle. In the initial depressions of the function it is curious to note the cases in which in the tracings from time to time an auricular systole is not transmitted to the ventricle, thus causing intermittent gaps in the radial pulse. In this way there occur the numerous cases of relatively slow pulse that are observed in the zones of the trypanosomiasis with less than sixty radial pulsations per minute.

When the bundle of His is more attacked, more profoundly disturbing the conductibility of the muscle, there result cases of complete heart block, the true Stokes-Adams' syndrome, in which there are not lacking the concomitant nervous disturbances. The number of patients already observed with this syndrome is very high; and we can state that, in this particular, trypanosomiasis presents a pathologic condition that is peculiar to it, there existing no other disease in which

the slow pulse is observed with so great a frequence. And especially notable here is the observation of heart block even in young individuals of eight to twelve years.

Without doubt, the cardiac form represents one of the most curious clinical aspects of the new disease and also that of the greatest fatality in the chronic forms. Death caused by this diseased condition usually occurs from asystole due to progressive weakening of the heart. The patients then present generalized and progressive edema, visceral congestion and other symptoms that characterize cardiac asystole.

Another mode of death that is of great frequence in the zones infested by trypanosomiasis is sudden death from cardiac syncope. The occurrence of this fact causes wonder in all those regions where we have studied the disease; young individuals in conditions of relative health suddenly die, at times while at work, without any recent symptoms of the disease that could make one foresee this event. The exact mechanism of this death has been the object of prolonged investigations in our studies and it is possible to interpret the accident under two hypotheses: either they are cases of complete heart block, the death occurring in the long pauses in the cardiac pulsations, or we are dealing with a phenomenon of ventricular fibrillation which is still poorly understood in man. Of this last hypothesis we have a curious observation, the report of which cannot be included within the limits of this summary description. Be that as it may, sudden death in trypanosomiasis is of very frequent observation and is associated with the profound changes of the myocardium caused by the localization of the parasite.

NERVOUS FORM

Histopathologic studies carried out in autopsies of individuals who had presented nervous symptoms simultaneously with other symptoms of the disease have shown localizations of the parasites in the central nervous system and lesions caused by them there. From the beginning of our clinical studies we observed numerous cases with organic affections of the nervous system coexisting in individuals with other signs of the disease.

The high coefficient of nervous syndromes in the zones of trypanosomiasis, the cases of paralysis, of aplasia, of idiocy, observed principally in children or individuals of retarded development soon formed one of our greatest clinical surprises, indicating at the same time the high pathogenic importance of the parasite, in case it would be possible to demonstrate it as the etiologic agent of such nervous changes. And we were naturally led to the association of the nervous syndromes with trypanosomiasis by the existence of other clinical signs of trypanosomiasis in the patients referred to, and by the negative result of all investigations attempting to find another etiologic factor; negative Wassermann reaction, absence of physical signs of lues, exact clinical studies—all excluded the interference of the treponema of Schaudinn in such alterations.

The first autopsy on a child that had died with signs of acute meningo-encephalitis gave an anatomic base to our clinical observations and justified the creation of the nervous form of the disease. The principal anatomic characteristic of the localizations of the parasite in the central nervous system and of the lesions there produced is that they are in multiple foci, scattered in different zones of the brain, in the cortex, bulb, etc., and without any relation to the arterial system. This multiplicity of localizations is well expressed by the various forms in which the nervous syndrome presents itself in the clinical cases. Among the motor disturbances the type most frequently occurring is cerebral diplegia, in which as a rule the spasmodic phenomena predominate over the paralytic. However, such diplegias, which are generally consequent upon infections acquired during early life, from the point of view of extension and intensity of the disease present great variations of aspect, from simple bilateral dysbasia expressive of anatomic scars consecutive upon lesions of slight extent up to the forms of generalized rigidity, the true Little's syndrome.

In any of the nervous forms of the disease the historical data usually refer the beginning of the nervous changes to acute attacks, probably of meningo-encephalitis occurring in early life; however, we know of cases of primitive localization of the parasite in the brain, the disease proceeding from its beginning with a silent course without symptoms of an acute meningo-encephalitis.

The intelligence is always affected in the nervous forms of the disease, and intellectual deficiency is here observed from the most complete idiocy to the simple states of retardation, and there is no obligatory relation between the intensity of the motor disturbances and the degree of mental decadence. Many cases classifiable as complete idiocy present slight motor changes expressed simply by exaggeration of the tendon reflexes, dysbasia, etc.; on the contrary there are cases of profound motor disturbances with relative preservation of the intelligence.

Alterations of speech are also not rare, and there are a large number of diplegics who show a total aphasia. While this, on the other hand, is almost always accompanied by motor disturbances, at times it constitutes the most salient manifestation in patients with slight alterations of motility. Generalized or partial convulsions are also frequently observed in the disease and express lesions of the cerebral cortex. They have been observed with any of the clinical aspects of the nervous form of this disease. There are also many times observed the facts of a suprabulbar paralysis, sometimes present in the cases of diplegia amplifying the nervous syndrome, and sometimes constituting isolated paralytic manifestations in individuals with other signs of the disease but with the general motility and the tendon reflexes normal. It is not difficult to understand the existence of these suprabulbar paralyses once we know of the diffusion and multiplicity of the parasitic foci in the neuraxis.

The results of trypanosomiasis on the nervous system having thus been described in a summary way, let us proceed to refer in bare outline to some other aspects of the disease concerning which there still are sustained certain objections, either relative to their association with the infection or as to the method of interpreting their exact pathogenesis.

