Pan American Health Organization

PAHO/ACMR 12/13
Original: English

TWELFTH MEETING OF THE
ADVISORY COMMITTEE ON MEDICAL RESEARCH

Washington, D.C.

25-29 June 1973

NEEDS AND OPPORTUNITIES FOR RESEARCH ON CHAGAS' DISEASE IN BRAZIL

Draft Report

1 June 1973

CONTENTS

		Page
I.	Introduction	1
II.	General Background	2
III.	The Present State of Knowledge	
	A. The Organism	4
	B. The Disease	8
	C. Distribution of T. cruzi Infection and Chagas' Disease in Man	13
	D. Chemoprophylaxis and Chemotherapy	15
	E. Entomology	18
	F. Sociologic Aspects of Prophylaxis and Control	22
	G. Organization and Funding of Research on Chagas' Disease in Brazil	24
IV.	Recommendations	
	A. The Organism	28
	B. The Disease	30
	C. Distribution of T. cruzi Infection and Chagas' Disease in Man	31
	D. Chemoprophylaxis and Chemotherapy	33
	E. Entomology	34
	F. Sociologic Aspects of Prophylaxis and Control	36
	G. Organization and Funding of Research in Chagas' Disease in Brazil	37
	H. Recommendations to the Pan American Health Organization	38
V.	Annexes	
	Annex 1 Itinerary	40
	Annex 2 Individual Reports	41
	Annex 3 Curriculum Vitae	86

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5 May - 1 June 1973

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**Dr. Minter accompanied the group in the first and last weeks of the tour.

I. INTRODUCTION

This Report is based on a series of visits between 6 May and 1 June 1973 to research institutions in Brazil concerned with Chagas' disease and related subjects (for itinerary, see Annex 1). The visits were made by a team of experts led by Dr. C. E. Gordon Smith, who was with the team only from 26 May to 1 June to help with the writing and presentation of this Report. The team members and their disciplines were (curricula vitae are given in Annex 3): Prof. D. S. Bertram, entomology; Prof. W. H. R. Lumsden, protozoology; Dr. P. D. Marsden, clinical tropical medicine; Prof. W. Peters, protozoology and chemotherapy; and Dr. B. A. Southgate, epidemiology. Dr. M. Martins da Silva, Chief, Department of Research Development and Coordination, Pan American Health Organization (PAHO), coordinated the study and accompanied the team to Rio de Janeiro, São Paulo, and Brasilia. The team was joined by Dr. D. M. Minter in the first and last weeks of its visits.

At the outset the team wishes to record its gratitude for the great help and kindness received from all whom they visited. The team was, inevitably, unable to meet all the research workers concerned with Chagas' disease in Brazil, and many of the visits were brief and sometimes rather superficial. This Report is therefore to be read with the clear understanding that it is based on a hurried tour, not on detailed probing and investigation. Brazilians, who know so much more detail, will inevitably find fault with some of the impressions recorded herein.

The team was organized at the request of the Brazilian Government by PAHO's Department of Research Development and Coordination with financial assistance from the British Government, and its members were chosen by its leader, Dr. Gordon Smith. Its terms of reference were: (1) to appraise the current information and identify gaps in knowledge regarding the organism, vector(s) and reservoirs, host-parasite interaction, and the disease in man; (2) to make recommendations on research priorities in the epidemiology, diagnosis,

treatment, and prevention of the disease; and (3) to examine the research resources (scientific personnel and physical facilities) available in different centres in Brazil and the studies being conducted in them, and to recommend how they can best be strengthened and coordinated through joint efforts.

II. GENERAL BACKGROUND

Infection with Trypanosoma (Schizotrypanum) cruzi is widespread in Latin America and is transmitted by various species of triatomid bug, the most important to man being species that dwell in the walls or roofs of houses. Because such bugs, which may be infected, tend to be transported in the belongings of migrant populations and in vehicles, the infection is probably extending to new areas with the widespread movements of rural populations to the cities and, especially in Brazil, with the rapid development of communications (particularly roads) and the colonization of new areas (particularly around Brasília and in the Amazon basin). Infections of domestic and sylvatic mammals also appear to be widespread, although their significance to man is probably small at present. With increasing control of the domestically maintained infections, however, they could become of greater importance as a source of reinfestation and reinfection. The infection in man is usually prolonged, though its duration requires further study.

In a proportion--of very uncertain magnitude--of people who become infected, varying degrees of Chagas' disease become apparent and may be both serious and fatal either early or late in the course of infection. The early stage of the disease is an acute febrile illness with a variety of other manifestations; the late stage mainly affects the heart and intestinal tract. The pathogenesis of these disease states is still incompletely understood, especially the part (if any) played by immunologic factors. Because of the behaviour of the main bug species which transmit the disease to man, it is an infection and a disease of poor people who are ill-educated and live in

badly constructed houses with many cracks and crevices in their walls or roofs that harbour bugs. Education (and housing improved by perhaps even so simple a measure as better wall maintenance) could greatly reduce the incidence of infection and eventually of disease. Large-scale control is practised by insecticide spraying, the effectiveness of which needs further and more careful evaluation since insecticide resistance in triatomid bugs has already appeared in Venezuela.

It is in the nature of this infection, however, that even if all new infections were stopped now, the disease would continue to appear for many years because no satisfactory treatment yet exists. This is because the disease processes are incompletely understood and, perhaps more important, because new drug research and development are seldom carried out commercially if sales would be almost entirely to very poor populations. Similar factors have probably inhibited the development of more effective drugs and vaccines for prevention of infection.

This Report is written with the view that research on trypanosomiasis and Chagas' disease in Brazil should be visiby (even if distantly) directed towards providing the means for the prevention or cure of the infection, the disease, or both. We attempt to assess the quantity, quality, and balance of existing research work in Brazil, and to some extent elsewhere, and try to identify places and subject areas that, if given priority in funding, might provide exceptional improvements in the overall quality and balance of research. We also give attention to the need for research into the application of known and new knowledge. Finally, we try to identify those situations in which foreign assistance would be particularly helpful to the development of a balance programme of research during the next decade or so. Our time and knowledge of Brazil prevent us from adequately assessing the training and educational needs for provision of research workers for various aspects of a balanced research programme, but we draw attention to certain deficiencies and to possible solutions.

It will be noted that few workers are named in the first section below, but all are named in the geographic sections.

III. THE PRESENT STATE OF KNOWLEDGE

A. The Organism

1. Occurrence and importance

T. cruzi is a kinetoplastid flagellate which exists as amastigotes and trypomastigotes in mammalian hosts and mainly as epimastigotes and trypomastigotes in the guts of triatomid bugs. Organisms of this sort are widely distributed both in mammal hosts and in bugs in the Americas, from the southern United States to the middle of Argentina. Numerous cycles of transmission clearly exist over areas of such diverse ecology, and only a few involve man. A primary difficulty is that all strains of these organisms are morphologically identical at both light and electron microscope levels, which prevents the easy identification of those cycles that do involve man. Secondly, when man is infected, the pathologic outcome varies greatly, from a clinically inapparent infection to a highly pathogenic one either in the chronic stage of the infection or, more rarely, during the acute phase. Clinically inapparent infections may well be very much in the majority. Thus, clear definition of the distribution and incidence of infection, morbidity, and mortality due to T. cruzi is an essential preliminary to any rational plan for its control or eradication.

2. Characterization

The various pathologic outcomes of T. cruzi infection in man may be due to differences among strains of the organism. Many attempts have therefore been made to differentiate T. cruzi populations, so far without much success. Studies on the course of the disease in experimentally infected laboratory animals involve many uncontrolled variables and are difficult to evaluate. Immunologic differences (e.g., in precipitation reactions in agar-gel double diffusion) have been demonstrated but do not correspond clearly to other characteristics such as geographic distribution or pathogenicity. In related protozoa, promising results have been

obtained by identification of particular enzyme patterns and DNA sequences. Both immunologic and biochemical approaches should be pursued.

For such studies, precise identification and standardization of the materials studied are necessary, and changes in populations by selection during their maintenance in the laboratory through serial passage in animals or in cultures must be avoided. Cryopreservation of isolates at the earliest possible passage level should be standard procedure. Although simple methods for cryopreservation are available, most workers have not yet adopted them. Only at Belo Horizonte and Salvador is the technique now established.

In addition, to avoid the possibility of confusion arising from experimentation with mixed populations, strains should be cloned whenever possible.

3. Diagnostic and survey methods

i. Protozoology. At present the main problem in diagnosis arises from the very low levels of parasitaemia characteristic of chronic infections. Xenodiagnosis is widely used and is probably the most sensitive diagnostic method, but it is distasteful to the patient, laborious, and slow to give an answer (some workers recommend keeping the bugs for as long as 90 days). It is also potentially dangerous to workers using it. Partial comparisons have been made with other methods (e.g., centrifugation, culture, and animal inoculation), but an exhaustive comparison with these methods has still to be made. Also, the factors influencing success with xenodiagnosis itself must be studied; how far, for instance, is it determined solely by the amount of blood ingested and how much by other factors such as bug instar or species.

ii. Serologic diagnosis. Complement fixation (CFT, Machado Guerreiro) is still the most widely used test, although indirect fluorescent antibody (IFA) and indirect haemagglutination (IHA) tests are being introduced in some centres. Comparisons and interpretation of results from

these tests are impeded by the variety of antigens in use, however. Some workers use antigen prepared at Ribeirão Preto or at Belo Horizonte and others prepare their own. Methods used for sampling populations are also varied and result in difficulties of comparison. It is understood that, as a result of the World Health Organization's interest, a manual will shortly be available that will lay down methods and criteria for the acceptance of antigens. Other serologic tests for possible field use are being explored in São Paulo.

4. Immunology

Most studies have been directed towards measuring antibodies in relation to diagnostic tests. The complexity of these antibodies has as yet been little analysed, and it is therefore not surprising that protective antibodies have not been clearly identified or that passive transfer of serum has given irregular results. Cell-mediated allergic mechanisms have been less studied, though delayed-type hypersensitivity has been demonstrated in infected monkeys and guinea pigs, and, with infected mice, macrophage spreading has been shown to be inhibited by T. cruzi antigens.

5. Protection by vaccination

Because of the irregularity of the protection obtained by attempts to immunise hosts by passive methods or by the administration of killed vaccines, considerable attention is being paid to the investigation of organism strains that might be used as living vaccines. These fall into three main groups:

i. Strains attenuated by long-term serial passage in culture. This appears to lead to culture populations that are predominantly epimastigote, although a small proportion of trypomastigotes still persist. Such vaccines have been shown to protect against subsequent challenge with virulent bloodstream organisms, but the "vaccines" induce the formation of amastigote forms in the cells of the host and lead to a

low-level parasitaemia of the "vaccine" strain. In addition, the virulent challenge organism can be recovered from the experimental animals by blood culture. These "vaccines" therefore appear not to protect the host completely but simply enable it to control the parasitaemia at a low level, and continuing pathogenic effects are thus possible. Efforts are being made to elucidate the factors that determine transformation to the trypomastigote form so as to develop cultures free from these forms.

ii. Separation of epimastigote and trypomastigote forms by use of DEAE cellulose fractionation. This has been accomplished but trial of these materials as "vaccines" has not yet been made.

iii. Search for kinetoplastid flagellates in the guts of insects with a view to their cultivation and use of the cultured forms for vaccination. Particular attention has been paid to "Leptomonas pessoai," a mixed population of several genera of insect flagellates isolated from a plant-feeding bug. Some protection has been shown to follow inoculation of living culture forms into mice, though it is by no means complete. Detailed biochemical studies are in progress on the nutritional requirements of these organisms with a view to controlling their transformation and so designing effective vaccines.

6. Transmission and epidemiology

It is generally accepted that most infections are acquired through abraded skin or the conjunctiva, but some recent work with mice shows that the nasal mucosa is also highly susceptible--as bugs defaecate liquid material in houses, infection by aerosol is a possibility. Transmission by blood transfusion is a danger which may not always be guarded against even by rejecting CFT-positive bloods, a precaution that may not always be observed. The addition of gentian violet (1:4,000) to the blood is reported to be an effective precaution against transfusion infections, but some patients will not accept it.

Congenital transmission is reported to lead to a macerated stillborn foetus rather than to a living infected child, but further study of this is desirable.

B. The Disease

1. Pathogenesis

Multiplication of T. cruzi occurs by binary fission in tissue cells in the amastigote phase only. Initially this takes place at the site of infection, but blood-stream dissemination of the resultant trypomastigotes means that almost any tissue can be affected: this can be demonstrated by infecting experimental animals with a large dose of a virulent strain. In such animals, some strains have been characterized in crude pathologic terms as viscerotropic, neurotropic, and the like.

T. cruzi appears to have a predilection for muscle, especially heart muscle, the smooth muscle of the gut, and striated muscle, in that order. Initially amastigote pseudocysts in muscle fibres are not associated with an inflammatory infiltrate, but, within a short time, chronic inflammatory cells appear. As far as is known, amastigote multiplication persists at a low level for life in tissues and, although the host is capable of reducing the level of circulating trypomastigotes to below detectable levels, elimination of the parasite and spontaneous cure have not yet been documented.

Acute Chagas' disease is not usually fatal (5 to 10 percent), and when death occurs it is due either to acute heart failure or, less often, to meningoencephalitis. Post-mortem examinations reveal pseudocysts of multiplying amastigotes in many tissues, with a varying inflammatory infiltrate. The heart is never spared.

The evolution of the disease is such that, with the exception of a rather rare subacute form, the main complications of T. cruzi infections in man (namely, chronic chagasic cardiomyopathy and "mega" syndromes) do not usually appear for decades. Exceptions do occur, however, and children have been seen with megaoesophagus.

