

The Discovery of Trypanosoma Cruzi and of American Trypanosomiasis

Historic retrospect

by

DR. CARLOS CHAGAS

Directeur of the Instituto Oswaldo Cruz.

The discovery of american trypanosomiasis and chiefly the methods of reasoning which led to definitive results, furnish a new line of action for conducting similar research-work yet to be undertaken with a view to solving other obscure problems of human pathology.

This biological observation was carried out in a way completely different to that usually employed in recognising the etiology and pathology of diseases or in describing new ones. Furthermore, as in this discovery there are to be found interesting aspects and incidents which may be of use to other research workers, there follows an exact and minute description of the facts especially those concerning the more important points.

The discovery of the parasite here preceded the recognition of the disease and when in the blood of a feverish

child I found the pathogenic trypanosome I had already acquired a complete notion of its biology.

But for greater clearness it is more advisable to expose the facts in their uninterrupted order :

As a consequence of the outbreak of a malaria epidemic amongst Government workmen on the Central Railway of Brasil, in the valley of the Rio das Velhas (State of Minas Geraes) the Minister MIGUEL CALMON applied to OSWALDO CRUZ for steps to be taken. OSWALDO CRUZ immediately complied, intent as he was on proceeding with the anti-malarial campaigns successfully undertaken in other parts of the country and decided to entrust me with the sanitary measures.

Together with Dr. BELISARIO PENNA whom I invited to be assistant in this commission, I started out for the interior of Minas Geraes and installed

myself on the banks of the Rio Bicudo where the works on the railroad lingered belated by the epidemic. The malaria prophylaxis was undertaken with the most satisfactory results and regular work on the railroad was once more begun.

We remained more than a year in this region without becoming aware of the existence in the local huts, of a blood-sucking insect known popularly the name of *barbeiro*, *chupão* or *chupança*. By this time we had already had the opportunity of carrying out locally a good deal of clinical observation and of studying a great number of cases not only amongst those subject to malarial infection, in the valleys of big and small rivers but also among the inhabitants of mountainous regions who were entirely exempt of this disease.

And from that time on, experimental laboratory methods and the most careful semiotic consideration of the cases were alike of no avail in diagnosing some of the cases submitted to us. In these there remained unknown something new in the dominion of pathology to stimulated our curiosity.

On a journey to Pirapora and while spending the night in an engineers' camp Dr. BELISARIO PENNA and I first made the acquaintance of the *barbeiro*, shown to us by Dr. CANTARINO MOTTA, chief of the engineering committee.

Once we had heard of the blood-sucking habits of this insect and of its proliferation in human dwelling-places, we became very interested in knowing its exact biology and above all in ascertaining if by any chance it were as I immediately supposed, a transmitter of any parasite of man or of another vertebrate.

The rôle of several blood-sucking insects in the transmission of human diseases and of several trypanosomiasis of mammals, directed my line of thought and led me to obtain some more specimens of the insect, so as to search

for the parasites which it might harbour in its digestive tube and salivary glands. Dissecting the insect, I found in the posterior intestine of each one numerous flagellates with the appearance of crithidias. This fact elicited two hypotheses: either the flagellate was a harmless natural parasite of the insect, or else it represented a stage in the evolution of a hæmo-flagellate of some vertebrate perhaps even of man.

Previously I had found a new species of trypanosome in the monkey *Callithrix* (*Callithrix penicillata*) and given the frequency of the infection of monkeys by *Trypanosoma minasense*, the species I described, I supposed the crithidias seen in the intestine of the *barbeiro* to be a phase in the evolution of this trypanosome which would then be transmitted by the insect. And as all the monkeys of the region proved to be infected the experiments of transmission with the purpose of confirming this hypothesis could not be carried out for obvious reasons. For this reason I sent some of the insects to my unforged table chief OSWALDO CRUZ, so that they should be allowed to suck healthy monkeys of the genus *Callithrix*. 20 or 30 days later when once again back in Manguinhos, I examined the blood of one of these monkeys that had been sucked by *barbeiros* and found in it a trypanosome, which at first sight and before examining it by the technical methods I took to be *Trypanosoma minasense*. After having seen the flagellate alive, between cover-glass and slide I made some fixed and stained preparations in which it was seen to show characters entirely distinct from those of *Trypanosoma minasense* and to show no similarity to any other trypanosome. It was undoubtedly a new species whose chief character lay in its blepharoplast, the biggest I had yet seen and located at the hind end (the end opposed to the free flagellum).

