THE ADVISORY COMMITTEE ON HEALTH RESEARCH

BENJAMIN OSUNTOKUN MEMORIAL LECTURE

CHAGAS DISEASE
FROM DISCOVERY TO CONTROL - AND BEYOND
HISTORY, MYTHS AND LESSONS TO TAKE HOME

Delivered by Carlos M. Morel

World Health Organization
Geneva
This lecture has been instituted to honour the memory of Professor Benjamin Osuntokun, past Chairman ACHR, by offering new ideas for health development in relation to biomedical research and policy analysis.

Professor B. Osuntokun was a distinguished scholar who made important contributions to the field of neuro-epidemiology and to public health. A first lecture describing his work and entitled “Health Research for Humankind” has been delivered by Dr A.O. Lucas in 1996.

It has been a pleasure to invite Professor C. Morel for the 1997 lecture.

Professor T.M. Fliedner, Chairman

Dr B. Mansourian, Secretary
INTRODUCTION
It is a real honor to be distinguished with the invitation to give the 1997 Ben Osuntokun Memorial Lecture at this annual meeting of the Global Advisory Committee on Health Research. The challenge facing me is a particularly difficult one, for last year this committee had the privilege of listening Prof. Adetokunbo O. Lucas speak on “Health Research for Humankind”. It took me a long time to accept the invitation - I think I have to thank Prof. Fliedner and Dr. Mansourian for their most kind and efficient “pressure”, which finally convinced me to talk to you today on a subject related to, as they asked, “health and health research in South America”.

It is not by chance that the word “research” is not present in the title of my lecture, in spite of the fact that it is the very concept of research that will be the common denominator of all the stages of the saga I will talk about. Why this paradox? Because this reflects better what we see in real life, and in this way I could start calling your attention to the sad dissociation between the crucial role that research plays in improving health and the general lack of recognition of its role, importance and priority in public health policies. For some reason we tend to forget how much we owe to research once a success story in disease control achieves a happy end. How many times I heard health authorities and policy makers say that they wanted “the real thing” - in other words, disease control, now - and not “lose time and money with unnecessary and odd expenses” - in other terms, health research for tomorrow? Too many times, unfortunately.

Therefore, I decided to choose as the subject of my lecture a success story in disease control in South America and to point out to the role research has played along its development. It starts at the very beginning - the discovery of the disease - and goes until the most recent chapter - its elimination as a major public health problem in large regions of the Southern Cone countries. Although no one can yet as-
sure a final "happy end" to this story, progress in its control has been very successful, to the point that CTD calls it now "a disease whose days are numbered" [1]. It is a long story - 90 years of history - that illustrates the fundamental importance of research in improving health. By analyzing it, studying the actors, the personalities, the facts, the true or false stories - in other words, the myths - I think we can derive some universal notions and also some lessons to take home, to keep in mind and put into use when time and opportunity comes.

It is a real story that touches me deeply - since I was a student at the Medical Faculty of Recife, State of Pernambuco, in the poor Northeast region of Brazil - and in a multi-faceted way: as an inhabitant of a developing region where this disease still infects millions of people; as a researcher working in this area during the last 20 years; as a civil servant of the Ministry of Health of Brazil; and finally as a former President of the Institution where the disease was discovered and where some of the major research breakthroughs in the development of efficient control tools were made, the Oswaldo Cruz Foundation (FIOCRUZ). I will talk today about Chagas disease, from its discovery in 1909 by the Brazilian scientist Carlos Chagas working at the Oswaldo Cruz Institute in Rio de Janeiro to its successful control in the large regions of the Southern Cone countries in the 90s.

THE INCREDIBLE - AND IMPROBABLE - DISCOVERY

The discovery of American trypanosomiasis by Carlos Chagas has been described and reviewed in a number of publications in Portuguese [2-8] and English [9-13]. However, it is only by reading the original articles of Chagas himself2, particularly his classical paper on "Ueber eine neue Trypanosomiasis des Menschen", published in Portuguese and German in the first volume of the Memórias do Instituto Oswaldo Cruz in August, 1909 [14] that one can fully apprehend the quality, the extension and the impact of the work of that 29-year old researcher. His genius enabled him to describe the agent, vectors, clinical signs in human beings, animals and the existence of animal reservoirs of a new disease3.

How could one of the major medical discoveries happen in a poor country in the tropics, be published on the first volume of a local institutional journal4 and yet receive world-wide recognition and be one of the seeds of a whole school of thought and research which still today has such a profound influence in Latin American science?