Some of the damage, particularly in the acute phase, can be attributed to the direct destruction of myocardial muscle by amastigote invasion. Later effects are attributed more to indirect causes such as

the destruction of autonomic ganglion cells by parasitization of their satellite cells, or by release of a hypothetical toxic substance from degenerating, nontransforming, amastigotes by the rupture of pseudocysts in the vicinity of the ganglia. Allergic mechanisms may also be involved in this process.

Fritz Köberle, at Ribeirão Preto, has made a fundamental contribution to our understanding of the pathogenesis of "mega" syndromes by emphasizing the destruction of peripheral parasympathetic ganglia that occurs and its effect, especially on the gut. Once the number of ganglia has fallen below some critical level, disordered peristalsis and eventually aperistalsis result. In those parts of the gut that contain large bulks of food or residues (i.e., oesophagus and large bowel), such disordered function in time results in dilatation and stasis. This concept neatly explains the slow development of these complications, but there is disagreement between various workers as to how rapidly this irreversible damage to the peripheral parasympathetic ganglia occurs. Köberle feels that damage is complete within weeks. On this interpretation the onset of functional changes is then determined by the natural process of loss of ganglion cells with advancing age. Other workers believe that it is a long-term process in which amastigotes continue to damage ganglion cells for years. The rare occurrence of "mega" syndromes in other hollow viscera (e.g., bladder or gall bladder) also needs explanation.

It is unlikely, however, that destruction of the parasympathetic ganglia concerned with cardiac function can fully explain the development of chronic cardiomyopathy, and it may not even be the major factor. The degree of muscle disintegration, haemorrhage, and chronic inflammatory infiltration is such as to represent important myocardial damage resulting in a weak, flabby, thin cardiac muscle. Amastigote nests are hard to find in such hearts and the degree and extent of round-cell infiltration suggest other mechanisms, e.g., allergic and antiallergic* ones. Disturbances of intracardiac conduction are extremely common and inflammatory reactions have been demonstrated in both the AV bundle and the right branch in human material using multiple serial sections by Zilton A. Andrade.

*Also referred to as "immunologic" and "autoimmune".

This pathologic observation fits in with the clinical presentations of arrhythmia, the left bundle being spare more frequently because it is more diffuse. Workers disagree on how frequently amastigotes can be found close to affected ganglion cells or Purkinje fibres.

So far, most pathologic studies on T. cruzi have been carried out on infections induced in experimental animals by the inoculation of much larger numbers of organisms than seem likely to occur in nature and also with blood-stream forms rather than the metacyclic forms responsible for most infections of man. The effect of the inoculation of more realistic doses of metacyclic forms and of repeated infections with both blood-stream and metacyclic forms should be studied.

2. Clinical presentation

Under natural conditions, transmission is by contamination of the conjunctiva or of a skin abrasion by bug faeces containing metacyclic trypomastigotes. Field observations and laboratory work in London show that skin contamination with bug faeces occurs frequently without resulting infection, and much may depend on the survival time of organisms on the skin and perhaps on the concentration and infectivity of the organisms on it.

The acute phase occurs when amastigote multiplication is widespread and at its height, and parasitaemia is patent. The best definition of the acute phase is that trypanosomes can be seen in fresh peripheral blood films. The presence of a chagoma and constitutional symptoms such as fever, tachycardia, hepatosplenomegaly, lymphadenopathy, or skin rash are all variable. This phase is frequently asymptomatic, so that many patients give no history of such an episode.

This is followed by what has been called the latent or indeterminate phase. Here the only indications of infection are positive serologic features and, more surely, positive xenodiagnosis.

The acute phase occurs mainly in the first 10 years of life. Chronic cardiac and gut complications appear in the third, fourth, and

fifth decades, most often in men who do hard physical labour. This third phase--the clinical appearance of cardiac and gut damage--is the most important and constitutes chronic Chagas' disease.

Chronic chagasic cardiomyopathy presents as: (1) biventricular failure; (2) cardiac arrhythmias due to conduction defects varying from ventricular extrasystoles to complete heart block; and (3) embolism of mural thrombi to the lung or systemic circulation, e.g., brain. Gut complications due to disordered peristalsis are: (1) megaoesophagus, in which functional abnormalities may be present without dilatation and are detectable only by radiography or pressure readings; (2) megacolon; and (3) other "megas" of hollow viscera.

The history of difficulty in swallowing described by patients is relatively specific in the case of megaoesophagus.

Transmission of the infection by such routes as by blood transfusions or by contaminated syringes in drug addiction, and by accidental laboratory infections, is followed by rapid development of the initial acute phase, particularly in some blood transfusion cases. Congenital transmission may result in a stillborn or moribund infant with massive amastigote tissue multiplication.

3. Prognosis

It is in this area that facts are badly needed. In general the morbid anatomy, clinical features, and pathogenesis of the acute and of the chronic (cardiac and gut damage) phases have been well documented. What determines whether an infected person will develop the target organ damage, i.e., disease, is, however, still not clear. Several suggestions have been made.

i. A parasite factor. Different strains may be capable of inducing either a mild, relatively undestructive infection retained for life without ill effects or highly pathogenic infections, both acute and chronic.

ii. A host factor, depending on either the amount of parasympathetic ganglion cell destruction in the acute phase or on the degree to which the host can suppress the parasite activity and subsequent tissue multiplication.

These are only hypotheses with little to support them. Longitudinal studies of the evolution of Chagas' disease in man are vital if it is to be possible to make any predictions regarding the prognosis in an infected person. Such longitudinal studies, particularly those now under way in Bambui and São Felipe, need considerable logistic support.

4. Diagnosis

This is easy in the acute phase since trypanosomes are then numerous in the blood, can be recognized in blood films, and can easily be isolated by mouse inoculation, culture, or by xenodiagnosis. The complement-fixation test and the indirect fluorescent antibody test do not become positive for about a month, but though seldom used, the Muniz precipitin test is positive in the acute phase. A lymphocytosis is often present. In the latent or indeterminate phase, diagnosis depends on reliable serology, or a xenodiagnosis.

i. Serology. This is the basis of most surveys for the prevalence of human infection, and the CFT is mainly used. A standard antigen has recently become available and the method of José Oliveira de Almeida is widely regarded as reliable. Unhappily, few of the studies in the past met current criteria and the CFT is a relatively complex and lengthy procedure. IFA and the indirect haemagglutination test both have the advantage over CFT of being possible on dried filter paper blood specimens. Further comparative studies of these tests are necessary with the standard CFT before they can be used alone. At the moment, ideally all three tests should be done.

ii. Xenodiagnosis. This is also usually an unstandardized procedure which uses variable numbers and various species and instars of bugs examined in varying ways. The method is sensitive because of the

general high susceptibility of bugs to infection with T. cruzi. A positive result is irrefutable evidence of infection, but the significance of a positive result in relation to the development of subsequent disease is not known.

C. Distribution of T. cruzi Infection and of Chagas' Disease in Man

Any sensible planning of Chagas' disease research or control programmes must depend on a knowledge of the geographic distribution, prevalence, and annual incidence of a number of indicators of human infection and disease. This information is required: (1) to assess the extent and public health importance of the infection and of related disease syndromes; (2) to identify areas of ignorance which might profitably be remedied by research; and (3) to serve as a baseline for the planning and evaluation of control measures and subsequent surveillance operations.

The best available account of the distribution of infection and disease in Brazil is given in Doença de Chagas, edited by J. R. Cançado, but it is not yet possible to obtain a clear picture of the importance of the infection in the country as a whole. A determined effort should therefore be made to collect information on the distribution, prevalence, and incidence of the infection and the disease as one of the major first steps in developing a research programme into Chagas' disease. The study should cover both its incidence and prevalence.

1. Incidence studies

These could most rapidly be carried out through a national system for the reporting and registration of the first occurrence of infection or disease recognized in areas not known to be infected, as follows: (1) detection for the first time in any place of positive serologic tests of Chagas' infection; (2) detection of T. cruzi in man for the first time in any place; and (3) deaths from Chagas' disease detected at post-mortem examination for the first time in any place.

Reports could be made on a standard form that would require a tick only against the categories above and otherwise list only name, age, sex, and address. Reporting in new areas should be followed up by an epidemiologic investigation to confirm and evaluate the situation in the area, perhaps by SUCAM or INERU.

Such a system would of course present difficulties and the information collected would have numerous defects. Nevertheless, despite the incompleteness and inaccuracies in reporting, valuable information could be obtained and put to practical use. We would have liked to recommend a comprehensive reporting scheme backed by legislation, rewards, and penalties, but have concluded that this would not at present be practicable. Only such measures, however, would enable the annual incidence of T. cruzi infections and Chagas' disease in Brazil to be accurately estimated.

2. Prevalence studies

In addition to the recording of new infections and of deaths described above, it is necessary to know the current prevalence of T. cruzi infections and Chagas' disease. Prevalence studies could be completed fairly quickly if sufficient priority was given to them. They should consist of a random choice of some 10 percent of municipios within states known to be affected. From the 1970 census (some up-dating process might be needed because of population movement) a random choice of households could be made, and the following procedures carried out on all members of the selected households: (1) IFA test on filter paper blood samples, and (2) the electrocardiographic four-lead technique using only four or five criteria as evidence of Chagas' cardiomyopathy. This could be done in two stages if desirable, (2) being applied by a better qualified investigator on people found positive in (1).

Such prevalence studies would provide an ideal opportunity for assistance by foreign workers with experience of field research. The studies should of course be correlated with entomologic investigations of transmission potential and possibly with animal host studies.

The studies proposed would involve the examination of perhaps 20,000 people and could probably be completed in two years at a cost of less than Cr$2,000,000.

D. Chemoprophylaxis and Chemotherapy

1. Chemoprophylaxis

No drug is yet known that has any value whatsoever for prophylaxis against naturally transmitted T. cruzi infection in man or even in animal models. Gentian violet is used in some centres as an addition to stored blood in blood banks to minimize the risk of transmitting T. cruzi infection.

2. Chemotherapy

i. Antiparasitic drugs. Two phases of T. cruzi infection have to be considered: (1) the circulating trypomastigote forms which occur both during the initial acute infection and subsequently as spillovers from tissue forms during chronic infection, and (2) the amastigote tissue forms which are responsible for both the acute myocarditis and other pathologic manifestations of the acute stage of Chagas' disease and probably also for progressive tissue destruction in chronic infections.

Two classes of drugs are known to exert a parasiticidal action on the trypomastigotes in man: 8-aminoquinolines and nitrofurans. Only the latter appear, however, to destroy the amastigote forms.

(a) 8-aminoquinolines. Neither of the two compounds of this class so far tested in clinical trials in Brazil and elsewhere has proved capable of clearing parasitaemia at a nontoxic dosage. WIN 5037 was examined by Prof. Durval T. de Lucena (Recife) in six patients, but results were unsatisfactory and the compound, originally studied as an antimalarial, was dropped by the manufacturers (Winthrop).

A Wellcome 8-aminoquinoline was claimed by workers in Panama (e.g., Dr. Karl Johnson) to be curative, but clinical trials in Brazil (e.g., by Prof. J. Romeu Cançado of Belo Horizonte and Dr. Vanize Macêdo of Bahia) failed to confirm this. It proved toxic in a number of patients who remained xenodiagnostically positive and has been withdrawn by the manufacturers.

(b) Nitrofurans and related compounds. Several older nitrofuran derivatives have received clinical trial in Brazil and elsewhere. These studies were reviewed in an earlier report to PAHO (RES 4/10, 1965). While apparently exerting a trypanocidal action against T. cruzi if given in prolonged dosage, these compounds were poorly tolerated by the patients. Moreover, they failed to exert any significant action on the tissue forms and the cure rate was therefore minimal.

A new Bayer compound, nifurtimox (LAMPIT: Bayer 2502) is currently undergoing extensive clinical trials in a number of countries including Brazil. The response to this drug appears to vary according to geographic location. In Argentina and Chile it is claimed to cure a high proportion of patients treated either in the acute or chronic phase of infection. Results in Brazil have so far been less encouraging. Side effects are common and, at a recent CIBA symposium held in Caracas, the opinion was expressed that the treatment was worse than the ailment in patients with chronic Chagas' disease. In Belo Horizonte, Prof. Cançado initially reported poor results with doses of 25 mg/kg/day, a dosage that failed to produce xenonegativity and was toxic. He is now making a carefully controlled hospital trial using about 10 mg/kg/day to a total of 600 mg/kg. At this dosage several patients became xenonegative, but some have again become xeno-positive three months after the end of treatment. Side effects include nausea, digestive disturbances, weight loss, and polyneuritis. Psychosis sometimes develops. The only valid criterion of cure appears to be consistent negative xenodiagnosis.

The significance of this result becomes greater the more tests are done. Neither complement-fixing antibody levels nor IFA titres appear to be reliable indicators of response to treatment, but the significance of such serologic tests and their value as indicators of active T. cruzi infection in man appear to be poorly understood.

Dr. Sonia Andrade (Bahia) finds that nifurtimox is effective in clearing parasitaemia in acute infections but is unsatisfactory in patients with chronic infections. She believes that these are likely to be differences in drug response related to infection with different T. cruzi strains, a view supported by experimental studies in the United States. Dr. S. Andrade has shown in mice that combined therapy with nifurtimox plus dexamethasone leads to a decrease of myocardial infiltration, and hence decreased muscle loss, in animals infected with the virulent Y strain of T. cruzi. Dr. Vanize Macêdo has given two acutely infected patients this combined therapy; after three months one has become xenonegative, but the other remains xenopositive. The addition of an anti-inflammatory agent to the therapeutic regimen in patients with severe myocarditis or meningoencephalitis may be of value.

Dr. Vanize Macêdo (Bahia) has treated some patients with nifurtimox in the acute phase with some success, but she does not appear enthusiastic about the compound. Prof. Aluizio Rosa Prata reports that 70 percent of his patients became xenopositive during a one-year follow-up.