After having studied the new parasite's morphology I started to work on its biology. In repeated experiments, I obtained new laboratory infection not only in monkeys of the genus *Callithrix*, but also in guinea-pigs, rabbits and puppies. These infections were obtained in some cases by the stinging of the insect but mostly by inoculation of the flagellates taken from its intestine. Lengthy experiments thus allowed me to characterise the trypanosome as a new species and to establish the part played by the *barbeiro* in its transmission. Besides this I made sure of the pathogenic properties of the trypanosome which brought about the death, in a variable period, of small laboratory animals, generally by septicæmia and without the disappearance of the parasite from the peripheric circulation. The remainder of the experiments I carried out related to the double evolutive cycle of the trypanosome in the vertebrates and in the insect transmitter, the forms of evolution in the intestine of the *barbeiro*, the artificial cultivation of the protozoon etc.

And it was then after having acquired ample knowledge of the parasite, in its morphology, general biology and pathogenic action that I undertook the second part of my research-work that was to give the more remarkable results as regards human pathology.

To the new species of trypanosome I gave the name of *Trypanosoma Cruzi*, in honour of my unforgettable leader, to whom I owe everything in my scientific career, and who in these studies was to me the most broad-minded of counsellors: to the impersonation of scientific capability and kindness, always ready to let me partake of the benefits of his knowledge and to harbour me in the warmth of his friendship. What little work has been accomplished by me in my professional career

is more his than mine, and what there may be of useful in this work I attribute with pride and sincerity to the value of his teaching and to the example of his high faith, to that decisive sway of his strong personality and great abnegation upon all those who had the good-fortune to encounter him during their lifetime and to reap the benefits of that influence that shaped their careers.

This is the exact truth concerning the discovery of *Trypanosoma Cruzi*, known up to this point only as a parasite of a vertebrate of unknown species and transmitted by the sting of an insect. The latter was determined as *Triatoma megista* BURM. by Dr. ARTHUR NEIVA who in lengthy studies described its whole biology.

In this first period of our work the most interesting point was the observation of a hemipteron as a transmitter of parasites. This observation was far-reaching as regards general biology and was by itself a scientific fact of real importance.

I will now proceed to describe the discovery of *Trypanosoma Cruzi* in man and the observation of the new disease.

Returning to the triatoma-infested regions, it became my object to ascertain the vertebrate host of *Trypanosoma Cruzi*, inasmuch as the monkeys and laboratory animals I had worked upon were all of them experimentally infected and did not demonstrate the ordinary host of the parasite.

The difficulty of interpretation of the local clinical cases together with the supposition based on careful observation and lengthy research-work of the existence of a pathological condition that escaped identification with any established disease, facts which I had reflected on for some time and which made me suppose an unknown etiologic cause, became the starting-point for the work I then undertook. To add to this was

the primary circumstance of the triatoma's being a domestic insect with habitat, perhaps confined to human dwelling-places, and preferring to nourish itself on human blood during sleep. Under these circumstances, and to judge by the biology of blood-parasites it was to be admitted that the flagellate of the intestine of the blood-sucker, whose food is chiefly human blood, should undergo a gradual adaptation to the blood-medium and, at a given moment of its philogenetic evolution, become a parasite of man. Up to this point I was frankly in the realm of hypotheses, undoubtedly based on exact biological reasons but that nevertheless still awaited confirmation. Furthermore I was at that time unaware of the important fact that even in uninhabited regions, armadilloes (*Tatusia novemcincta*) are frequently infected with *Trypanosoma Cruzi*. This observation, completed by the finding of *Triatoma geniculata*, infected with trypanosomes in armadillo-holes led me to the conviction, justified by various arguments that the natural and ancestral host of the parasite is really the armadillo and that the human infection is the result of a later adaptation.