The roots of this breakthrough have to be analyzed in conjunction with the role played by Oswaldo Cruz and the institution created by the Brazilian Government in 25 May 1900 to fight endemic diseases
and which bears his name since 1908. This extrapolates the aim of this presentation and I have no choice but to limit myself just to cite some key references [15; 16] and point to some of the major factors contributing to this “miracle”:

- Oswaldo Cruz spent some time at the Pasteur Institute in Paris, and was convinced that the Pasteurian philosophy of combining strategic research, development, production (e.g. of sera and vaccines) and education of young researchers in a single institution would be the key to success; in contemporary words, he was a firm believer in a scientific research system [5];

- By propagating the role that science should play in the development of Brazil, Oswaldo Cruz managed to conquer and receive support from the highest political level (President Rodrigues Alves); being nominated Director of the Federal Department of Public Health, he could efficiently fight the diseases that were devastating Brazil’s economy, particularly yellow fever and plague;

- Having acquired national leadership, he could mobilize the funds for building up a first-class institution, whose main building - a Moorish-style palace, based on original drawings by Oswaldo Cruz himself, inspired on the Observatoire Météorologique de Montsouris in Paris - still today attract the curiosity of the lay person, facilitating another of his primary goals: legitimizing the role of science in society;

- Very early in the life of the Institute, after his first successes against yellow fever epidemics - which brought to the Institute the Golden Medal of the XII International Hygiene Conference in Berlin in 1907 -, Oswaldo Cruz could attract the collaboration of scientists from developed countries, particularly from Germany, who would come to visit and work in Rio de Janeiro, interacting with the team of young Brazilian students and researchers recruited to work at the Institute;

- The access to information was always a priority to Oswaldo Cruz; with the funds he could raise, either directly from the government or through the selling of sera and vaccines, he started to build up a very complete biomedical library, acquiring whole collections of contemporary periodicals, some of them dating back to the 18th century.

With the premature death of Oswaldo Cruz in 1917, when he was only 45 years old, Carlos Chagas became Director of the Institute. Already recognized as a great scientist, he was able to keep the national and international prestige and recognition needed for the consolidation of a genuine Brazilian school of tropical medicine, the “Escola de Manguinhos” [16].
Ninety years later, when we are still discussing the role and the place of health research in development [17-21], it is surprising to note how many of the principles and factors underlying today’s proposed policies and strategies were already present in a poor country in the beginning of the century.

**Lesson to take home, #1:**
The “impossible” can happen - do not underestimate the potential and the capacity of developing countries to identify and manage their own health problems.

**UNVEILING THE DISEASE**
Owing to his discovery, Carlos Chagas received several prizes, honorary degrees and distinctions	extsuperscript{10}. This success provoked open opposition, which culminated in 1916 with the denial of his findings by Rudolf Kraus, one of the most prominent German microbiologists, during the 1st Pan-American Congress in Buenos Aires, with the argument that he had been unable to find cases of Chagas disease in the Argentine Chaco [22; 23]. As Chagas had also strong opposition in the Brazilian National Academy of Medicine this episode had a devastating effect and Chagas disease was forgotten for almost 20 years [11]	extsuperscript{10}.

The “resurrection” of Chagas disease is mainly due to the work of Salvador Mazza in Argentina, who described more than a thousand cases particularly in regions which Kraus had studied 20 years before [24; 25]. Mazza was also the first one to raise the possibility of transfusion-transmitted Chagas disease [26].

However, it was not until the 80s that country-wide surveys were conducted using standardized protocols and the overall prevalence of human *T. cruzi* infection could be reliably estimated: 18 million cases in 21 endemic countries, with 100 million people - 25% of all the inhabitants of Latin America - at risk of infection [1]. The burden of the disease, measured in DALYs and according to data from the World Bank in 1993, showed that in Latin America Chagas disease ranks 1st among the tropical diseases, and 4th among the transmissible diseases, only behind acute respiratory infections, diarrhoeal disease and AIDS [27].

Why did it take so long to fully disclose the extent of this scourge, if Carlos Chagas in his early papers already called the attention to the social, economic and public health relevance of the disease he had discovered? Was it lack of scientific evidence?
Not so simple, it seems. In this long period - almost 80 years, from discovery to the large-scale mapping of its prevalence and social impact in the American continent - important information was in fact building up continuously as the result of laboratory, clinical, epidemiological, socioeconomic and applied field research studies. However their results did not translate easily into action. The analysis of the reasons why this did not happen points to the fact that the disease affects mainly poor rural areas that traditionally receive little or no political priority [28], and shows how deep can be the gap among researchers, decision makers, politicians and public interest.

Lesson to take home, #2:
Solid research findings and sound scientific evidence alone, are not sufficient for establishing or imposing political priorities.

TRANSFORMING RESEARCH INTO ACTION, RESEARCHERS INTO POLICY-MAKERS (OR: THE SUCCESSFUL MOBILIZATION TOWARDS CONTROL)
As knowledge about the disease and its prevalence increased, a small group of researchers working at the now legendary Bambui field station of the Oswaldo Cruz Institute in the State of Minas Gerais, was slowly coming out with the notion that Chagas disease, unlike many other parasitic diseases, could be controlled by eliminating vector populations, chiefly by using insecticides and housing improvements [28].

The crucial experiments were the field trials conducted by Dias and Pellegrino in Brazil and Romaña and Abalos in Argentina in 1947 showing the efficacy of organochlorine insecticides against domiciliated triatomine bugs [29-31]. So good were the results, in fact, that a telegram was sent to the Brazilian Ministry of Health, suggesting that Chagas disease transmission could be eliminated throughout the territory [12; 29; 32; 33].