(c) New drugs. Roche has a new compound (Ro 7-1051) that is in the preliminary stages of clinical trial. Dr. Vanize Macedo has preliminary data on two acutely infected patients; initially they were to receive 10 mg/kg/day for 28 days, but Roche now recommends 8 mg/kg/day for eight weeks. So far the drug has been well tolerated. The first patient treated was xenopositive two months after commencing therapy but both patients show marked clinical improvement. This compound will also be tested by Prof. Cançado and Dr. S. Andrade. Promising preliminary results are also reported by Prof. Prata and Prof. Rassi (Goiânia).

ii. Supportive therapy. Apart from the use of appropriate corticosteroids or other anti-inflammatory compounds in association with trypanocidal agents (see 2.i(2) above), supportive therapy is that dictated by such conditions as acute myocarditis or meningo-encephalitis in acutely ill patients, and chronic heart failure and disturbances of gastrointestinal function in those with chronic Chagas' disease.

E. Entomology

1. Systematics, geographic distribution, and habits of triatomid species

Identification and distribution of triatomid species in South and Central America and the southern United States have been well studied in conventional terms of morphology and satisfactory keys for identification are available. Triatoma infestans, the principal domestic vector in Chile and Argentina, occurs in Brazil as far north as Goiás State, with some introductions to northeastern states (e.g., Pernambuco), but is now eliminated over much of its range by BHC insecticide control. Rhodnius prolixus, the domestic vector of Colombia and Venezuela, is uncommon in Brazil but T. maculata, a sylvatic species that is increasingly invading houses in Venezuela following successful control of R. prolixus in much of that country, occurs as maculata or pseudomaculata in northeastern and northerly states of Brazil. Panstrongylus megistus is essentially an eastern lowland species and, in areas north of southern Minas Gerais State, is considered domestic; farther south it is considered sylvatic, with a facility for invading houses. The important species in Brazil are T. infestans (domestic and readily controllable by BHC), P. megistus (likewise controllable where domestic, but less so where it is sylvatic and invades houses), and T. brasiliensis, T. maculata (or pseudomaculata), and T. sordida in central and northeastern Brazil, which appear to require fuller study in the field to provide methods for their control other than indefinitely recurring insecticidal treatment of houses. Their efficiency as vectors (including the pathogenicity for man of the sylvatic T. cruzi-like infections which they carry from

wildlife) as well as their competence to maintain human T. cruzi foci, and to become established and breed in houses should be determined.

Development schemes, such as hydroelectric projects, new roads to and into Amazonas, and new human communities along roads in formerly rural or forested terrain should be closely surveyed and monitored for introduction of known vector species or for domestic adaptation of local sylvatic species of potential importance. Such species require studies of their ecology and adaptability to environmental changes. Major factors such as deforestation, improved lighting in new houses and townships, and the spread of triatomids through movements of people and merchandise by road transport must be taken into account. Future research into such problems should be concentrated in well-planned intensive studies of representative situations, rather than statewide surveys of the kind that in past years have laid a foundation of substantial knowledge of the distribution of species, their habits, and the vector role of the commoner domestic, peridomestic, and sylvatic bug species throughout much of Brazil.

2. Control by insecticides

Insecticide spraying (BHC) twice at three- to six-month intervals, the standard control measure, is now highly effective against the domestic species T. infestans, P. megistus, and T. rubrofasciata, but, as has occurred in Venezuela for R. prolixus, insecticide resistance should be considered a probable development. Baseline susceptibility levels of the important Brazilian species must be established by standard WHO methods and spot checks made periodically where control appears unsatisfactory. Close liaison is recommended with the WHO Chagas' Disease Vector Research Unit recently set up in Venezuela, which will particularly study R. prolixus and T. maculata in relation to new insecticides, methods of application (sprays, dusts, ultralow volume spraying), cycles of treatment, susceptibility tests, and evaluation methods. All this is of interest for the range of Brazilian species. Assignment of a Brazilian worker to the Venezuelan unit for a substantial period is recommended.

3. Alternative control methods

No practical alternative to BHC spraying of houses is yet available, apart from improved housing as circumstances and policy by federal or state authorities permit. The following, mainly long-term possibilities should be noted.

i. Hormones. Brazilian workers have made interesting advances in the use of juvenile hormone mimics to prevent normal development of immature bugs into adults. This research is still in the laboratory stage, but with deposits remaining effective for 1-1/2 years on an asbestos-asphalt substrate, it is a promising line of investigation. The effects of juvenile hormone mimics on adult fecundity and on the susceptibility of treated bugs to T. cruzi infection are necessary extensions under investigation in Brazil, and London. Hormone treatment of houses, particularly if restricted by suitable trap/attractant devices, offers a prospect for dealing with continuous invasion by sylvatic species.

ii. Repellents. Proposals being developed in Rio de Janeiro for experiments with repellents in long-lasting deposits are worth pursuing.

iii. Predators and parasites. Theory would require mass releases of hymenopteran egg parasites species of Telenomus to control bug populations, but it would be important to find out first to what extent these Hymenoptera are already present in Brazil. A programme of "baiting" for hymenopteran adults with poisoned honey baits, or exposure of colony-reared Triatoma eggs in bug-infested houses should be tried out as a method for surveying the distribution of hymenopteran egg parasites before concepts of biologic control are elaborated. Intensive laboratory studies are now in progress on hymenopteran egg parasites (T. fariai of the Americas and Cryon spp. from India) in Venezuela and London, but so far as is known not in Brazil at present. Ant and assassin bug predation should also be studied quantitatively

and the possible nature of selective competition between triatomid species sharing domestic environments should be investigated.

iv. Genetic control. The basic disadvantage of genetic control by sterile hybrids, or males sterilised by irradiation or chemicals, is that release of the sterilised insects increases the vector potential of the bug population. The literature indicates that irradiation causes debility and mortality at sterilising doses. Chemosterilants are more successful but dangerous to use, and current Brazilian work on crosses of related species suggests that the hybrid male technique may not be entirely successful; but this line of work is necessarily slow and continuing experimentation is worthwhile. Cytogenetic work on triatomid species and crosses in progress in Brazil and London should be fostered.

4. Triatomid behaviour

This is a much neglected laboratory and field subject. There have been a few field studies in Brazil, Venezuela, and elsewhere on dispersion, flight and walking ranges, attraction to light, and survival in natural populations, including experiments with radioactivity or otherwise marked bugs. Research on these aspects should be encouraged, particularly in relation to sylvatic species that invade human habitations.

5. Sampling of bug populations

This is an important problem because current methods, with or without use of pyrethrum to dislodge bugs, depend on timed or even untimed catching periods of short duration, which may not yield bugs if in low density and do not measure the total bug population in a house. The Domestic Risk Factor* developed at São Felipe is an informative advance. There is much need for trapping devices and for combining them with mark-release-recapture experiments to improve estimation of bug densities

*$\frac{\text{Bugs/man-hour} \times \% \text{ infection rate}}{100}$

in relation to T. cruzi transmission and to assay the effectiveness of insecticidal or other control methods, including even simple improvements in house walls.

6. Susceptibility of triatomids to T. cruzi infection

This should be studied on sound genetic principles. It would be long-term work but might lead to development of a highly susceptible strain of T. infestans or other species generally in use for xenodiagnosis tests. This work has hardly been undertaken except on a limited scale in London and Salvador.

F. Sociologic Aspects of Prophylaxis and Control

1. Present state of knowledge

It is clear that domestic bug infestations are chiefly confined to houses of the simplest construction--mud and wattle walls with palm-thatch roofs--especially those with unplastered walls that are some years old. Improvement of housing standards alone would largely reduce or eliminate dangerous infestations. Reduction of the wall crevice habitat and thus of bug infestations in existing houses can be accomplished with simple mud plaster, especially if a binding agent such as cattle dung is incorporated. The durability of the plaster would largely depend on the clay content of local soils. Application costs are negligible. Some bug species (T. infestans, Rhodnius spp.) inhabit palm roofs; in such houses infestation would be reduced if corrugated iron were used as roofing, but this would increase the cost of roofing considerably.

2. State of present research

No research seems to be in progress but some is contemplated in the State of Bahia, in which householders would be encouraged to improve the condition of their houses on a "do-it-yourself" basis. Raw materials (i.e., cow dung) and their transport would be provided

where necessary. Some form of assessment of the effects of such measures (e.g., a pilot project), giving consideration to their cost plus acceptability, is desirable as a basis for education and promotion of the wider use of such methods if successful.

3. Future priorities

i. Health education. In schools and by simple-posters aimed at adult illiterates, it could be explained in simple visual terms that better houses, especially improved wall surfaces, mean less vermin and hence less disease. Explanatory notices are known to have been issued to rural householders in Minas Gerais and instruction has been given in schools along these lines. Research may be needed into the most effective educational techniques in various situations.

ii. Self-help schemes. Groups of householders should be encouraged, as by SUCAM in Pernambuco State, to cooperate in rebuilding or improving their houses and to clean them and their movable contents of bugs. Insecticides could be supplied by SUCAM and provided at cost through the prefeituras. Groups of householders should be instructed how to: (1) make and apply durable mud plaster to the walls of their houses, and to maintain the walls in good condition, and (2) carry out new construction with mud blocks cast in standard wooden moulds and where possible to replace palm-thatch roofs with corrugated iron. (N.B.: The use of the conventional Roman roof-tile should be discouraged in areas where T. brasiliensis and some other species occur, since these tiles provide a favoured habitat for them.). The possible importance of infected cats, dogs, and other domestic animals in the dissemination of T. cruzi infection should be made clear, as should the role of domestic and peridomestic rodents, opossums, and other mammals.

iii. The role of the domestic chicken in household bug infestations. Work in Venezuela (Gómez Núñez) has shown that chickens are important predators of bugs. Chickens are also an important source of blood meals to bugs, and work in Bahia has shown that two bug

populations, one substantially chicken-supported and the other man-supported, can coexist in the same house. Chickens are insusceptible to infection with T. cruzi and bird-feeding populations of bugs have much lower infection rates than those feeding mainly on man.

Further work is required to decide whether the presence of chickens roosting in houses is beneficial because of bug predation and reduced infection rates in bird-feeding bug populations, or dangerous because chickens may increase the overall bug populations in houses.

G. Organization and Funding of Research on Chagas' Disease in Brazil

1. São Paulo State

São Paulo State is substantially autonomous in terms of research organization and funding and therefore warrants separate treatment.

The majority of research groups work in various departments and institutes of the São Paulo State University, which pays salaries and provides basic facilities. Research support is otherwise chiefly derived from the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) to which the State Government donates approximately 1 percent of the state's gross annual product. Grants are awarded by FAPESP in much the same way as by the Conselho Nacional de Pesquisa (CNPq) elsewhere, but only a relatively small proportion of the available funds are allocated to biomedical research, including Chagas' disease. FAPESP grants, like those of the CNPq, are awarded to individuals or collaborating groups for specific projects and chiefly cover equipment and materials, seldom expendable materials, salaries, or transport. Some, but relatively few, individuals have obtained funds from the CNPq. Some research support is also derived from the pharmaceutical industry.

There is a São Paulo State organization (SUSAM) responsible for control of endemic diseases which parallels the Federal Health Ministry control organization operative elsewhere in Brazil (SUCAM).

So far as is known, SUSAM (and SUCAM) personnel are not engaged in research.

PAHO/WHO resources for research are mainly used to support the PAHO/WHO Immunology Research and Training Centre and the Regional Library of Medicine in São Paulo. These two organizations are important auxiliaries to the development of research in the biomedical sciences in general but neither is specifically connected with research on Chagas' disease. The Regional Library of Medicine (BIREME) has eight regional centres throughout Brazil and provides a largely free service to the regions, mainly in the form of Xerox copies of journal articles. BIREME also receives funds from São Paulo State, the Federal Government, the Commonwealth Fund, and the Kellogg Foundation.

2. Other states of Brazil

i. Research in universities. Most Chagas' disease researchers hold full- or half-time staff appointments in the federal universities in each state except São Paulo. The federal universities are funded directly by the Federal Ministry of Education and Culture and the universities pay staff salaries and provide space and basic facilities for research. University research is financed chiefly by the CNPq in awards to individuals or small groups that mainly provide salary supplements, materials, and equipment, and occasionally salaries for supernumerary staff, travel expenses, and the like. Vehicle purchase is specifically excluded by the CNPq.

CNPq and the Federal Ministry of Planning are about to distribute Cr$10 million for research on Chagas' disease. Awards to scientists recognized by their published work and other information were recommended by a committee in late 1972 at a minimum of Cr$50,000 per scheme over one or two years. Recommendations will be made to the Ministry of Planning by CNPq. During this initial period, research workers will be expected to show useful results as a basis for detailed proposals for extensions of the grants. The grants are expected to be available by mid-1973.

A grant may be used for salaries, equipment, recurring expenses, transport, or fuel, but CNPq is firmly against purchase of vehicles, although the Ministry of Planning is less rigid on this. Throughout the country field studies are severely handicapped or impracticable because of lack of suitable vehicles, except for SUCAM units supplied with transport for survey and control. There must be provision of suitable vehicles to university or other research workers for field programmes, and of fuel allowance when personal cars are used.

The availability of grants should be more widely publicized.

No financing specifically for research is provided to the federal universities by the Federal Ministry of Education and Culture.

Other financial support is obtained by individuals from the pharmaceutical industry foundation (ABIFE) on a small scale. Some workers obtain grants from outside Brazil, chiefly from the United States (the National Institutes of Health, the U.S. Armed Forces, or philanthropic organizations such as the Rockefeller Foundation.