This point of view hardly to be opposed, since it has in its favour positive facts of observation as well as undeniable biological arguments, would explain the existence of infected triatomata in regions where the disease is unknown. As a matter of fact, some people, with the curious object of denying *Trypanosoma Cruzi* any pathogenic action, state that the *barbeiro* has been found in some regions of Brasil and other countries carrying in its digestive tube flagellates that could be inoculated into small laboratory animals and that nevertheless the disease had not been reported in these regions.

Now, in the first instance it would be advisable to relate the clinical and experimental researches proving the inexis-

tence of the disease, whose parasitological diagnostic is not an easy matter and as a rule is possible only post-mortem. And as for acute cases, to happen upon them it would be necessary to remain some time in the region. It would be of more use in excluding the existence of trypanosomiasis to carry out minute clinical observations based on an exact knowledge of the symptoms that characterise the different forms of the disease. Only after this had been done could one claim, that in this or that country, in one or another region, there were triatomata infected with parasites that could be inoculated in small laboratory animals without there having been observed any human infections.

But granting the opinion of those who disbelieve in american trypanosomiasis, unless we want to deny the existence of the disease altogether, which would be absurd in view of the exactness of the clinical observations, the post-mortem findings, and the experimental results, demonstrating in full the scientific interest and social importance of the disease, we are obliged to accept the above-mentioned apparently contradictory fact, taken from my conclusions, namely that in these regions the adaptation of the trypanosome to man is not yet accomplished and that the races observed in the blood-sucking transmitter are not virulent for human beings. In any case this is a question in itself, but under no circumstances will it be possible to find bona-fide and logic arguments to displace the evidence of facts acquired by observation and experiment.

It was along these lines, that I started a new phase of my work by searching for trypanosomes in those patients for whose disease I had found no interpretation.

At first all attempts gave constantly negative results a fact which was later explained by the absence of parasites

in the peripheric circulation and their existence in the tissues of these patients. My observations were made in human dwelling-places abundantly infested by triatomata. In one of these I found a cat evidently ill and in whose blood upon examination, was found *Trypanosoma Cruzi*. This did not, however, allow of a definite conclusion, since the cat, being a domestic animal, passes the night in human dwelling places and is consequently exposed to being sucked by the insects, so that its infection could be no surprise. And besides, from later examinations I came to the conclusion that the cat is a reservoir for trypanosomes, and for this very reason a factor in the spreading of the disease.

Pursuing my work, and I must admit I did it with a well-founded certainty of success, I had the chance of finding in a feverish condition a child from the house in which I had found the infected cat. Now, a fortnight or twenty days before, I had spent a night in the house and had seen a great number of insects stinging the dwellers including the little girl who now lay feverish and who at the time had been in perfect health.

Among the chief clinical symptoms of this child, whose fever had come on some eight or ten days before examination, were the following: Axillary temp. 40°C.; spleen enlarged and to be felt under the edge of ribs; liver also enlarged; groups of peripheric lymphatic glands swollen etc. Most noticeable was a generalised infiltration, more pronounced in the face, and which did not show the characters of renal oedema but rather of myxœdema. This last symptom, which I later found to be one of the most characteristic of the acute form of the disease, already then revealed some functional alteration of the thyroid gland, perhaps affected by the pathogenic action of the parasite.

Examination between cover-glass

and slide revealed the existence of flagellates, in good number and the fixing and staining of blood-films made it possible to characterise the parasite's morphology and to identify it with Trypanosoma Cruzi, first seen in crithidia-form in the intestine of Triatoma and transmitted by the sting and by inoculation of the flagellates taken out of the intestine, first to the monkey Callithrix (Callithrix penicillata) and then to several small laboratory animals.