Again, was this discovery powerful enough to mobilize the political forces of the nation? Not at all. In spite of the heavy burden of the disease and of the proven availability of appropriate technology for fighting its vectorial transmission, only isolated actions were taken between 1950 and 1975 [33].

All that changed in the 90s, when political decisions at the highest level in 6 countries established the so-called Southern Cone Initiative - and what we saw in the following years already deserves a special place
in history. How and why did that happen? Which were the forces that
promoted such a radical change? Which were the major factors respon-
sible for this major shift in priority?

A scientific answer to these questions is surely to be looked for by
social scientists, not by a molecular biologist such as myself. Therefore,
what follows is just a very personal view of a curious observer and a partici-
pating scientist. It may simply be a myth. But as in some cultures a myth is
just another way of telling a true story, why not share it with you today?

In 1974 the National Research Council of Brazil (CNPq), which
had just started its successful “Integrated Programme on Endemic Dis-
eases” (Programa Integrado de Doenças Endêmicas, PIDE), organized a
very small meeting at its headquarters in Rio de Janeiro, with less than
10 participants, to discuss some problems in the study of Trypanosoma
cruzi. One important issue of the meeting was the development of a
common protocol to cultivate better this parasite in the laboratory.
After this was agreed upon, the idea came to organize a second meet-
ing, in one year’s time, to evaluate progress made. Prof. Zigman Brener,
of the “René Rachou” Regional Research Center of FIOCRUZ in Belo
Horizonte, State of Minas Gerais, was selected by the participants them-
selves as the organizer of the next meeting.

Owing to the limited CNPq facilities at that time in Rio de Janeiro
and also to the fact that the interested participants were working in
Rio, São Paulo and Belo Horizonte - and surely because Zigman Brener
is from Minas Gerais - the second meeting was arranged to take place in
the city of Caxambu, state of Minas Gerais, which is sort of equidistant
from those three cities, therefore facilitating travel by car or bus and
reducing the costs. In this way the 2nd Annual Meeting on Basic Re-
search on Chagas Disease was organized in November 1975. Although
the scientific progress had been solid in one year time, new questions
arose and there was still an unfinished agenda at the end of the meet-
ing. The 3rd meeting was planned, again in one year time, again in
Caxambu, and again the participants themselves selected the organiz-
ers of the next meeting - and what follows is also history.

The Annual Meetings on Basic Research on Chagas Disease, which
have run uninterruptedly all these years (the 25th Annual Meeting will
be held in November 1998) became a world-class scientific event [34]
and a forum where scientists, research managers, policy makers and
government authorities meet and discuss science and public health. From
a round table discussion with 10 participants, a huge, 700-people an-
nual meeting became established (Table 2).

At the same time, a very important partner came into being and
provided much of the grounds needed for international collaboration:
I do not hesitate to attribute a pivotal role to TDR in the building up of a critical mass of well trained and informed Latin American scientists interested in Chagas disease.

1984 saw the starting of the Annual Meetings on Applied Research on Chagas Disease, which used to be held in Araxá and now moved to Uberaba, both cities also located in Minas Gerais and at a driving distance from Caxambu, so that one can attend both meetings which take place 1-2 days apart.

These Annual Meetings, in Caxambu and Uberaba, became a major driving force for research in Latin America - and much more. They turned into an annual forum of debates and policy-making. Three examples will illustrate how they helped to transform research into action:

- **Sensitizing scientific and public opinion**: During the military regimen Brazil decided to buy from France some 15 Mirage air fighters; Zigmant Brener presented careful calculations showing that if instead of buying 15 planes we bought 13, the savings would be sufficient to carry out a nation-wide vector control program which could stop transmission of the disease, as it had been demonstrated in the Bambui field station. At the same moment he also showed us numbers on how many new cases of Chagas disease could have been avoided if such a program had started immediately after the 1948 work of Dias and Pellegrino demonstrating the efficiency of insecticides against domiciliated vectors [29]. These data became information in the brain and mouth of the participants - although all the planes were finally bought and no national program started, we all realized that something could be done if we could fight more efficiently towards a higher political priority for public health problems;

- **Influencing the government**: In 1979 - 70 years of the discovery of Chagas disease - it was decided to have the meeting in Rio de Janeiro, to transform it on an international event and to have the President of the Republic at the inauguration ceremony. Prof. Carlos Chagas Filho, the son of Carlos Chagas and himself one of the most highly respected scientists in Brazil, was asked to organize the event. As the result of this strategy, at the end of the meeting funds could be secured for the starting of a pilot vector control programme against Chagas disease;

- **Stimulating leadership formation and decision-making**: the turning point came years later, when one of our Caxambu fellow scientists, Dr. João Carlos Pinto Dias, became the Director of the Chagas Disease Division at the Ministry of Health, when the military regi-
men ended. The transmutation of researchers into policy-makers, as in his case, opened new perspectives in Chagas disease control and radically changed the priority-setting mechanisms at the Ministry of Health. Finally, research was in action.