In addition to the federal universities, there is normally a Catholic university or private universities in each state. Since these are not involved in research on Chagas' disease, they are excluded from consideration here.

ii. Research by the Federal Ministry of Health. Research by the Instituto Nacional de Endemias Rurais (INERU) is second in importance to that in the universities: INERU is part of the Federal Health Ministry's Fundação Instituto Oswaldo Cruz (FIOCRUZ), whose headquarters are in Rio de Janeiro. FIOCRUZ has regional branches in Jacarepaguá (Guanabara), Belo Horizonte (Minas Gerais), Salvador (Bahia), Recife (Pernambuco), and Belém (Pará). Research in the INERU centres is chiefly of an applied nature, aimed at improving methods of control that are undertaken by the federal SUCAM organization. Some considerable effort is devoted to pure research also, but usually towards a practical end. Financing of INERU research is limited and largely internal, from the Federal Ministry of Health. Individuals or groups are also eligible to apply for CNPq awards in the normal way.

iii. Research by the state governments. This seems to be relatively rare, except for the Fundação Gonçalo Moniz in Bahia. Funds for research purposes are very limited at this level and recourse is therefore necessary to grants by the CNPq, ABIFE, and sources outside Brazil, e.g., PAHO/WHO, the United States, Great Britain, or France.

iv. Other research support from federal sources. Some federal bodies provide facilities and support for research on a relatively small scale. Among them are the armed services and the Departamento Nacional de Obras Contra as Secas (DNOCS, or National Irrigation Board).

3. General observations

i. In general, financial support for materials and equipment is adequate, support for technicians and junior staff much less so, and that for travel and maintenance purposes very inadequate. It is extremely difficult to find funds to cover the necessities of field research from resources available in Brazil. There is a serious restriction of research activities caused by the nationwide lack of trained technical staff and by the difficulty of obtaining funds for transport, consumables, and general maintenance purposes.

ii. The highest salary scales of research workers are those of the National University at Brasília, followed by those of the federal universities, but by international standards these are mostly very inadequate. Even investigators with senior, full-time appointments in certain federal universities are forced by economic necessity to earn money elsewhere, usually in private medical practice.

The salaries paid by Federal Ministry of Health organizations such as FIOCRUZ or INERU fall far below university levels and are totally inadequate to attract full-time workers. Salaries paid by state-run institutions such as the FGM at Salvador are even lower, and full-time employment of professional workers is economically impossible.

If full value is to be obtained from the human resources available for research in Brazil, a radical revision of salary scales

is imperative, with full parity between workers in universities, other federal organs, and state organizations. Salaries should be raised to a level such that full-time employment would be adequate to support a family without recourse to a supplementary income from work elsewhere.

iii. Outside financial help for research. This is very necessary and would be generally welcomed by Brazilian workers, both in terms of financing and trained senior personnel in most fields except that of clinical medicine. There seems a general lack of awareness of existing possibilities for training, exchange of personnel, and the nature and availability of outside assistance from foreign countries and international organizations. PAHO should help keep Member Governments fully informed about bilateral and international support, and ensure that this information is widely known to workers in the field.

IV. RECOMMENDATIONS

A. The Organism

1. Definition, standardization, and characterization

Comprehensive knowledge of the characteristics and behaviour of strains of T. cruzi and of their relationships with their mammal and insect hosts are basic to the understanding of practically every aspect of Chagas' disease. Relevant studies should, therefore, be supported wherever possible, both in Brazil and elsewhere.

a. Some T. cruzi are difficult to isolate in mice and many strains cause only low parasitaemias. Special attention should be paid to improving methods for enhancing parasitaemia of these strains.

b. Whenever possible, cloned organisms and cryopreserved stabilates should be used.

c. Characterization of trypanosomes by observation of infections in defined strains of laboratory animals, and by immunologic, biochemical, and other methods should be expanded.

2. Immunology

Most work so far has been on humoral antibodies in relation to diagnostic tests.

a. Studies are required to identify which of the antigens of T. cruzi, if any, are immunogens, and which of the antibodies produced against them are protective.

b. Cell-mediated mechanism in T. cruzi infections should receive special attention. Suitable syngeneic lines of laboratory mice should be established for this work and their availability made known.

c. Criteria for the acceptance of T. cruzi antigens for CF and IHA testing should be laid down and standard antigens and control antisera provided. Slide antigens for IFA testing should be standardized. The use of the soluble antigen fluorescent antibody test in T. cruzi infection should be further studied.

3. Vector-parasite relationships

a. Factors deciding the establishment and development of T. cruzi infection in triatomid bugs should be further studied.

b. The vector potential of important bug species should be compared, both for xenodiagnostic and epidemiologic purposes.

4. Development of methods for detecting extremely low parasitaemias of T. cruzi, other than by xenodiagnosis, especially concentration and culture, should be vigorously pursued.

5. The behaviour of defined trypanosome strains in possible domestic and wild animal hosts and in triatomid vectors should be investigated, together with studies of their ecology.

6. The mechanisms of pathogenesis of T. cruzi infection should continue to be studied, especially whether subpatent parasitaemia

infections induced with metacyclic trypanosomes, or repeated infections cause different degrees of organ damage.

Research on the pathogenicity and immunizing capacity of organisms possibly usable as living vaccines should be expanded and include studies on physiology and metabolism. Strains attenuated in culture, culture epimastigote and trypomastigote forms separated by DEAE cellulose fractionation, and kinetoplastid flagellates other than T. cruzi should be investigated. Dogs and primates should be included, as well as mice.

B. The Disease

1. The relative importance of parasympathetic ganglion cell destruction, chronic myositis, and specific damage to the conducting system of the heart should be established. The extent to which the pathology of chronic Chagas' disease results from progressive damage, or from the after-effects of a short acute phase, needs further elucidation.

2. Refinement of diagnostic techniques is essential if the prevalence and importance of human infection and disease are to be assessed.

a. Serology

i. A central reference laboratory for Chagas' disease serology should be established.

ii. Facilities for IFA and IHA testing should be provided and comparative testing encouraged in parallel with a quantitive CFT.

b. Xenodiagnosis. Methods vary widely and much further research is required to standardize them. Meanwhile, the following procedure is recommended: Five, or multiples of five, fifth instar T. infestans, should be examined 25 to 30 days after feeding, by direct microscopical examination of the rectal contents of each bug.

3. Clinical measurements

a. In the field. Further data should be assembled on the prevalence of electrocardiographic changes in infected populations. Continuously recording machines should be used so as to detect intermittent ECG changes.

b. In hospitals

i. The management of ventricular failure and arrhythmias should be further studied.

ii. Studies of the progress of dysfunction in the oesophagus and colon and of the management in different phases should be encouraged.

c. The effects of various associated factors on chronic chagasic cardiomyopathy should be elucidated; e.g., malnutrition, anemia, and alcoholism.

d. The serologic screening of blood donors for T. cruzi antibodies should be enforced and positive reactors excluded.

4. Longitudinal studies of the disease. Two studies (Bambui, São Felipe, see pages 62-63) are already in progress and they should be strengthened. Data analysis should be expedited and personnel augmented to permit extended work. Further carefully designed and executed longitudinal studies should be encouraged elsewhere in Brazil.

C. Distribution of T. cruzi Infection and Chagas' Disease in Man

1. Assessment of the importance of Chagas' disease in Brazil

Existing knowledge should be rapidly supplemented: first by analysis of information already in existence at the Fundação Instituto Oswaldo Cruz, at SUCAM, and in the hands of many individual workers throughout the country; second by introducing a reporting system designed

to identify newly affected endemic areas; third by cross-sectional prevalence surveys in selected localities; and fourth by IFA surveys of suitable populations where the place of residence can be accurately identified, e.g., school children, pregnant women, blood donors, and military and police recruits.

2. Incidence studies

These could most rapidly be obtained by a national system for the reporting and registration of the first occurrence of infection or disease recognized in areas not previously known to be infected, as follows:

a. Detection for the first time in any place of (1) positive serologic tests for Chagas' infection, (2) of T. cruzi in man, or (3) deaths from Chagas' disease detected post mortem.

b. Reporting in new areas should be followed up by an epidemiologic investigation to confirm and evaluate the situation in the area, perhaps by SUCAM or INERU.

3. Cross-sectional prevalence studies

These should be conducted as described in Section III of the main report.

4. Cross-sectional research studies

More detailed cross-sectional studies have already been carried out in defined areas (e.g., see page 14). Similar studies should be performed in situations of contrasting ecology where a different epidemiologic pattern or natural history of the disease process might occur.

5. Epidemiologic surveillance after control operations

Insecticide control of bug populations should be followed by regular serologic testing of the new cohorts born after completion

of control operations. Clearly, only an absence of positive results will indicate interruption of transmission.

D. Chemoprophylaxis and Chemotherapy

1. Experimental chemotherapy

a. No satisfactory drugs are known that will eliminate infection with T. cruzi. The amastigote tissue stages are especially refractory to chemotherapy. A compound effective against these stages could serve as a chemoprophylactic and prevent development of the late stages of Chagas' disease. Every encouragement should therefore be given to pharmaceutical companies, universities, and other organizations to screen compounds for activity against T. cruzi.

b. A more satisfactory screening model for drugs with activity against amastigote, for example the use of tissue culture, should be encouraged.

c. Improved trypanocidal agents for addition to stored blood are needed to prevent transfusion infections. Support should be provided for suitable studies including physical procedures.

d. The results of experimental chemotherapy are difficult to judge in vivo other than by xenodiagnosis. See A4 (page 29) for alternative approaches.

e. Strain differences in drug response may be important. Further investigations should be made of this problem, both with in-vitro and in-vivo models.

2. Parasite biochemistry and physiology

Basic research on these topics is fundamental to the logical (as opposed to empirical) search for new trypanocidal drugs, and should be supported.

3. Clinical trials

a. Further controlled drug-effectiveness trials are required in both acutely and chronically infected patients. These should be multicentred but centrally designed, coordinated and analyzed. Carefully designed sequential trials would probably be most effective and expert statistical advice on them should be sought.

b. Nifurtimox (Bayer) and a new Roche compound (Ro 7-1051) are worthy of more extended clinical trials.

c. The value of supplementary corticosteroid therapy in the treatment of acute cases requires further study in man and animals, perhaps also by trials.

E. Entomology

1. Sylvatic and peridomestic triatomid species

a. Sylvatic and peridomestic triatomid species require fuller field study in central and northeastern Brazil to determine their ability to establish breeding populations in houses, maintain existing human T. cruzi foci or initiate new human foci from sylvatic T. cruzi-like organisms.

b. Well-planned intensive entomological studies should be undertaken of representative situations, rather than statewide surveys, particularly at development projects, such as hydroelectric schemes, and in new human communities in rural or forested terrain, or along new roads.

c. Surveillance should be maintained for extensions of the distribution of domestic T. infestans or other species.

2. Insecticide resistance and control methods

a. Baseline levels of susceptibility to BHC of the important Brazilian species must be established by standard WHO methods, and checks

made for resistance where control appears unsatisfactory. Close liaison is recommended with the WHO Chagas' Disease Vector Research Unit recently set up in Venezuela, including assignment of a Brazilian worker to the Venezuelan unit for a study period.

b. Research on juvenile hormone mimics in long-lasting formulations should continue and field trials be promoted. Repellents for surface application to houses may also be worth pursuing.

c. Natural biologic control by predators of bugs and parasites of bug eggs may be eliminated by standard BHC sprayings. The distribution and biology of such predators and parasites should be determined for representative unsprayed domestic environments to provide basic biological information.

d. Genetic and cytogenetic studies of triatomid species and crosses should be encouraged as an essential basis to assessing prospects for bug control by various sterilization techniques.

3. Sampling for triatomids

There is need for trapping devices to improve estimations of bug densities in relation to domestic transmission of T. cruzi, assay of effectiveness of control measures, and in studies of invasion of houses by sylvatic, or peridomestic species. In the meantime, manual bug collections on a timed basis is recommended to provide the Domestic Risk Factor for each household $\frac{(\text{density of bugs/man-hour} \times \% \text{ infection rate})}{100}$ as an assessment of the comparative risk of infection in different households. (E5, p. 21).

4. Triatomid behaviour. There should be laboratory research, and extension of the new field studies in Brazil and Venezuela, on the behaviour of domiciliated and sylvatic species of bug, with special regard to dispersion and attraction to light, including use of radioactive, or other, marker techniques.

5. Susceptibility of bugs to T. cruzi infection

This long-term work must be based on sound genetic principles. Bug colonies highly susceptible to T. cruzi infection could improve the xenodiagnostic test.

F. Sociologic Aspects of Prophylaxis and Control

1. Reduction of the wall crevice habitat in infested houses by application and periodic maintenance of simple mud plaster with a binding agent (e.g., cattle dung) would largely reduce or eliminate dangerous infestations. Trials should be made to evaluate these measures.

2. Some bug species also inhabit palm-thatch roofs. Infestations would be reduced if corrugated iron were used; Roman roof tiles are less suitable because they provide suitable habitats for T. brasiliensis and other species.

3. Self-help schemes. Groups of householders should be encouraged to cooperate in improving or rebuilding infested houses and to clean them and their movable contents of bugs. Insecticides could be supplied at cost by SUCAM and distributed through the prefeituras.

4. Investigations should be made of the effectiveness, cost, and acceptability of the do-it-yourself house improvements suggested.

5. Brazilian expertise in architecture and building construction should be utilized to develop cheap alternative materials that could be widely used for new construction in rural areas (e.g., cement-stabilized mud blocks).

6. Health education. Health education is required in schools and by simple posters in rural areas to explain that improved house maintenance and hygiene mean fewer bugs and less disease. Research is needed into the most effective educational approach in various situations.

7. The importance of chickens roosting indoors in houses as a factor in reducing, by predation, or in promoting increased bug populations as alternative hosts to man, should be further studied.

8. The role of cats, dogs, domestic and peridomestic rodents, opossums, and other mammals as disseminators of T. cruzi must continue to be assessed.