Thus was proved the existence of a new trypanosomiasis of man. This was the second one known; its parasite showed well defined morphologic and biologic characters distinguishing it from any other known trypanosome. The transmitter of the new disease as shown by undeniable laboratory experiments was a heteropteron of the genus triatoma, Triatoma megista.

There remained now to be carried through careful studies as to the pathogenesis, symptomatology epidemiology and geographic distribution of the new disease which I had discovered in its acute form. Was it always like this or did it show well-defined chronic forms? My clinical experience and knowledge of the unusual diseased condition of local inhabitants led me to admit that in this trypanosomiasis, besides the known acute form, other chronic ones awaited detection and description.

I was only able to take up again these researches some months later, with the clinic and epidemiologic problems of the disease, up to then almost entirely obscure, now as my object. In this also my knowledge of the local nosology, in which I had come upon conditions impossible to understand, was of great use to me. Returning to the study of the disease with a better grasp of the problem, I tried to systematise the facts so as to get a starting-point for possible generalisations. Among the symptoms what most impressed me was the fre-

quency of alterations in the rhythm of the heart-beat among the local inhabitants especially among those who lived in *triatoma*-infested houses. This was extremely common and generally took the form of extrasystoles frequently with slow pulse. I must mention that in view of the anatomical alterations of the thyroid commonly observed in these patients, either as a great hypertrophy or as an almost inappreciable enlargement of the gland, I at first believed these cardiac perturbations to be ascribable to goitre.

Soon, however, I made sure that patients showing an unrhythmic heart-beat had not infrequently a normal thyroid. About this time I got the opportunity of practising a post-mortem on a child in whom I had diagnosed the acute form of the disease with trypanosomes in the peripheric circulation. The material I obtained I sent to the Instituto Oswaldo Cruz where it was examined by the regretted GASPAR VIANNA, whose high technical ability and great competence in the field of pathological anatomy were of the greatest help to us.

GASPAR VIANNA described, within the cardiac fibres of the child's myocardium some very curious parasitical forms, very numerous and taking the form of actual kysts. Similar aspects of the parasite were observed in other organs.

There was at the time, as I heard from OSWALDO CRUZ, some doubt as to the interpretation of these parasitic forms, VIANNA believing them to be special stages of *Trypanosoma Cruzi*. All doubts were dispelled, however, when, at Lassance, OSWALDO CRUZ, showed me sections and smears from the myocardium, in which I recognised parasitic forms identical to those I had obtained in artificial cultures of the trypanosome. No doubt could be left over, therefore, as to VIANNA's observations

of the localisation of the trypanosome, under a special form in the myocardium, within the muscle-fibres. This furnished the acceptable interpretation to one of the most frequent clinical symptoms of the disease, disturbance of the rhythm of the heart. The histopathological results of the first autopsy were so interesting that OSWALDO CRUZ decided to become better acquainted with my work and made with this purpose the fatiguing journey to the interior of Minas Geraes where he remained for a week in the enthusiastic appreciation of the clinical cases and experimental facts which were opening a new chapter in human pathology.

I must here allude to a cause of error in the first laboratory work for the diagnostic of the disease.

In the earlier studies on *Trypanosoma Cruzi* I had connected with the evolutive cycle of the trypanosome in vertebrates, special forms found with great frequency in the lungs of infected guinea-pigs. It was from this interpretation, in which I had the assent of PROWAZEK and MAX HARTMANN, that came the forming of the genus *Schizotrypanum* in which to place the new species of parasitic flagellates. In view of this observation I for some time made use of these forms founds in the lungs of the guinea-pig as a factor in the diagnostic of patients whose blood had been inoculated in guinea-pigs. It was later observed, first by Prof. CARINI and DELANOË and then by some research-workers of the Institute, that the parasitic forms from the lungs of the guinea-pig hady nothing to do with *Trypanosoma Cruzi* and were really another parasite, *Pneumocystis*. This parasitologic diagnostic was thereby rendered valueless and we had to base on other grounds our opinion regarding the chronic forms of the disease. Numerous post-mortems in which the parasites were seen localised

In different organs and the lesions for which they are responsible amply justified the clinical diagnostic of the different forms of the disease by establishing beyond doubt its cause.