As there are several ways of telling one story, my perception is surely not the only valid one. But it would be hard to analyze the 1975-1990 period and not share similar thoughts. Therefore:

Lesson to take home, #3:
Health researchers must meet, share their findings, doubts and uncertainties, discuss the constraints on their work and on public health issues, raise public consciousness - and eventually become policy-makers, a very efficient shortcut to the long road needed to transform research into action.

THE NEXT RESEARCH AGENDAS
The “post control” research agenda
We are now at a crossroads in relation to research in Chagas disease, and tension is mounting due to opposing views among researchers, health authorities and policy makers.

On one extreme there are those who think that Chagas disease is well under control, that the existing tools have proven their efficacy and therefore no further effort or resources should be spent in this field. Their arguments seem to be so more valid as the burden of other diseases or unhealthy conditions is skyrocketing in the Third World due to epidemiological and demographic transitions. In fact it is common knowledge that in several developing countries the burden of infectious and parasitic diseases is now being diluted by the toll of chronic and degenerative illnesses, aging and violence and also by emerging and re-emerging diseases, such as AIDS [20].

On the other side there are those that insist that the threat from Chagas disease is as serious as it has ever been, that reinestation of the houses will happen soon in most of the places and that we are in real danger of spoiling all the efforts of the last years by underestimating the adversary.

History has shown us how complex this kind of dilemma can be, and one could pick up whichever example fits better in one’s own position, forgetting those that point in the opposite direction. Underesti-
mating the possibility of resurgence of "controlled" diseases can be a fatal mistake (remember tuberculosis control and malaria eradication). On the other hand, several announced apocalypses did not materialize.

I do not think I innovate by saying that one should avoid the extreme scenarios. Although it is true that official data demonstrate the progress made in the control of Chagas disease [35], particularly in relation to its vectorial transmission which has been virtually eliminated from Brazil [36], it is also true that this disease still remains as a scourge in large regions of Latin America [37]. It is therefore imperative that control programmes against Chagas disease in these areas receive high priority at the local, national and international levels [27], for "as it was established by Carlos Chagas and Emmanuel Dias long ago, more than technical innovations, the final overcoming of human Chagas disease involves mainly political will and social responsibility" [38].

Although the persistence of the disease is in part a consequence of this lack of political will to adopt available and proven control tools, e.g. in blood banks, there is undoubtedly the need for a focused, operational research agenda addressing additional key issues related to control activities. In the words of João Carlos Pinto Dias, "it must be remembered that research must be a continuous feature of the surveillance phase, because the program involves such a close relation between local communities, technical support groups and the rapidly changing environment" [38]. This is particularly true for the Andean and Central American countries, where the vectors of Chagas disease are not strictly domiciliary [1]. This research agenda will have to be a rather different one from that of the heroic old times of Lassance, where Chagas disease was discovered, and Bambuí, where the control tools against domiciliated triatomines were first tried. This new agenda will have to focus on non-domiciliated vectors, their systematics, distribution, evolution, genetics, behaviour and population biology [39]. In addition, it should also address topics such as: monitoring of insecticide resistance; diagnostics in areas of low disease prevalence; mathematical modelling and epidemiological impact of control activities [31; 40].

The unfinished R&D agenda
Even if Chagas disease is eliminated as a public health problem from all Latin American countries, we still would have to cope with the problem of millions of chronically-infected people of the region. Recent data indicate that the development of chronic lesions, which seem to be mediated in a large extent by autoimmune mechanisms [41-44], seems to depend on the persistence of parasite infection [45-49]. Therefore the need to find appropriate new drugs, or new protocols with
existing drugs, that can be used in the treatment of Chagas disease in order to prevent the development of serious clinical forms [50-52]. As a corollary, one has to define reliable criteria for the cure of these patients, ideally based on the actual determination of parasite load before and after treatment [53].

Another yet unsolved problem in clinical studies on Chagas disease is the question of possible relationships between the different clinical forms, their morbidity and the different parasite strains [54]. The recent demonstration that there are two major phylogenetic lineages of Trypanosoma cruzi [55] will surely stimulate new approaches to this old question [56; 57]. In addition, it has brought new perspectives for those interested in molecular epidemiological studies of Chagas disease [58-63].

An agenda for the future
The ideal strategy against tropical diseases, synthesized in the TDR motto “investigate, eliminate, eradicate”, is unfortunately inapplicable to Chagas disease. Due to its zoonotic nature, one can think of elimination of this disease as a public health problem, but eradication of the parasite is not a feasible goal. There is therefore the need for a long-term research agenda for the future, aiming at the development of new prevention and control tools, such as efficient vaccines and safer drugs.