G. Organization and Funding of Research in Chagas' Disease in Brazil

1. An impartial multidisciplinary national committee with a rotating membership should be set up to coordinate the distribution of funds and the dissemination and exchange of information.

2. It is most important that organizations applying the results of research in the field (e.g., SUCAM, SUSAM, SESP) should be consulted about the allocation of funds for applied research.

3. It is also important that these organizations should be brought into formal liaison with organizations responsible for research and development of buildings and building materials so as to facilitate the economic and effective improvement of housing for bug control.

4. Coordination between control and research organizations should be improved to facilitate information exchange.

5. Salary scales for professional research workers differ widely and are generally inadequate. If full value is to be obtained from the human resources available, a radical salary revision is essential, with full parity between workers in the National University at Brasília, federal universities, and other federal and state agencies. Salaries should be such that full-time employment would be possible without the necessity of obtaining a supplementary income from work elsewhere.

6. Increased training facilities and an adequate career structure are required for technical staff to rectify the present widespread shortage of supporting staff for research.

7. Funds for expendable materials, transport, travel expenses, maintenance, and general running expenses (particularly for field work) are now very difficult or impossible to obtain. It is vital that adequate funds be made available for these purposes. Funds should also be made available so that field training can become a more important element in the training of postgraduates in appropriate disciplines.

8. Foreign help for research (finance and personnel)

a. This is desirable and would be generally welcomed by Brazilian workers. In general, assistance for research would best be provided by supplying expertise in additional disciplines to multidisciplinary Brazilian teams engaged on comprehensive and well-designed studies. The help can be both by seconding workers to Brazil and by undertaking complementary laboratory research in foreign countries. Means for enlisting international collaboration should be known at ministerial level and disseminated widely to workers on Chagas' disease.

b. Fellowships should be provided in all relevant disciplines for the overseas training of carefully selected professional and technical workers with appropriate experience.

H. Recommendations to the Pan American Health Organization

1. The Organization should appoint an independent, high-level, multidisciplinary coordinating committee for Chagas' disease research to assist in the implementation of the recommendations contained in this Report. The coordinating committee, or its constituted subcommittees, should advise PAHO on matters such as training of personnel, standardization of diagnostic materials and procedures, designation of centres of excellence for the study of different aspects of Chagas' disease, testing of therapeutic agents of promise, and the strengthening of communications among scientific personnel working in this field.

2. The PAHO Regional Library of Medicine (BIREME) should include Chagas' disease in its programme for the dissemination of selected information. Efforts should be made to acquaint all potential users with the services that the Library provides.

ANNEX 1

Itinerary of the Research Advisory Group on Chagas' Disease in Brazil

Rio de Janeiro	6 - 8	May
São Paulo	8 - 10	May
Campinas	10	May
Ribeirão Preto	10 - 12	May
São Paulo	12 - 13	May
Belo Horizonte	13 - 16	May
Rio de Janeiro	16 - 17	May
Salvador	17 - 21	May
Fortaleza	21 - 23	May
Recife	23 - 25	May
Rio de Janeiro	25 - 28	May
Brasilia	28 - 30	May
Goiania	30	May
Brasilia	1	June

ANNEX 2

INDIVIDUAL REPORTS

RIO DE JANEIRO

7 May 1973

The Ministry of Health, the Oswaldo Cruz Institute, the Carlos Chagas Pavilion, the FIOCRUZ Research Center for Rural Endemic Diseases, and the Marine Research Institute received the visit of the team.

I. Ministry of Health

Courtesy calls were paid to Dr. Nelson Moraes, Deputy Minister of Health; Dr. E. Mota, Director SUCAM; and Dr. C. Arcoverde, in charge Chagas' disease control, SUCAM.

Dr. C. Arcoverde

Dr. Arcoverde described the general situation with regard to Chagas' disease, bug distribution, and control measures in Brazil as a whole. Of the 3,951 Municipios in Brazil, 1,760 have been surveyed and 1,238 of these have been found infested with triatomid bugs. The main vectors are Triatoma infestans in the south, Panstrongylus megistus in coastal and central territory, and T. brasiliensis, T. pseudomaculata, and T. sordida centrally or in the dry northeast. Areas for control are selected on the basis of three criteria: socioeconomic importance, proportion of bug-infested houses, and serological surveys. The control involves, a general survey, a house-to-house search of bugs using pyrethrum, and the treatment of infested houses with 30 percent benzene hexachloride (BHC) and 1 percent pyrethrum. A second survey follows. Because of limitations in funds, control is sporadic and frequently interrupted.

SUCAM is responsible for control over the whole of Brazil with the exception of the São Paulo State, which exercises its own control through SUSAM. São Paulo State has special problems, particularly of immigration from poorer areas of Brazil; at present approximately 600,000 persons per year enter the State and about 200,000 of them go to São Paulo City.

In general, it is believed that the main transmission of the disease is domiciliary and the human infection from sylvatic cycles is unimportant. Transmission of Chagas' disease by the transfusion of infected blood, however, is important.

II. Oswaldo Cruz Institute

Discussions were held with Dr. H. A. Penna, Acting Director of the Institute, Dr. G. Nobrega, Director of the Institute's Evandro Chagas Hospital, and Drs. G. Teixeira (Pathologist), N. Rodrigues (Cardiologist), and J. C. P. Dias (Epidemiologist).

In the same compound as the main building of the Institute, which is now given over to administrative, library, and museum functions, are the Evandro Chagas Hospital and separate buildings housing the Departments of Microbiology, Pathology, and Medical Zoology, and a yellow fever vaccine production unit. The Institute has also a field research station in Minas Gerais, west of Belo Horizonte.

Of most interest from the point of view of Chagas' disease was the longitudinal study of the disease conducted in Bambui, Minas Gerais State by Dr. J. C. P. Dias. This study, begun in 1943 by Dr. Emmanuel Dias, suffered occasional lapses but is now again in progress. Selected clinical cases from Bambui are transferred to the Evandro Chagas Hospital in Rio for study by Dr. Nobrega. For information about the Bambui study area, see section on Belo Horizonte.

The Institute is regarded as SUCAM's base laboratory and various other laboratories are affiliated to it, such as the laboratories of Dr. Alina P. Szumlewicz at Guanabara. The Institute could, clearly, be developed as a center for gathering basic epidemiologic data on the distribution and significance of Chagas' disease in Brazil. The organization of the Institute is said to be currently under review by a small team appointed by the Ministry of Health, headed by Dr. J. Coura, and including an economist. The Institute deserves support, particularly for the function of gathering information about the distribution of Chagas' disease in the field, as well as in the Bambui survey.

III. Carlos Chagas Pavilion

This hospital's staff includes, Dr. José Rodrigues Coura, Professor of Tropical and Infectious Diseases at the Federal University of Rio de Janeiro, Dr. Walter Petana, recipient of a research grant from the Overseas Development Administration to work with Dr. Coura, and Dr. Fernando Peres, a mammalogist at the National Museum in Rio de Janeiro.

Dr. Coura's Unit in this small hospital in the centre of Rio de Janeiro counts 26 beds and 100 outpatients per day. It provides a routine parasitological diagnostic service and has in addition two research laboratories, one for Chagas' disease and one for schistosomiasis. The hospital will be transferred next year to the main university campus.

Dr. Petana set up an immunofluorescence diagnostic facility for T. cruzi infection, with a capacity of 100 sera per day. He has done some research on the course of the parasitaemia and on the mortality in mice infected with various strains of T. cruzi isolated by xenodiagnosis in the Rio area. Dr. Petana is studying the pathology of these infections in collaboration with Dr. F. Köberle of Ribeirão Preto. Field work is proposed at Iguatama and Pains in the Minas Gerais State, but implementation is difficult because of transportation difficulties.

Dr. Peres collaborates with Dr. Petana for mammal taxonomy and ecological aspects.

Additional support for the development of the field project is recommended.

IV. FIOCRUZ Research Center for Rural Endemic Diseases (Jacarepaguá, Guanabara)

Dr. Alina Perlowagora-Szumlewicz is head of the Laboratory of Insect Biology and Control. She, with the assistance of Dr. M. Figueiredo and several technicians is responsible for breeding species of triatomid bugs. She is engaged in:

(a) Genetic studies on triatomid bugs including cross-mating to determine taxonomic relationships and the possibility of creating sterile

hybrid males for use in genetic control; and the mechanisms of insemination.

(b) A study of the effects of juvenile hormone mimics, in collaboration with Dr. B. Gilbert of the Marine Research Institute. One compound, incorporated in asbestos-asphalt substrate, is still effective after 18 months and induces supernumerary instar larvae instead of fertile adult bugs.

(c) Biologic studies on the dynamics of triatomid reproduction.

(d) Studies on attractants and repellents, also in collaboration with Dr. Gilbert.

(e) The supply of bugs for xenodiagnosis.

Fundamentally all this work is slow, as bug-life cycles last many months. Good progress is being made, however, in many fundamental aspects of bug biology and the group deserves enlarged financial support for the addition of at least one full-time graduate scientist to follow up particularly interesting lines. The group, also, is somewhat isolated at Jacarepaguá and would benefit from a more central position in Rio, both as regards library and laboratory facilities.

V. Marine Research Institute

Dr. Benjamin Gilbert, an English biochemist, is a resident scientist who also holds a university appointment at the Faculty of Pharmacy of the Federal University of Rio de Janeiro. He is developing research on juvenile hormones as a possible method in the control of triatomid bugs. He provides juvenile hormone mimics, obtained from the United States and Europe, in asphalt-asbestos substrate for trial against the triatomids by Dr. Alina P. Szumlewicz at FIOCRUZ, Jacarepaguá, and also by Dr. de A. Salgado of FIOCRUZ (SUCAM), Belo Horizonte, Minas Gerais. He is helped by Dr. Carl Castleton, primarily a field officer engaged in field trials of molluscicides, who will assist in the future with juvenile hormone mimic tests for the control of triatomids.

This work and the assays by Drs. Alina P. Szumlewicz and Salgado, deserve support as the method used seems now promising and preferable to those for control involving releases of bugs sterilized by chemicals, or by other means.

STATE OF SÃO PAULO

9-10 May 1973

I. University of São Paulo's Institute of Tropical Medicine

A. Professor Carlos da Silva Lacaz

Professor Lacaz described the history of the Institute. It was founded in 1969. It has four chairs--of Microbiology, Parasitology, Tropical Medicine with Dermatology, and Preventive Medicine. The Institute runs an intensive course in tropical medicine, accepting each year 25 physicians from all parts of Latin America. It is the place of publication of the Revista do Instituto de Medicina Tropical de São Paulo.

B. Dr. Mario Camargo

Dr. Camargo is in charge (part-time) of the Immunology Section of the Institute which comprises two physicians, three biochemists, and eight technicians. The unit is concerned with the development of serological methods for the diagnosis of Trypanosoma cruzi and other infections, particular attention being paid to methods that do not require complex laboratory facilities. An indirect IFA test is promising; work is going on on the bentonite and latex flocculation tests and also on modifications of the IFA and IHA tests. These modifications are being tried out in a longitudinal study of two groups of 100 individuals, one group with positive, the other with negative, CFA tests.

The Immunology Section has financial problems - capital funds are comparatively easy to come by, recurrent funds more difficult; technician's salaries are low and no proper career structure exists so that the work is done by part-time students earning "pin-money", who are therefore transitory.

This group, despite its rather precarious technical support, appears to be active and original, and deserves more stable support.

C. Dr. Judith Kloetzel

Dr. Kloetzel studies the immunologic differences between epi- and trypomastigote forms of T. cruzi, and between different strains, mainly in culture forms. She is interested also in the mechanisms of resistance to T. cruzi, studying the reactions of macrophages in culture to the different forms of T. cruzi.

D. Dr. Regina Milder

Dr. Milder is an electron microscopist interested in the structure and cytochemistry of T. cruzi amastigotes in tissue cells. She is particularly interested in the amastigote-host cell interrelation--the vacuolation or nonvacuolation of the cell in response to invasion and the membrane structures intervening.

Both Dr. Kloetzel and Dr. Milder represented that they had great difficulty in procuring funds for their work. Technical help was minimal. These lines of work are important and should be supported, particularly for increased collaboration with the workers in the Immunology Unit.

II. University of São Paulo's School of Hygiene and Public Health

A. Professor O. P. Forattini

Professor O. P. Forattini, a full-time professor at the University, is well-respected for his books on medical entomology, Vol. 5 on triatomid bugs being at present in preparation. He maintains colonies of about 38 species of triatomid bug, working out life-cycle data for several of the species. From a series of some 1,400 xeno-diagnostic tests for T. cruzi infections in domestic and wild rodents, marsupials and other small mammals of São Paulo State, he identified the opossum (Didelphis azarae) as deserving further study as a reservoir host of infection; some domestic rats were also positive for T. cruzi. Of particular interest are his field experiments in three different terrains of São Paulo State. He studied the migration, by flight and walking, of adult and larval bugs (Triatoma sordida, T. arthur-neivei,

and Panstrongylus megistus) using chicken-baited traps, artificial shelters, and marked bugs in their natural environment. He is now also interested in investigating betalights as an attractant for trapping bugs. The field work was supported over 3 years by a U. S. Army research, but this was not renewed in June 1972.

Support is recommended from Brazilian funds to enable his field research to be resumed.

III. Paulista School of Medicina's Department of Parasitology

Dr. E. Camargo

Dr. Camargo is essentially a protozoologist interested in morphology, taxonomy, and life cycles. He has only recently come to São Paulo, after 5 years in the University of Wisconsin working on Blastocladiella spp. He is interested in the development of chemically defined media for the culture of T. cruzi, and in the use of DEAE cellulose columns for the separation of different forms of the organism. Dr. Camargo emphasized the desirability of more frequent contact among workers on Chagas' disease in Brazil

Dr. Camargo deserves support so as to allow an opportunity for the planning of ideas and techniques derived from his work with Blastocladiella in experimentation with T. cruzi.