But to proceed to the detail: Of the acute forms of the disease, characterised by the easily observed existence of the trypanosome in the peripheric circulation within a short period. I obtained several clinical observations to which no objection can be made.

As to the chronic forms, my conclusions were no less conclusive, based as they were on a great number of post-mortems with parasitological and at the same time histo-pathological study. Of the clinical cases in which cardiac symptoms dominate, I quickly obtained a great number of observations and also several post-mortems. In the latter the uniformity of the lesions of the myocardium and the constant occurrence of the parasite in it founded on anatomical reasons the diagnostic of chronic cases, carefully studied while alive. The clinical diagnostic of these lesions became one of the characteristics of the new disease. Recent researches of CROWELL prove that the cardiac lesions in american trypanosomiasis can be recognised independently of the finding of trypanosomes and are to be considered as a well characterised specific lesion.

Contrarily to what those who say we only know a few cases of american trypanosomiasis, a patient with dominant cardiac symptoms is, according to the acceptation of the disease, infected with *Trypanosoma Cruzi*: besides the rhythm other symptoms indicating lesions of other organs can be found. And judging the number of cases by the cardiac forms our opponents would certainly admit that there has been no exaggeration in estimating as very high the number of endemic cases.

The ascertaining of the nervous forms was also based on clinical observation and post-mortem findings of undoubted value. The numerous cases of cerebral diplegia, of organic idiocy, of monoplegias, of aphasias etc., observed in the regions where we worked had long since impressed me. The first supposition of syphilis to which these lesions might have been attributed was quickly dispelled by all clinical and laboratory methods of syphilis-diagnostic. And contrarily to the fallacious tradition, this disease is an extremely rare occurrence amongst the inhabitants of the interior, where it is taken only by new comers from more civilised and contaminated zones. In another publication we will speak of this subject proving that in the remote zones of the interior syphilis remains unknown until it is introduced with the advent of the railways.

Could the nervous phenomena be attributed to endemic cretinism as KRAUS later proposed? Certainly not, since under the most strenuous observation, they were far from showing, what several authors have considered to be the classical nervous manifestations of cretinism. And this is not a question to solve by hypotheses but rather by the surer methods of pathological anatomy.

The first post-mortem was carried out on a case of cerebral diplegia that had lasted for 22 years. According to information given by the family, the subject had been paralytic since she was 3 years old and had suffered from organic idiocy with excitable phases. Death ensued from accidental burning. Autopsy showed the existence of trypanosomes and well defined cerebral lesions distributed in foci. Histo-pathological studies carried out by GASPAR VIANNA left no doubt as to the etiological cause of the nervous phenomena studied. After this, other post-mortems followed and among them those of cases of acute me-

nyngo-cephalitis in which the seat of the parasite in the brain and the lesions produced amply justified the recognition of a nervous form of the disease, casting light on numerous obscure points of the local nosology.

This precludes the basing on sound scientific reasoning of the denial of nervous forms of the disease, with disturbances affecting motility, intelligence, speech etc. and the great number of cases of paralysis, organic idiocy, aphasia, observed in *triatoma*-infested regions cases which reproduce the symptoms of those which were submitted to post-mortem examination, and must consequently be attributed to the same etiological cause. As an additional confirmation of this way of thinking, experiments made by EURICO VILLELA and MAGARINOS TORRES elicited paralyses in dogs and monkeys with the consecutive finding of the trypanosome and lesions in the central nervous system.