In my vision the road to the future will be strongly based on what is being called the new (molecular) biology, based on the information generated by the various ongoing genome projects, addressing the human, pathogen and vector genomes. Progress in this area has been truly remarkable, with the area now known as “Genomics” evolving from “Structural-“ to “Functional-“ and “Evolutionary Genomics” [64]. The results already accumulated are good enough to allow us foresee how biological research will be in the so-called post-genome era [65]. It is hoped that the Trypanosoma cruzi genome project will allow a better understanding of the parasite biology and its interaction with the vertebrate and invertebrate hosts, as well as the development of new control tools such as vaccines and therapeutic approaches based on the molecular structure of new targets and rational drug design.

Developing countries are already participating in these efforts, in view of the benefits one can expect from these projects and despite the immense challenges to be faced [66; 67]. The T. cruzi genome project, which matured in several meetings in 1993 and 1994 and was officially launched in 1994 in a TDR-FIOCRUZ co-sponsored meeting held at FIOCRUZ’s headquarters in Rio de Janeiro, is now well under way through the concerted action of more than 20 laboratories, most of them in the South [67-75].
The research agenda for the future will probably be tackled in a very different way from that used by the founding fathers of Chagas disease research. The new biology - technology intensive and addressing complex problems - has to be carried out through networks and international collaboration, and will have to rely on the newest communication and information technology [74].

FINAL COMMENTS
The TDR motto “investigate, eliminate, eradicate” carries in it the notion of different stages of the never-ending fight against diseases. Our microbial enemies and their vectors are smart and able to develop different strategies for coping with our weapons [76-82]. We have no choice but to be imaginative, flexible and devoid of prejudices in the selection of the new priorities that will shape our next research agendas.

As we move forward in the direction of Chagas disease elimination, entering into a “post-control” era, we will face new and unknown challenges, and the lessons of history will become less and less useful. This brings us to the last lesson to take home:

**Lesson to take home, final:**
After a given point there are no lessons to take home - we will have to rely on further research to shape the road to the future.

In other words,
“Caminante, no hay camino, se hace camino al andar”(Antonio Machado, Spanish, 1875-1939)15

ACKNOWLEDGEMENTS
I would like to thank Prof. W. Lobato Paraense, Dr. C. J. Schofield, Dr. A. Moncayo and Dr. O. Fernandes for their most helpful comments and suggestions and to the FIOCRUZ’s Units “Casa de Oswaldo Cruz” and “Biblioteca de Manguinhos” for the access to historical documents and photographs.
NOTES

1. Senior researcher and former President, Oswaldo Cruz Foundation (FIOCRUZ), Ministry of Health of Brazil. Mailing address: Dept. Biochemistry and Molecular Biology, Oswaldo Cruz Institute at FIOCRUZ, Av. Brasil 4365, Rio de Janeiro, RJ 21045-900, Brazil. E-mail: morel@fioercz.br, cmorel@ax.apc.org

2. A magnificent collection of all the papers published by Carlos Chagas was organized by Prof. A. Prata and published in 1981 by the University of Brasilia.[110]

3. In this paper, which has superb color plates, Chagas describes the human infection, the parasite (then known as Schizotrypanum cruzi), the cycle in the digestive tract of the invertebrate vector, cultivation in agar-blood and transmission to vertebrates of flagellates from infected triatomines [11].

4. The Memorias do Instituto Oswaldo Cruz, now at its 87th year of continuous life and nowadays fully available online at the Internet (http://www.pobox.com/~memorias)

5. Gustav Giemsa, Stanislas von Prowazek, Max Hartmann, among others.

6. In 1911 the library had already more than 10,000 volumes, making it the largest specialized collection in South America [15]

7. A position he kept until his death in 1934 at the age of 55.

8. Manguinhos (= little mangrove) was the name of the farm where the Institute was built.

9. Extraordinary Member, Brazilian Academy of Medicine; Schaudinn Prize, awarded every four years to the best work in Parasitology and Tropical Medicine in the world, Tropical Diseases Institute of Hamburg; Great Prize of the Pasteur Centenary Commemorative Exposition in Strasbourg, 1922, among others.

10. According to some researchers Kraus may have been right because Chagas disease would have spread in the Argentine Chaco only some years later (Schofield, personal communication and [111])

11. A detailed description of the major findings is again beyond the scope of this lecture. Table 1 is meant as an initial guide to those interested in further readings.
Prof. Carlos Chagas Filho created the Institute of Biophysics of the Federal University of Rio de Janeiro, which now has his name. He was Brazil’s Ambassador at UNESCO, 1966-1970 and President of the Vatican Pontifical Academy of Sciences during almost two decades (1971-1988).

A similar situation occurred in Argentina, when Prof. Elsa Segura became the Minister of Health of the Province of Catamarca.

For a overview on the trends in Chagas disease research see [39; 112]

“Caminante, son tus huellas
el camino e nada más;
caminante, no hay camino,
se hace camino al andar.
Al andar se hace camino,
y al volver la vista atrás
se ve la senda que nunca
se ha de volver a pisar.
Caminante, no hay camino,
sino estelas en la mar.”