IV. Department of Biochemistry of the University of São Paulo's Institute of Sciences

Dr. J. Fernandes Ferreira

Dr. Ferreira is experimenting with vaccines of T. cruzi culture forms attenuated by long-term culture in the presence of Actinomycin D. The challenge is by a virulent strain maintained by serial passage in mice. He has worked also with irradiated vaccines, and on the factors inducing transformation in T. cruzi.

As this work is going on in a highly developed Biochemistry Department, it offers particularly favourable opportunities for the expansion of study in that direction and so it should be supported.

V. PAHO/WHO Immunology Research and Training Centre at the Butantan Institute

Drs. Otto Bier and I. Mota

Dr. Mota, the present Head of the Centre is interested in delayed hypersensitivity and in the immunology of snake venoms. The staff consists of Dr. Mota, two biologists, a technician, a secretary, and a janitor. Teaching is mainly by visiting immunologists of high standing who come for a period of some 3 months to run the course and conduct the examination. The Centre is supported by an annual grant from PAHO/WHO. Some students stay on after the course to extend their training and carry out research projects. The course is specifically one on the fundamentals of immunology and the Institute has no special interest in Chagas' disease. However, it is a first-class institution with obvious "back-up" possibilities for the training of researchers on Chagas' disease immunology. It should be supported.

VI. PAHO Regional Library of Medicine (RLM)

Professor Amador Neghme

This institution is supported by a wide range of donors - governments, foundations, and international organizations. It provides a complete library service to the whole of Latin America including xerox copying and mailing of articles and will complete on request bibliographies on particular subjects, using an Olivetti computer terminal, linked to the MEDLINE computer at the USNLM by satellite.

The resources of RLM are excellent and do not require supplementation. The library obviously fulfils a very great role in medical research in Latin America.

CAMPINAS

10 May 1973

Department of Microbiology and Immunology
of the University of Campinas

Professor Umberto Rangel

A new and rapidly developing institution. Prof. Rangel is still in temporary accommodation, but his department will be completed next year. Staff salaries are paid from university funds; other support is adequate and comes from CNPq, CAPES, and FAPESP.

Prof. Umberto Rangel has special interests in Chagas' disease and schistosomiasis. He teaches a 2-year course in immunology with an accent on immunochemistry for students from Brazil, Chile, Argentina, and Uruguay. Prof. Rangel qualified in Salvador (Bahia) and took an immunology course at the Butantan Institute in São Paulo. His main work on Chagas' disease comprises characterization of strains of T. cruzi; separation of epimastigotes and trypomastigotes; agglutination analysis and DEAE cellulose separation; and characterization of T. cruzi surface antigens by separation of macromolecules (lipid-protein-carbohydrate).

Patients with Chagas' disease are available for study in Campinas, in collaboration with Prof. Silvio Carvalhal, of the Department of Clinical Pathology. There is no local transmission of the infection.

Prof. Rangel needs more young staff, teachers from overseas (especially someone who could set up cryopreservation techniques), and less rigidity in finance.

This is a new department of considerable potential.

Prof. Rangel is energetic and dynamic and is very worthy of a long-term support.

RIBEIRÃO PRETO

11-12 May 1973

Visits were paid to the Ribeirão Preto School of Medicine of the University of São Paulo, which is administered and financed by the São Paulo State.

I. Department of Pathology

It provides a morbid anatomy and histology service to hospitals in Ribeirão Preto. The quality of research has been very high but is now almost at a standstill because of the lack of funds for equipment and material. Staff is more than adequate in numbers and quality.

The work is mainly in morbid anatomy and histology but there has been no real advance since the study by Köberle, F. (Adv Parasitol 6:63, 1968).

A. Professor Fritz Köberle

Köberle's work is irrefutable as far as observation goes; his hypotheses on (1) the importance of ganglion destruction only in the acute phase of Chagas' disease; and (2) on the production of a neurotoxin are more controversial. The department has a wealth of material and should be kept active in Chagas' disease at all costs.

B. Dr. João Oliveira

Dr. Oliveira is a master of his subject, and has original ideas. He would be well-worth supporting, but must not be allowed to become isolated.

There is little cooperation with other institutions, and it would be profitable for Dr. Oliveira to receive support to collaborate with Dr. Dalmo S. Amorim (see below) in testing Köberle's hypotheses.

Foreign participation is said to be welcome and possible.

There is a mass of material for an unbiased pathologist to study, and this would be worthwhile if only to remove the doubts that exist in Brazil about some of Köberle's observations.

II. Department of Microbiology, Parasitology, and Immunology

A. Dr. J. O. de Almeida

Dr. Almeida's work falls into three main sections, financed both by grants from the University of São Paulo and PAHO.

1) Refinement of the CFT for Chagas' disease, production of standardized antigen, and provision of facilities for diagnosis and checking of serologic results obtained in other laboratories. Dr. Almeida says he offers this facility to anyone in Latin America. The CFT antigen used, and details of his semiquantified technique are given by Almeida, J. O. (In: Doença de Chagas, J. R. Cançado (ed.), Belo Horizonte 1968, pp. 279 et seq.).

Dr. Almeida's main research advance since his paper is the preparation of a standardized antigen for Chagas' CFT. Details on this antigen will be published in a PAHO document in July 1973.

2) Preparation of a lyophilized standardized antiserum, for reference checking of Chagas' serology. Basically, a pool of strongly positive sera was prepared from specimens collected from all over Latin America, adjusted by Almeida to give a standard CFT result with his antigen, lyophilized, and stored in ampoules in appropriate aliquots at -20°C. These are supplied on request to diagnostic or epidemiological laboratories, at the rate of 15 per month. Approximately 6,000 ampoules remain.

3) IFA tests for Chagas' disease, using dried filter-paper samples. The demonstration of this looked very good, and the techniques and equipment are excellent, but the group was unhappy about the use of culture epimastigotes as the slide antigen.

Almeida reported that cooperation was excellent. He is keen on providing a service to the whole of Latin America. Foreign participation

is probably not necessary. Almeida says he has enough money and equipment and nearly enough technicians.

This department impressed the group. It appeared to be the best potential serologic reference centre for large-scale field investigations of the prevalence of Chagas' infection.

B. Dr. A. F. de Siqueira (Head of the Parasitology Section of Dr. Almeida's department)

Dr. Siqueira has three main lines of work:

1) He claims a 100 percent isolation of T. cruzi from xenopositive patients by repeated culture of multiple blood samples on Warren's medium.

2) He claims a 90 percent recovery of T. cruzi from xenopositive individuals using a single concentration technique.

3) He claims that the average T. cruzi blood level in chronic cases is 20,000 parasites per ml.

Clearly these techniques could be important epidemiologic tools, and this work must be supported, repeated, and followed-up.

C. Dr. José da Rocha Cavalheiro (Under Prof. A. F. de Siqueira)

His main work is testing insecticide susceptibility levels of colonized T. infestans on WHO standard papers. His main interest is to conduct an epidemiologic survey of health standards in the Ribeirão Preto area of São Paulo State. He will start with a health survey of family groups in Ribeirão Preto, on a pilot scale, later to be extended to 50,000 houses in 5 pilot areas in São Paulo. The scheme is funded by the São Paulo State Health Department at £33,000 for each of the first 2 years, and may be extended up to 5 years.

The survey group consists of 15 persons, including clerical and recording assistants, and drivers.

D. Dr. M. P. Barreto was not available. Now has other administrative work at the School of Pharmacy and Dentistry, and maintains

limited studies on animal hosts of T. cruzi, using Prof. Siqueira's methods.

Little or no significant laboratory or field entomology is now in progress on bugs although this group has done a great deal in the past on sylvatic bugs and the zoonotic basis of Chagas' disease.

III. Department of Medicine, Clinical Hospital

Dr. Dalmo S. Amorin

Dr. Amorin received NIH grants up to 1968 and is now supported by SESP and CNPq. He took his postgraduate training at the Mayo Clinic and with Prof. K. Somers in Kampala, Uganda. Since 1963 he has tried to obtain evidence in support of Köberle's hypothesis on autonomic nervous system damage. In patients with complement-fixing antibody and a positive ECG, he has studied:

1) The reflex heart rate response to alterations in the circulation by exercise and Valsalva's manoeuvre.

2) Pharmacological tests including:

a) Parasympathetic block by atropine;
b) Sympathetic block by propanolol;
c) Parasympathetic stress;
d) Sympathetic stimulation by amyl nitrite. Responses in these tests were measured by: i) heart rate; ii) blood pressure; iii) blood flow studies.

Dr. Amorin has found a poor correlation of clinical heart disease with evidence of autonomic block, but he has obtained evidence of denervation with a normal heart, and severe heart disease with normal innervation.

This work is potentially of considerable importance. Dr. Amorin should be supported in collaborative studies with Dr. João Oliveira (see above) to conduct combined human investigations with animal experiments, both perhaps, collaborating with a circulatory physiologist.

IV. Department of Genetics

Prof. Humberto Menezes

Dr. Menezes recently worked in the Department of Pathology (Prof. Köberle) but left and transferred to the Department of Genetics following a dispute with colleagues.

The main research topics discussed were:

1) The use of the avirulent PF mutant of T. cruzi Y strain to protect against virulent strains (such as the Y strain itself).

Mice are infected intraperitoneally once only with 500 epimastigotes of the PF strain (from Warren's medium) per gram of body weight. This protects against subsequent challenge with the Y strain. Follow-up is by blood films, survival time, xenodiagnosis. The minimum protective dose for mice is 100 parasites per gram of body weight. Although cultures contain 5 percent trypomastigotes, epimastigotes alone are claimed to protect.

Dr. Menezes has now inoculated himself and one assistant; 1st dose was 50,000; 2nd dose (40 days later) 3×10^7 parasites.

Haematological follow-up and serologic study showed no pathological changes. OHA titre rose from 1:20 to 1:20,000 after 70 days. Three years later, there was no evidence of Chagas' disease.

His next move is to study the effect in marmosets (Callithrix penicilliata), challenging them with a virulent strain. He wanted to immunize the population of one village to test the effectiveness of the "vaccine" in an area of natural transmission but permission was refused. He is now looking for a medium that will grow only epimastigotes.

2) Culture forms of Leptomonas pessoai were also said to protect mice against the Y strain of T. cruzi but up to seven inoculations subcutaneously of 20,000 promastigotes per gram of body weight are needed. This species is cultured at $4^{\circ}C$ in Warren's medium, and the culture (see Z. Brener, Belo Horizonte) is regarded as a mixture of organisms.

Dr. Menezes has been criticized by his colleagues in São Paulo and Ribeirão Preto for prematurely infecting human volunteers. Funds for this work were refused by CNPq and São Paulo State on grounds of the danger involved. The work was paid for by himself and the staff by the University.

This is a potentially very important work that certainly should be followed up only in animal experiments at this stage.

BELO HORIZONTE (MINAS GERAIS)

13-16 May 1973

I. Federal University of Minas Gerais (UFMG)

A. Prof. Zigman Brener (Department of Parasitology)

Now full-time Head of Department, he retains his research facilities at the INERU Research Center "René Rechou", while teaching at the Institute of Biological Sciences. Professor Brener is a leading authority on T. cruzi which he has studied for many years from the points of view of morphology, developmental cycle, cultural characteristics, and chemotherapy. In the last field he has helped to pioneer work both in vivo and in tissue culture on the mode of action of trypanocidal drugs for use against T. cruzi. His current research topics in which he is joined by several research assistants (graduates carrying out M.Sc. projects as well as more senior research workers) are: (1) Studies on T. cruzi cryopreservation techniques; (2) Morphology and behavioural characteristics of geographical variants of T. cruzi (with Dr. Filardi); (3) Protection against T. cruzi by vaccination with "Leptomonas pessoai".

A dynamic and extremely capable research scientist and teacher, Professor Brener is responsible for the organization of the UFMG course for M.Sc. (Parasitology) which is attended by students from many different Brazilian universities. He is a member of the CNPq's advisory group on Chagas' disease.

Further support is recommended for Professor Brener, with particular emphasis on his studies in the fields of cryopreservation and chemotherapy.

B. Dr. Egon Chiari (Department of Parasitology), Prof. G. Gazzinelli, and Dr. A. A. Pereira (Department of Biochemistry)

Dr. Chiari is one of the teaching staff of the Institute of Biological Sciences and a graduate student of Professor Brener. He has

carried out useful work on strain characterization and is now engaged on studies with the avirulent PF strain of T. cruzi. Dr. Chiari works in close collaboration with Professor Gazzinelli and Dr. Pereira of the Department of Biochemistry. Their current projects include: (1) effects of passage of PF strain on its virulence, (2) separation of epimastigotes by use of Sephadex 100 columns; (3) localization of complement-fixing and haemagglutination antigens; (4) amino-acid uptake by cultured epimastigotes; and (5) use of irradiated T. cruzi vaccines. Dr. R. E. Howells (see below) is closely associated with the biochemical aspects of these projects. Dr. Chiari and his biochemical collaborators form an energetic and imaginative group. Their current programme relating to the development of a vaccine against T. cruzi and the related biochemical problems merits further support.

C. Dr. R. E. Howells (Institute of Biological Sciences, seconded from Liverpool School of Tropical Medicine)

Dr. Howells has been seconded to UFMG in order to assist in post-graduate teaching and, in particular, in the development of parasitological research techniques in the Institute of Biological Sciences. In close collaboration with other staff members, his current research projects include: (1) Strain characterization of T. cruzi by isoenzyme analysis; (2) Electron microscopic cytochemical studies on T. cruzi respiration and on the factors controlling transformation from blood to tissue forms; and (3) The nature of T. cruzi surface coat.