INFANTILISM

Cases of retarded growth with total arrests of physical development are very frequent in the zones of trypanosomiasis. Many of the individuals of this group represent classic types of myxedematous infantilism with evidence of hypofunction of the thyroid gland; others, however, are far from that type and do not show appreciable signs of hypothyroidism. Must we establish relations of cause and effect between this infantilism and infection by the *trypanosoma cruzi?* Certainly yes. In the first place, aside from arrest of development, other signs indicative of the disease are found in such individuals. And in some autopsies the parasite has been found in its seats of preferred localization. Aside from this, it must be emphasized that the parasite localizes itself in the essential endocrine organs and systems, as the thyroid gland, the genital organs, the suprarenals, etc. Here it has localized itself and caused lesions that change the functional correlations between such systems or destroys the necessary antagonism. This being so, it would not be possible to deny the influence of such changes on the total physical development of the individual.

Nor is it to be wondered at that infantilism figures among the results of infection by the *trypanosoma cruzi*. The analogy for this aspect of the disease is found in syphilis, the pathology of which presents notable points of contact with that of trypanosomiasis. Does syphilis not count infantilism among its consequences? And why may it not be so in relation to American trypanosomiasis, when the contagion in this disease may also take place during intrauterine life, or the infection may be acquired during the first months or even during the first days of existence? I have no doubt that in the zones of the "barbeiro" infantilism constitutes a result of the disease and investigations are in progress on this point that may better elucidate it.

ENDEMIC GOITER AND TRYPANOSOMIASIS

A point that is also debatable is what is said with regard to the relations, if any, between American trypanosomiasis and the goiter that is endemic in the regions where the disease exists. In rapid synthesis let us expose the reasons that bring us to consider the goiter that is endemic in the infested regions as a result of infection by the *trypanosoma cruzi.*

Among the most salient clinical signs in the acute form of the disease figures the mucoid infiltration of the subcutaneous tissue. This is a constant sign and indubitably expresses the interference of the thyroid gland in the pathologic condition. We must note that, in the large number of observations that we possess, we are treating of children who were formerly free from any of the signs of myxedema, this having appeared days after the beginning of the infection, that is, as an immediate consequence of it. Furthermore, in autopsies on acute cases the parasite has been observed in the thyroid gland, which forms another argument in favor of our opinion.

On the other hand, in numerous cases of goiter studied in the zones of the "barbeiro," the coexistence of symptoms of trypanosomiasis is constant, and if in many cases of the disease it is easy to verify absence of appreciable hypertrophy of the thyroid gland, it is difficult to verify the inverse condition.

The facts of the epidemiology and of the geographic distribution of the disease also give foundation for the same opinion. Thus it is that in the infested zones goiter is only found in individuals who reside in houses where the transmitting insect is encountered; while the inhabitants of houses free from infestation by the hematophage, although under the same conditions of life, fed in the same way and drinking the same water, do not show lesions of the thyroid nor the effects of goiter. As to the geographic distribution of the disease and of endemic goiter in regions of the interior of Brazil, our observations superabundantly show the coexistence of goiter and the hematophage that transmits the *trypanosoma cruzi*, and as yet, we have not been able to find any region infested by the triatome in which goiter does not exist.

It is true that the presence of goiter in some of the zones along the coast of the country in which the "barbeiros" have not been found seems to contradict this doctrine; however, we

must state that we have never affirmed that goiter is always a consequence of infection by the trypanosome, which would be absurd. We believe in the diversity of etiologic factors of struma and even in our country we have the conviction of the diversity of the goiter observed in certain regions of the coast and that which constitutes the great endemics in the zones where the trypanosomiasis exists. To recapitulate our idea in this respect, we will say that we associate the endemic goiter observed in the regions of the interior of Brazil which are infested by the transmitting triatome with infection by the *trypanosome cruzi*. We have strong arguments that lead us to think in this way; in spite of this, however, we do not consider this point definitely elucidated, and we believe necessary other investigations which we will take up in order to give our doctrine indisputable proof or to make it unsupportable.

HOST OF THE PARASITE IN THE OUTER WORLD

The existence of the parasite in the outer world, where it is found in the organism of a vertebrate, *tatusia novemcincta*, is of great interest in the epidemiology of this disease. This animal lives in holes in the ground and is very abundant in any of the regions of the interior of Brazil. In the holes in the ground inhabited by this animal we also found another species of triatome, the *triatoma geniculata*, in the intestines of which we found a species of trypanosome, identified as *trypanosoma cruzi*. Investigations on this subject demonstrated it to be the trypanosoma of *tatusia novemcincta*, the same as that of man, and further that the transmitter of the parasite between the armadillos is the *triatoma geniculata*. We must also report, as an epidemiologic fact of great importance, that the *triatoma geniculata*, although habitually found in the holes of the armadillos, may emigrate to the human residences, and this constitutes a possibility of infection of the recently constructed houses in the zones where the armadillos are infected by the *trypanosoma cruzi*.

We must emphasize the biologic importance of the existence of a protozoon parasitic for man in the organism of another vertebrate for which the parasite is inoffensive, according to the observations that have been carried on up to the present. We believe, as a result of arguments too long to reproduce here, that the *tatusia novemcincta* is the natural host of the *trypanosoma cruzi*, the infection in man representing a later adaptation of the parasite attributable to the habit of the triatome of feeding on human blood and of the flagellates of the organism of the insect living in it.