“Voyageur, le chemin
sont les traces de tes pas, c’est tout;
voyageur il n’y a pas de chemin,
Le chemin se fait en marchant.
Le chemin se fait en marchant
et quand on tourne les yeux en arrière
On voit le sentier que jamais
on ne doit à nouveau fouler.
Voyageur, il n’est pas de chemin
Rien que sillages sur la mer”

### Table 1  Selected dates in Chagas disease R&D and control

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
<th>Refs.</th>
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<tbody>
<tr>
<td>1872.</td>
<td>August 25: Oswaldo Cruz is born in São Luís de Paraitinga, State of São Paulo, Brazil</td>
<td>[15]</td>
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<tr>
<td>1878.</td>
<td>July 9: Carlos Chagas is born in Oliveira, State of Minas Gerais, Brazil</td>
<td>[6]</td>
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<tr>
<td>1892.</td>
<td>Oswaldo Cruz gets his MD degree at the Medical Faculty of Rio de Janeiro, at the age of 20</td>
<td>[15]</td>
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<td>1896 - 1899:</td>
<td>Training of Oswaldo Cruz at the Pasteur Institute, Paris</td>
<td>[15]</td>
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<tr>
<td>1900.</td>
<td>May 25: Creation of the “Instituto Soroterapico Federal de Manguinhos”</td>
<td>[15][83][84]</td>
</tr>
<tr>
<td>1904.</td>
<td>Carlos Chagas gets his MD degree at the Medical Faculty of Rio de Janeiro, at the age of 25</td>
<td>[6]</td>
</tr>
<tr>
<td>1907.</td>
<td>The “Instituto de Patologia Experimental de Manguinhos” receives the Golden Medal at the International Hygiene Exhibition in Berlin</td>
<td>[15]</td>
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<tr>
<td>1909:</td>
<td>Discovery of Trypanosoma cruzi and Chagas disease. Publication of the 1st volume of the “Memórias do Instituto Oswaldo Cruz”</td>
<td>[14]</td>
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<tr>
<td>1911:</td>
<td>Gaspar Vianna describes nerve cell lesions in the acute phase of infection</td>
<td>[85-87]</td>
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<td>1911-1913:</td>
<td>Expeditions conducted by the Oswaldo Cruz Institute Scientists to the Brazilian hinterland</td>
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<td>1913:</td>
<td>Complement fixation tests for Chagas disease</td>
<td>[88]</td>
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<tr>
<td>1914:</td>
<td>Introduction of xenodiagnosis</td>
<td>Joseph Emile Brumpt (1877-1951)</td>
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<td>1916:</td>
<td>Rudolf Kraus, one of the most prominent German microbiologists, denies Carlos Chagas findings</td>
<td>Chagas disease is forgotten for almost 20 years</td>
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<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Description</th>
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<tbody>
<tr>
<td>1917</td>
<td>February 11:</td>
<td>death of Oswaldo Cruz, at the age of 45 in Petrópolis, State of Rio de Janeiro.</td>
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<tr>
<td>1934</td>
<td>November 9:</td>
<td>death of Carlos Chagas, at the age of 55 in Rio de Janeiro.</td>
</tr>
<tr>
<td>1936</td>
<td></td>
<td>Mazza first raises the possibility of transfusion-transmitted Chagas disease</td>
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<tr>
<td>1941-</td>
<td></td>
<td>1958: Margarino Torres studies the pathogeny of cardiac lesions in Chagas disease and proposes that “allergic reactions” might be involved</td>
</tr>
<tr>
<td>1943, November:</td>
<td>by initiative of Aragão, then the Director of the Oswaldo Cruz Institute, creation of the legendary “Centro de Estudos e Profilaxia da Moléstia de Chagas”, a field station of the Oswaldo Cruz Institute in Bambuí, State of Minas Gerais, Brazil</td>
<td></td>
</tr>
<tr>
<td>1948:</td>
<td></td>
<td>first field trials of a “new insecticide” (gamexane) establish the basis for the chemical control of domiciliated triatomine vectors</td>
</tr>
<tr>
<td>1950:</td>
<td></td>
<td>creation of the first National Control Programmes in Brazil and Argentina</td>
</tr>
<tr>
<td>1951, January 15:</td>
<td>Creation of CNPq; July 11:</td>
<td>Creation of CAPES</td>
</tr>
<tr>
<td>1953:</td>
<td></td>
<td>Gentian Violet is proposed as a chemoprophylactic agent against transfusion-transmitted Chagas disease</td>
</tr>
<tr>
<td>1955-1956:</td>
<td>Koberle and others confirm that Chagas disease also affect the peripheral, autonomic and enteric nerves and establish the relationship between the denervation process and the disease’s anatomic and functional aspects for the hollow organs of the digestive system and the urinary tract</td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Event</td>
<td>Reference</td>
</tr>
<tr>
<td>------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>-----------</td>
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<tr>