Further support is recommended for Dr. Howells whose studies serve a double function, i.e. to investigate specific problems associated with Chagas' disease and to share with Brazilian workers appropriate research techniques.

D. Prof. W. L. Tafuri (pathologist) and Dr. M. Thaisa (electron microscopist)

Professor Tafuri is a histopathologist with much experience in the structure and pathology of the autonomic nervous system. His main

interest in Chagas' disease is in how the organisms damage the structure of the sympathetic and parasympathetic innervation of the heart and the gastrointestinal tract. His histological work is supplemented by ultrastructural studies, assisted by Dr. Thaisa and Dr. Howells, the latter in developing histochemical techniques.

Professor Tafuri has shown, in rodent and human material, that the main gastrointestinal lesion is loss of autonomic neurones through attrition due to destruction by T. cruzi amastigotes of the satellite cells.

In parallel, Dr. Thaisa is studying the ultrastructure of the parasite itself, particularly changes in mitochondrial structure during the life cycle. A Zeiss model 9 electron microscope in the department serves the whole university. Four ultramicrotomes are in use. There is need for a second microscope and more technicians.

This is an excellent group producing sound and important work of practical importance. Like most such workers they suffer badly from lack of funds for consumable supplies and for technical help at the bench, and further support is therefore recommended for Professor Tafuri.

E. Prof. J. R. Cançado (UFMG, Clinical Hospital)

A few years ago Professor Cançado edited a very successful book on Chagas' disease; it is now a standard Portuguese reference work. He has many years of clinical experience on Chagas' and other parasitic diseases. In particular, he has been active in making clinical trials of the few drugs available from time to time for the treatment of Chagas' disease. Five years ago his first report on the use of nifurtimox indicated that it was only temporarily effective in converting patients with the chronic disease from xenopositivity to xenonegativity. He is now making further, well-controlled clinical trials of nifurtimox in a new series of acutely and chronically infected patients at a different dosage level. So far his results are an improvement on the earlier ones, but there are still failures in some cases. Professor Cançado will also examine a new Roche compound (Ro. 7 - 1051) in the near future.

He is a key worker in clinical chemotherapy; most expenses are paid by UFMG and the hospital. Further support is recommended for Professor Cançado's clinical research.

F. Dr. Helio Espinola (Department of Parasitology)

Dr. Espinola completed in 1967 the course for the Diploma in Medical Entomology and Parasitology (DAPE) at the London School of Hygiene and Tropical Medicine. He has now assumed responsibility for the management of the Department of Medical Entomology, with the retiral of Professor Vianna Martins, and has planned accommodation for a new building to be opened in the new UFMG campus in 2 years. He is a young man, keen on research, with publications to his credit on radioactive markers for phlebotomines and mosquito biology. He requires help and direction in both teaching and selection of research programmes from among his numerous ideas. Mr. Paul Williams, an experienced entomologist supplied to UFMG by the Overseas Development Administration, meets this need to some degree although specializing on phlebotomines; Mr. D. Neves of the department staff gives moderate support, on mosquitoes, but he needs further specialized training, such as a course at London or Liverpool.

There is a serious shortage of insectary space, and funds for consumable supplies, technicians, and transport were negligible until some research grants were obtained. Dr. Espinola holds: (1) An award from the National Commission on Nuclear Energy (CNEN) for research on use of radioactive markers for tracing movements of triatomid bugs and their hymenopterous egg parasites; and (2) a CNPq grant (is expected) for biosystematics of the Panstrongylus megistus complex.

There is a good personal contact between Dr. Espinola and Dr. J. C. P. Dias of FIOCRUZ that should help foster these researchers.

While enthusiastic and active, this group would benefit from a more experienced person to direct the research.

II. INERU, Research Center "René Rachou"

Dr. A. de Abreu Salgado

Dr. Salgado at one time headed the SUCAM programme in Belo Horizonte. Numerous triatomid colonies are maintained by him in there "René Rachou" centre. The bugs are used for (1) xenodiagnosis, (2) biological measurement of insecticide levels in mud scrapings from sprayed wall surfaces, (3) tests of juvenile hormone mimics produced in special, long-lasting formulations by Dr. Benjamin Gilbert, of Rio de Janeiro. In this last project Dr. Salgado is assisted by a young U. S. entomologist, Mr. Carl Castleton.

On the whole, Dr. Salgado's work seems satisfactory and the juvenile hormone studies in particular are of potential value.

III. FIOCRUZ, Rio de Janeiro - Bambui Project

In 1943 the late Dr. Emmanuel Dias of the Instituto Oswaldo Cruz Institute, Rio de Janeiro, established the Chagas Disease Research Center at Bambui, some 200 km west of Belo Horizonte in an area highly endemic for Chagas' disease. Together with Dr. Genard Nobrega, the late Dr. Dias established a detailed case history recording system covering a population of about 6,000 seropositive people, of whom some 3,000 still live and can be identified in the study area. A constant medical check has been kept on this population by a devoted group of medical and paramedical workers, now headed by Dr. J. C. P. Dias (see below). Many individual records that include ECG, X-ray, clinical, serological and post-mortem data, have been maintained for 30 years in this valuable longitudinal study.

The area was sprayed with gamma- BHC in two campaigns, 1956-1958, 1963-1964, and a further campaign shortly to be carried out will be accompanied by a detailed 5-year entomogical survey.

Bambui is unique in that this longitudinal study has been carried out for such a long period, with complete collaboration both of the

population and of the 7 medical practitioners resident in the area. Several of the technicians, for example, have devoted the best part of their working lives to the project and know every member of the community better than any village priest or country doctor.

Dr. João Carlos Pinto Dias is a young physician, at present working for his M.Sc. (Parasitology) in Belo Horizonte, on secondment from the Oswaldo Cruz Institute in Rio de Janeiro. He desires and deserves the opportunity to study at a centre where he can become better qualified for epidemiological research. In the analysis of the vast volume of raw data at Bambui he is currently being assisted by a young French doctor on short-term contract to FIOCRUZ, Dr. Emmanuel Forichon. In a preliminary analysis of morbidity data, Dr. Forichon has found significant differences in the mortality by age between individuals: (1) seropositive and seronegative, (2) seropositive with normal or slightly modified ECG changes versus significant ECG abnormalities. He has also detected a significant sex difference, males being more at risk than females.

There is a wealth of invaluable information in the Bambui files but nobody with the appropriate epidemiological training available to analyse it. Since so little is known of the natural history either of cryptic infection with T. cruzi or of clinical Chagas' disease, it is vital that additional skilled help should be supplied, both by the secondment of appropriate Brazilian and/or international staff to Bambui, and by the further training of Brazilian staff in epidemiological data analysis. It may still, even at this late stage, be of value to transfer the bulk of these data to suitably designed computer cards for storage and analysis. This, however, needs careful examination and analysis of a sample. The costs would be considerable. This might be possible in Belo Horizonte, Rio de Janeiro, or Brasilia.

Further support for Dr. Dias and the Bambui project is strongly recommended.

Jequitinhonha Valley Survey

This is a river valley in the north east of Minas Gerais near the Montes Claros community development project (q.v.). The survey was described by Dr. J. C. Dias. It is a rural area with a falling population, now of about 650,000 people. CF-positive rates in children about 10 years old are 1-20 percent in the south end of the country, and 10-15 percent in the middle region. One locality had a 30 percent rate. Some ECG studies were made and 8-20 percent of the population showed abnormalities in a CF-positive group, none in the CF-negative group. Dr. Dias plans to expand this survey (done in 1972) by following up with examinations of the parents and the relatives of the children found CF-positive in the child surveys, conducted through schools.

IV. SUDENE, Montes Claros Project

Dr. J. Pinto Machado

Although Dr. Machado's interests in Chagas' disease are restricted, it is important to note the projected field study to be carried out by SUDENE at Montes Claros. One million people in 42 municipios will be included in a programme of community development supported by AID funds (US$4 million already approved) in association with Tulane University. Dr. Machado is concerned with the integration of the teaching of Community Medicine to undergraduates, into the Montes Claros project, in order to help produce doctors with an interest in the medical problems of rural communities. Here, as elsewhere, most physicians flock to urban centres and, as a result, at least 500 municipios in Brazil do not have a single resident physician.

SALVADOR, STATE OF BAHIA

17-21 May 1973

I. State Secretariat of Health

Dr. Enio R. Pinto, Secretary of Health

Dr. Pinto mentioned that plans were in progress to attempt to integrate the various research programs in Bahia (whether supported by Federal, State, or University sources) under the aegis of the State Secretariat of Health. This appeared to be a much needed reform to improve contact between the various groups undertaking research in Bahia but is still in the final planning stage.

II. Federal University of Bahia and University Hospital

Courtesy visits were paid to Dr. A. Mascarenhas, Vice Rector of the University; the Professor Edgar Santos Hospital (University Hospital); and Drs. Sonia Andrade (Pathology); J. Duarte de Araujo (Preventive Medicine); Celso Pugliese (Preventive Medicine); H. Rocha (Nephrology); A. Guimarães (Cardiology); and Drs. K. E. Mott and J. S. Lehman, PAHO consultants and Wellcome-Harvard Fellows.

A. Prof. Zilton Andrade and Dr. Sonia Andrade

These two scientists have made outstanding contributions to the morbid anatomy and experimental pathology of Chagas' disease, especially in the field of cardiac conduction defects. Their work is internationally known and recognized and warrants further support. Dr. S. Andrade has carried out studies on strain characterization of T. cruzi in mice, based on prepatent period, parasitaemia, mouse mortality, tissue tropisms, and morphology of bloodstream forms. She has found consistent differences between strains from different sources (Y, Colombian, Peru, and 15 strains from São Felipe). Her experimental procedures may be criticized but her work has produced much valuable data. Further characterization studies

on a quantitative basis using better defined materials are clearly important and worthy of support.

Therapeutic studies of LAMPIT (Bayer 2502) have been carried out (largely in mice) with and without cortisone as an anti-inflammatory agent. Long-term chronically infected mice develop a progressive myocarditis. The degree of inflammation is not influenced by repeated inoculations. These findings suggest that in nature, reinfection may not play an important role in the development of cardiomyopathy.

B. Prof. José Duarte de Araujo (Full-time Head), and Dr. Celso Pugliese, Department of Preventive Medicine)

Dr. Araujo and his department run a Health Centre funded by the Kellogg Foundation at Nordeste de Amaralina, a suburb of Salvador, partly as an extension of undergraduate teaching and partly as an exercise in community health care. Dr. Pugliese, who works at this health centre, estimates that he sees 2.6 patients with Chagas' disease per 1,000 in this population.

C. Drs. K. E. Mott and J. S. Lehman (PAHO consultants and Wellcome/Harvard Fellows)

Drs. Mott and Lehman have designed a survey which they regard as not so much an exercise in Chagas' disease epidemiology, but more as an exercise in the methods for population surveys. As both consultants consider themselves clinicians and not epidemiologists, they feel these studies will be beneficial. Basically, some 800 persons, derived from randomly selected households in an area containing 714 houses, will be censused for sex and age. A questionnaire will be completed and followed by testing for T. cruzi antibodies by the complement fixation and IFA tests. A 4-lead ECG (I, II, V_1, V_3) will be examined against 18 criteria selected by Dr. A. Guimarães, a competent cardiologist. Dr. Gumarães considers this will reveal any subclinical cardiac damage due to Chagas' disease. If the model used in Nordeste de Amaralina proves successful, it would later be used in a larger study in Cruz das Almas in cooperation with Prof. José Duarte de Araujo and colleagues (see above), who will have support from the Rockefeller Foundation. Cruz das Almas is a well-

developed commercial centre, disturbed by such indiscriminate spraying of insecticides that the pattern of T. cruzi transmission by P. megistus is scarcely likely to be typical of the area as a whole.

C. Drs. J. Faria (pharmacy graduate) and J. A. Souza Lopes medical graduate, Health Sciences Institute of the Federal University of Bahia.

Drs. Faria and Lopes are full-time staff of the Parasitology Department. Both are interested in research on Chagas' disease and have a joint proposal before the CNPq for an investigation into the aspects of congenital transmission of the disease. Neither man is at present working on Chagas' disease and both carry a heavy teaching load. Their proposed project is intended to test the hypothesis that trans-placental transmission is more common than supposed, in that it usually results in the stillbirth of a macerated foetus rather than a living infected child. The proposal includes the study and characterization of strains with regard to their capacity to cross the placental barrier. The project would be carried out in cooperation with physicians and others at the Salvador Maternity Hospital. The project may have real if minor value, but was badly thought out and is probably beyond the capacity of the workers involved.

D. Prof. Alexandre Leal Costa, Director, Biological Institute of the Federal University of Bahia

Dr. Costa, in the early 1950's, carried out an interesting study of the distribution of T. rubrofasciata and P. megistus in Salvador, and studied their infection, respectively with T. conorhini and T. cruzi. Most of the infected sites then studied have since been destroyed and replaced by new buildings or have been sprayed: probably few bugs, if any, now remain in the city area.

Since 1955 Prof. Costa has been devoting his main attention to taxonomic botany, plant ecology, and teaching. The Institute's staff carries a tremendous teaching load that leaves little or no time for active research. Although many staff members would be interested in

undertaking Chagas' disease research, particularly as it relates to genetics, entomology, and biology of wild animal hosts of T. cruzi, this possibility is very remote, in view of their teaching responsibilities and of the part-time status of many.

Dr. H. Barnett and his staff (University of Maryland) are also housed in the Biological Institute but are not concerned with research on Chagas' disease; their main interests lie in the fields of mosquito and snail genetics and in schistosomiasis.

III. The Gonçalo Moniz Foundation

A. Dr. José F. M. Figueiredo, Part-time Director of the Foundation

Dr. Figueiredo, who is also a lecturer in infectious diseases at the Hospital Prof. Edgar Santos, succeeded Prof. Aluizio Prata at the Foundation. He is not directly involved in Chagas' disease research but continues to facilitate the "São Felipe Project" initiated by Prof. Prata in 1965. The clinical studies in São Felipe are conducted by Dr. Vanice Macêdo (see below).