Infantilism and other dystrophies frequently seen in the regions where the disease is endemic, I ascribe to infection by *Trypanosoma Cruzi*, either as a residual form from infection in first childhood or what is still more probable as a consequence of hereditary infection. Are there any reasons wanting for conviction? How but by logical deduction from facts has syphilis been connected with infantilism? *Trypanosoma Cruzi* like the treponeme is found localised in the different organs of the endocrinic system whose rôle in the general phenomena of development: is no longer contested. In the adrenals of man and of experimentally infected animals for instance, the trypanosome and the lesions it produces have been amply demonstrated. The same, as regards testicles, ovaries and the thyreoid gland. And if these react, as has been observed, it is logic to admit the physio-pathological consequences of these anatomical alterations. Here also recent

experiments of EURICO VILLELA are being of great value. E. VILLELA observed new-born puppies of an infected mother with hereditary cephalitis and trypanosomes.

This subject, which needs detailed explanation, cannot be gone into fully in this work, in which I only desire to outline the essential motives for my convictions concerning infantilism and other dystrophies of the regions in which trypanosomiasis is endemic.

In the first phase of our work we took trypanosomiasis to be the cause of the *endemic goitre of the regions where the disease prevails*. The reasons we had were based, some of them on the pathogenesis, others on the epidemiology and geographic distribution of trypanosomiasis. At first, the frequency of goitre or of a simple alteration in the thyreoid with partial hypertrophy of some of its lobes in patients with other symptoms called my attention. What further impressed us was the infiltration observed in all acute cases and having the characters of myxœdema. This was a constant symptom in the the first phase of the infection, and was to be considered as a myxœdematous infiltration peculiar to trypanosomiasis and expressing the part the thyreoid played in the pathogenic process. Posterior examinations on acute cases showed the seat of the trypanosome in the gland, right inside the vesicular cells, and also showed the inicial reaction-processes that characterise the formation of the stroma. Furthermore a prolonged observation of some patients, from the acute phase, permitted to follow the progressive development of the goitre, which in some subjects attains a considerable size, while in others it limits itself to hypertrophy, complete or partial, of the thyreoid. The absolute absence of goitre in acute cases and the existence of it in children of the same age that might have got infected earlier were another argument

in favour of this way of thinking. Other reasons were of a pathogenic and epidemiologic order. Regarding the geographical distribution of goitre my experience like that of my informers, was that goitre was constantly seen in *triatoma*-infested regions and unknown in those where the insect is not found. And in the regions where we studied, persons, among them children, without any hypertrophy of the thyreoid and living in houses in which there were no *triatomata* where common whilst those living in infested houses all showed goitres or hypertrophied thyreoid glands. The high percentage of goitre in the rural huts, even in the ones round the cities and the absence of any lesions on the glands of the towns and villages the people dwelling in good houses, which do not offer the *barbeiro* favourable conditions for its proliferation, cannot fail to strike one. The factors usually held to be responsible for endemic goitre, among them the drinking-water, were excluded in this case seeing that both the persons who had goitres, chiefly the children, and the persons who living under the same conditions, using the same food, had no goitres and lived in houses in which there were no *triatomata*. These facts as well as many others which I do not refer to in this work, lead me to consider the goitre as one more element of the disease in *trypanosomiasis*-regions. And up to

now no definitive proof to modify our point of view in regarding the goitre as part of *trypanosomiasis* in the parts of the country in which this disease is prevalent. Yet, as we cannot give a positive demonstration for this as we gave for other aspects of the disease in 1916 at the time we were synthesising the pathology of the disease, we will consider the goitre a question apart, on the subject of which there may exist diverging opinions. And on this footing we stand as regards this discussed point, while we await research-work which will displace our way of thinking or will confirm it in a positive way.

Of late there has been a tendency, with a view to admitting the infectiousness of goitre, towards attributing the goitre to a filterable virus. And here I must point out that I think it absurd to consider only one etiologic cause of goitre, seen in different parts of the world and having very varied physio-pathological consequences.

Concerning opinions on the etiology and pathogenesis of goitre, and specially in *trypanosomiasis* as its cause I might give some lengthier arguments based on the epidemiology and geographic distribution and based also on the physio-pathology of endemic goitre in the regions in which I studied it. I will, however, return to the subject in later publications.