<td>1961</td>
<td>Berenice, the first patient identified to have Chagas disease, is found alive at the age of 53 and is extensively studied in Belo Horizonte, State of Minas Gerais.</td>
<td></td>
</tr>
<tr>
<td>1974</td>
<td>First meeting on Basic Research in Chagas Disease, in Coaxambu, MG, Brazil. Creation of PIDE (Integrated Programme on Endemic Diseases) in Brazil.</td>
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<tr>
<td>1975</td>
<td>Proposition of the role of autoimmunity in the pathogenesis of Chagas disease.</td>
<td></td>
</tr>
<tr>
<td>1975</td>
<td>Creation of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, TDR.</td>
<td></td>
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<tr>
<td>1975-1980</td>
<td>Conduction of national serologic and entomological surveys in Brazil.</td>
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<tr>
<td>1977-1979</td>
<td>Chagas disease control becomes a national priority in Brazil.</td>
<td></td>
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<tr>
<td>1979</td>
<td>A simple, common epidemiological methodology agreed to be used throughout Latin America to map Chagas disease and to quantify its prevalence.</td>
<td></td>
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<tr>
<td>1982</td>
<td>Large scale field trials of alternative insecticides and formulations for the control of triatomine vectors.</td>
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<tr>
<td>1986</td>
<td>Starting 1986 the Proceedings of the Annual Coaxambu Meetings are published in the Memórias do Instituto Oswaldo Cruz.</td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>Immunological and molecular data will later on support this proposition, but also rescue the importance of the continuous presence of the parasite in the pathogenesis of the disease.</td>
<td></td>
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<tr>
<td>1988</td>
<td>Strengthening of basic and applied research &amp; development activities; training of endemic country scientists and development of critical mass of researchers working in Chagas disease control.</td>
<td></td>
</tr>
<tr>
<td>1989</td>
<td>Production of the first reliable data on prevalence of human infection and vector distribution.</td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>Isoenzymes patterns (zymodemes); restriction fingerprinting of kinetoplast DNA (schizodemes).</td>
<td></td>
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<tr>
<td>1991</td>
<td>TDR Expert Meeting in Brasilia, DF, Brazil.</td>
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<tr>
<td>1992</td>
<td>Epidemiological cross-sectional studies using the standardised protocols.</td>
<td></td>
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<tr>
<td>1993</td>
<td>Replacement of chlorinated insecticides by synthetic pyrethroids; better residual effect and acceptance, lower mammalian toxicity and better cost-effectiveness.</td>
<td></td>
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Continued...
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>Chagas disease control programmes expanded to all infected areas in Brazil; National Chagas Disease Control Programme of Uruguay reorganised.</td>
<td>[33]</td>
</tr>
<tr>
<td>1984</td>
<td>Deane and collaborators demonstrate that the vertebrate and invertebrate cycles of <em>T. cruzi</em> can coexist in the same mammal host, the opossum <em>Didelphis marsupialis</em>. Collapse of Brazil’s PIDE Programme.</td>
<td>[101]–[103]</td>
</tr>
<tr>
<td>1986</td>
<td>First genes of <em>T. cruzi</em> cloned</td>
<td>[104]</td>
</tr>
<tr>
<td>1990</td>
<td>Multicentre double blind study for evaluation of <em>T. cruzi</em> defined antigens as diagnostic reagents. Fumigant canisters released to the market by Sintyol, Argentina.</td>
<td>[105]–[106]</td>
</tr>
<tr>
<td>1991</td>
<td>At a landmark meeting in Brasilia, the Ministers of Health of the Southern Cone countries (Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay) adopt a resolution calling for action to eradicate Triatoma infestans. Insecticidal points released to the market by Jharabras, Brazil.</td>
<td>[106; 107]</td>
</tr>
<tr>
<td>1991–1995</td>
<td>Industrial production of insecticide points, fumigant canisters and triatomine sensor/detector boxes in Brazil and Argentina.</td>
<td>[106]</td>
</tr>
<tr>
<td>1995</td>
<td>TDR meeting on the elimination of four diseases as public health problems (filarisis, onchocerciosis, leprosy and Chagas) <em>T. cruzi</em> genome project launched in TDR/FIOCRUZ meeting in Rio. Clone CL-Brener is selected as model organism.</td>
<td>[106]–[67]</td>
</tr>
<tr>
<td>1996</td>
<td>Randomised and controlled field trials of treatment with benznidazol conducted in young patients. The Southern Cone Initiative progresses towards interruption of transmission through vector elimination.</td>
<td>[51; 108]</td>
</tr>
</tbody>
</table>

Continued...
1997: Meeting of the Andean Countries Initiative, Bogotá, Colombia (February)  
Meeting of the Central American Countries Initiative, Tegucigalpa, Honduras (October).

1997: An analysis of the cost-effectiveness and cost-benefit of the Chagas Disease Control Programme conducted by the Ministry of Health of Brazil and PNUD showed that for each US$ 37.30 spent 1 DALY was gained and that for each dollar spent on prevention almost US$ 17.50 were saved.

1998: Latin American meeting scheduled to take place in April at FIOCRUZ headquarters in Rio de Janeiro in order to discuss and adopt a therapeutic protocol to treat young patients in order to prevent the development of chronic cardiac lesions.

Detailed plan of activities and budget were devised and elimination of transmission foreseen in 2010.

The study places the Program and its activities in the category of interventions with a very high cost-effectiveness and indicates that it is a health investment with good return. The study also showed that the decline in Chagas disease infection rates was due to the preventive activities and not due to general improvement in life conditions.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
</thead>
</table>
| 1997 | Meeting of the Andean Countries Initiative, Bogotá, Colombia (February)  
Meeting of the Central American Countries Initiative, Tegucigalpa, Honduras (October). |
| 1997 | An analysis of the cost-effectiveness and cost-benefit of the Chagas Disease Control Programme conducted by the Ministry of Health of Brazil and PNUD showed that for each US$ 37.30 spent 1 DALY was gained and that for each dollar spent on prevention almost US$ 17.50 were saved. |
| 1998 | Latin American meeting scheduled to take place in April at FIOCRUZ headquarters in Rio de Janeiro in order to discuss and adopt a therapeutic protocol to treat young patients in order to prevent the development of chronic cardiac lesions. |

**Figure 1** Evolution of annual meetings on basic research in Chagas disease

![Graph showing evolution of annual meetings on basic research in Chagas disease](image)
Table 2  Caxambu meetings, 1974 - 1998*

<table>
<thead>
<tr>
<th>#</th>
<th>Organizers</th>
<th>Mem. IOC</th>
<th>Year</th>
<th>C&amp;RT</th>
<th>BI</th>
<th>BQ</th>
<th>IM</th>
<th>QT</th>
<th>VE</th>
<th>PZ</th>
<th>Total</th>
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<tr>
<td>1</td>
<td>J. Ferreiro Fernandes</td>
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<td>1974</td>
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<td>2</td>
<td>Z. Brener</td>
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<td>0</td>
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<td>0</td>
<td>30</td>
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<tr>
<td>3</td>
<td>F. S. Cruz &amp; W. Leon</td>
<td></td>
<td>1976</td>
<td>50</td>
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<td>50</td>
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<td>4</td>
<td>W. Colli &amp; E. P. Camargo</td>
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<td>C. M. Morel</td>
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<td>C. Chagas Filho</td>
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<td>W. Souza &amp; M. Barcinski</td>
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<td>L. R. G. Travassos</td>
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<td>9</td>
<td>A. U. Kretli</td>
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<td>H. Krieger</td>
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<td>R. R. Santos</td>
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<td>D. F. Almeida</td>
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<td>13</td>
<td>B. Zingoles &amp; M. J. M. Alves</td>
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<td>S. Coutinho &amp; M. P. Deane</td>
<td>Vol B2 Sup 1</td>
<td>1987</td>
<td>12</td>
<td>68</td>
<td>51</td>
<td>111</td>
<td>22</td>
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<td>15</td>
<td>T. L. Kipnis &amp; W. D. Silva</td>
<td>Vol B3 Sup 1</td>
<td>1988</td>
<td>68</td>
<td>84</td>
<td>79</td>
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<td>16</td>
<td>E. Garcia &amp; S. Goldenberg</td>
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<td>E. Chiari &amp; J. Ramalha-Pinto</td>
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<td>I. Abrahamson 1 &amp; R. A. Mortara</td>
<td>Vol B6 Sup 1</td>
<td>1991</td>
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<td>N. Yoshida &amp; L. M. Floeter-Winter</td>
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<td>M.N. L. Meirelles &amp; J. Scharfstein</td>
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</table>

25 25 years of Annual Meetings! 1998 25th Meeting to be held in November, 1998

Total  509  1414  1370  1727  344  740  832  6936

Key:
Mem. IOC = memorias do Instituto Oswaldo Cruz; PZ = protozoology; VE = vectors; QT = chemotherapy; IM = immunology; BQ = biochemistry; BI = biology; C&RT = conferences, mini-conferences and round tables.

*The meetings of 1974 (1st) and 1979 (6th) were held in Rio de Janero; all the other in Caxambu, MG.
Figure 2
Carlos Chagas with the first case of Chagas disease, the girl named Berenice, 1909

Figure 3
Albert Einstein visits the Oswaldo Cruz Institute when Carlos Chagas was the Director, 1925
Figure 4
Carlos Chagas during a scientific expedition in the Amazon (Sao Gabriel, Rio Negro), 1913

Figure 5
The socioeconomic roots of Chagas disease
Figure 6
Work on triatomine control at the Bambui field station in Brazil

Figure 7
The insects which transmit Chagas disease live in the cracks in mud-walled houses
Figure 8
Southern cone initiative
Elimination of transmission: incidence of infection 1980-96

Source: Moncayo, A. Chagas disease: a disease whose days are numbered, WHO, Geneva 1996 and Reports by National Chagas disease control programmes, 1993-97

Figure 9
Interruption of transmission
Brazil: Human infections in 7-14 year olds