A group of French workers (Drs. Radovan Borojevic, Daniel Calmus, and Yves Carlier) are studying the immunopathology of schistosomiasis at the Foundation's Brotas Laboratory, in conjunction with Prof. Z. Andrade, of the Federal University of Bahia and a staff member of the Foundation. The immunologic techniques in use by this group can possibly be utilized in research on the immunology of Chagas' disease.

B. Dr. Vanize Macêdo, São Felipe

Dr. Macêdo has treated 50 acute cases, mainly with LAMPIT, and has also conducted a small clinical trial in acute cases with the Wellcome 8-aminoquinoline drug (which was ineffective) and a new Roche compound (Ro 7-1051) showing some promise in the first two cases. Arising from the work of Dr. Sonia Andrade, LAMPIT (Bayer 2502) has been used with cortisone in two patients with beneficial results.

More recently, dogs have been introduced in pairs into houses in São Felipe, one of each pair "immunized" with "Leptomonas pessoai", the other one as a control. Since more than 15 of the 50 animals died within the first few weeks, a conclusive result from this experiment is unlikely.

A nonrandom sample of 5,000 people in the area (roughly half) had a full clinical examination and most had an ECG, serologic tests for Chagas' disease (CFT performed independently at three centres), and xenodiagnosis using five R. prolixus. Barium swallows were also done. The concept of the study was most important, namely that by repeated similar examinations, it would be possible to assess the clinical evolution and prognosis of the cardiac and gut complications associated with T. cruzi infection. The area was divided into three parts: in one area, BHC spraying of houses was carried out twice a year; in another, once a year; and a third area was left unsprayed as a control. Dr. Italo Sherlock of INERU and his staff undertood this spraying and also collected basic epidemiologic data on bug populations in the study households.

Now in 1973, Dr. Macêdo is completing the second clinical survey and it will be possible to analyse certain data, particularly the ECG changes, in relation to the development of disease in infected individuals. The project however, has run into a number of unforseeable difficulties:

(1) A large road passing near the area has probably increased the population movement and over 1,000 of the initial study group have now left the area. (2) Techniques, both in xenodiagnosis and diagnostic serology, have improved since the first study. For example latex and IFA tests have replaced CFT in the second survey. As a result, the serologic data are not comparable between the first and second surveys. There is no doubt however, that much valuable information has been assembled, although it has not yet been analysed. Certainly, the ECG changes seem to be of particular importance. It is proposed to repeat the survey at intervals, as long as the study population remains sufficient in number for significant results to be obtained.

With this large survey concept, and the medical care provided as back up facilities at the "posto", it has been possible to do many smaller studies. An important one has been Dr. Macêdo's group of approximately 50 acute cases treated mainly with LAMPIT, which will be followed up over a period of years.

The visiting team was unable to visit São Felipe, as planned, due to heavy rain.

C. Drs. D. M. Minter, E. Minter-Goedbloed, M. A. Miles, and P. D. Marsden form the expatriate staff of the Chagas' Disease Research Unit within the Gonçalo Moniz Foundation. The local staff includes Sra. Vilma Sherlock, Srta. Solange Carneiro França, Srta. Florimar Silva Correia, and Sra. Annette Lensink (Secretary). The Unit has been carrying out research on the field of epidemiology of Chagas' disease in São Felipe since July 1971.

A cross sectional study was undertaken of 32 individual bug-infested houses. Since Chagas' disease is a household problem, this was thought to be a logical approach. The following information is available:

1. Field work:

   a. House maps, with sleeping position of inmates, and number of domestic animals (cats, dogs, chickens, and others).

   b. P. megistus collections/man/hour, infection rates, and feeding patterns.

   c. Evidence of human infection as shown by serology, xeno-diagnosis, and disease as evidenced by ECG and difficulty in swallowing (Barium swallows performed on patients with a positive history of the latter). The clinical investigation was carried out in cooperation with Dr. Macêdo.

   d. Survey of domestic and wild mammals within and around the houses as regards evidence of infection.

e. Using this information the concept of the Domestic Risk Factor $\frac{(\text{density of bugs per man-hour} \times \text{percentage bugs infected})}{100}$ has been developed and compared with evidence of infection in family members. This factor may have a useful predictive value to assess the risk of future household infections.

f. More than 1,600 P. megistus blood meals were identified by precipitin tests; these showed that the sole domiciliated vector feeds largely on man but also on chickens, and only very occasionally on dogs or other animals.

g. Animal infection rates were 30 percent for cats and rats; 20 percent for house mice; and 9 percent for dogs. Of sylvatic reservoirs, 18 percent of Didelphis azarae were infected.

h. Two nesting sites of wild mammals have been found to contain infested bugs, Rhodnius domesticus and T. tibiomaculata.

i. Three houses have been demolished at São Felipe and total bug collections made. In one house, many bugs were still present 6 months after vacation. It was found that separate bug populations supported by man and by chickens can coexist in the same houses. Infection rates of bird-feeding bugs were one-fifth of that of man-feeding bugs.

j. P. megistus was also frequently found in chicken houses but were not infected.

2. Laboratory studies encompassed:

a. Factors involved in the insusceptibility of chickens to T. cruzi infection.

b. Behaviour of bug, human, and animal T. cruzi strains from São Felipe in mice as regards prepatent period; parasitaemia, and mortality.

c. Natural and induced infections by São Felipe strains in wild animals, especially the opossum, Didelphis azarae.

d. Dynamics of T. cruzi infection in bugs with special reference to seeking improved methods in xenodiagnosis.

e. Serological examinations of animal infections, both natural and induced.

III. Salvador Research Center (INERU)

Dr. Italo A. Sherlock, Part-time Director.

The Research Center has recently moved to new rented premises, since SUCAM now occupies those originally acquired for INERU. Space and facilities available in the new building are strictly limited and it is unfortunate that the Center has been unable to regain its own building from SUCAM. INERU has a staff of eight physicians (only one full time) and two zoologists (one full time). Low pay scales are the cause of staff losses and the reason for the small number of full-time workers.

Dr. Sherlock and his group have participated in the São Felipe project but at present are chiefly concerned with insecticide trials both there (Baygon: propoxur) and at Castro Alves (Malathion). Dr. Sherlock is a competent taxonomist and has carried out interspecific crosses of bugs. He has in press a valuable paper on the distribution of triatomid bugs in the State of Bahia.

The Center does not receive adequate financial or staffing support. There are consequently many gaps in its programme of work, especially in the laboratory study of the effects of insecticides on bugs. It urgently requires a well-trained, full-time biologist to undertake the experimental work at present lacking. The FGM-London based Chagas' Disease Research Unit cooperates closely with Dr. Sherlock, who would also welcome other workers from Britain or elsewhere. Dr. Sherlock and his group deserve further encouragement and support, together with more adequate premises.

FORTALEZA, CEARÁ STATE

22 May 1973

Courtesy visits were paid to Dr. Walter Cantidio, Rector of the University of Ceará, Dr. Walder Sá, Director of the School of Medicine, Dr. Livino Pinheiro, Chief of the Department of Pathology, and to Dr. Julio Rego, Secretary of Health.

The main technical establishments visited were: The Institute of Preventive Medicine (Evandro Chagas Institute), the Julio Pinto Foundation, and the School of Medicine, Federal University of Ceará.

I. Institute of Preventive Medicine

A. Dr. J. E. de Alencar

Dr. Alencar returned to Brazil only about a year ago, after 4 years' absence while on assignment for PAHO, mainly in Mexico. He did not work specifically on Chagas' disease until his return, although he was a distinguished investigator of leishmaniasis in Brazil before 1962.

Dr. Alencar is promoting research on the epidemiology of Chagas' disease in Ceará.

(1) The ecology of the bug and mammal hosts of T. cruzi are being studied particularly at Russas, a hydroelectric dam locality about 150 km inland from Fortaleza. Of particular concern is the invasion of houses by T. brasiliensis and P. megistus which are readily attracted to lights.

(2) Eleven percent dogs and 6 of 25 cats were found by xenodiagnosis to be infected with T. cruzi at Russas.

(3) The pathological aspects of the disease in mice is under study and Dr. Alencar proposes to go on to studies of the disease in dogs in the near future, in which animals sudden death is reported to occur.

(4) CFT positive rates are being studied in 13 municipios in Ceará where the presence of human infection has been established by xenodiagnosis. Rates are positively correlated with age, rising from 20

percent or so in the 0-9 year old group to 60 percent in the group over 60 years of age.

Dr. Alencar is clearly a driving and integrative force in the study of Chagas' disease in Ceará and he, and his associates, deserve support in their endeavours.

B. Dr. Geraldo de Sousa Tomé

Dr. Tomé works also in the Department of Patology and collaborates with Dr. Alencar in the study of the pathogenicity to mice of the strains isolated from wild animals.

C. Dr. Raymundo Vieira Cunha

Dr. Cunha has, since 1970, been carrying out CF tests on sera of people from irrigation areas in Ceará. He records low percentages of positive reaction, the highest being 6 percent of 836 sera tested from Russas. He is a part-time worker.

II. SUCAM

Dr. Anibal Santos

SUCAM is essentially concerned with the control of bug infestation by BHC spraying and is, in addition to Dr. Alencar, a major source of information on the triatomid bugs of the State - their distribution, infection rates with T. cruzi, and the effects of BHC spraying on infestations and on reinvasion. The field work is well planned and documented. Studies, in collaboration with Dr. Alencar, are being made of the ecology of bug and mammal hosts of T. cruzi at Russas.

Although SUCAM is specifically excluded from engaging in research, its collaboration with Dr. Alencar is obviously a very fruitful one and deserves financial support.

III. DNOCS

Dr. F. de Pinho Pessoa Filho

Time did not allow for a visit to Dr. Pinho's site of work but Dr. D. M. Minter in early 1973 visited Morada Nova and was impressed by the possibility there to collaborate with DNOCS in further field studies of the ecology of Chagas' disease. This organization may offer field opportunities in other areas, and should be kept in mind.

In summary, the Institute of Tropical Medicine (Dr. J. de Alencar) together with SUCAM and perhaps DNOCS clearly offers an opportunity for the development of Chagas' disease research in Ceará. The Institute is financed at present almost entirely by university funds with small grants from PAHO and DNOCS. Applications to CNPq are planned at the end of 1973.

RECIFE, STATE OF PERNAMBUCO

23-24 May 1973

Dr. Guillermo Roviralta Cresne, PAHO/WHO, Recife met the group on arrival.

I. Federal University of Pernambuco

A. The University, under the energetic direction of the Rector, Professor Marciolino Lins, is progressively expanding. Development of teaching and research potential is fostered by promoting foreign assistance both in terms of visiting specialists from other countries who participate for considerable periods in the work of University departments and in secondment of Brazilians of high calibre for study overseas, and by attracting talented Brazilians from elsewhere in Brazil. British participation in Chagas' disease research would be welcomed.

B. Professor Ruy João Marques, Department of Tropical Medicine and Infectious Disease, Institute of Tropical Medicine

Of wide experience and interests, Professor Marques ranks Chagas' disease second in importance to schistosomiasis in his medical unit. He is encouraging undergraduates to take particular interest in Chagas' disease, and one of them, Fernando Cavalcanti, is reviewing chemotherapy of Trypanosoma cruzi infections in experimental animals. Dr. Mauro Siqueira, of his resident staff, is studying, by 6-channel polygraph, differences in oesophageal peristaltic waves in Chagasic and other patients, with particular interest in preclinical physiological disturbances. Dr. José Araujo de Carvalho, a pharmacist trained in immunologic methods in Japan, provides part-time serologic service to the Hospital and Institute including CF tests for Chagas' disease. He is experienced and collaborated at the Institute during 1970-72 with visiting Japanese immunologists. Much major Japanese equipment--electrophoresis apparatus, spectrophotometers, fraction collectors, centrifuges, and other apparatus--remains at the Institute and,

although mostly unused at present, is available for future work by staff, or other visiting workers.

This group, under Professor Marques, is well-equipped, active in Chagas' research, and fully deserves support. Professor Marques would welcome arrangements for a young protozoologist-immunologist to be seconded from London to participate in research and teaching.

C. Dr. Durval Lucena, Professor of Parasitology, Department of Tropical Medicine, has contributed substantially over the past years to knowledge of the distribution and biology of triatomid species in domestic environments throughout Pernambuco State. At present he is studying T. cruzi strains from bugs, passaged in mice, and is also interested in evidence for T. rangeli in the State. He is preparing a book on the triatomids of Pernambuco. He recognizes that there is much scope for field work on T. cruzi infections in the wild mammal hosts of sylvatic bugs, and on the biology of sylvatic bug species. Support to encourage research in this area, including funding of transport and research personnel, is recommended.

D. Dr. Ivan Alecrim, Department of Parasitology, collaborates with the Department of Biophysics in preliminary studies on the potentialities of ultrasonicated suspensions of cultured T. cruzi as a vaccine, as assessed in experiments with mice.

E. Dr. Aggeu Magalhães Filho, Department of Pathology, has a staff of 10 pathologists. Chagas' disease is recognized in about 1 percent of the 4,000 post-mortem examinations carried out per year. Dr. Aggeu is primarily interested in schistosomiasis.

II. Aggeu Magalhães Institute, INERU and SUCAM

Dr. James Dobbin of the Institute acted as chief spokesman to the PAHO consultant group of the activities of INERU in the past decade or more. The work consists of surveys of domestic and peridomestic triatomid species existing in Pernambuco, including their infection rates

for T. cruzi, and control programmes by BHC sprayings carried out since 1962 by SUCAM, mainly in the coastal Zona da Mata, where 70 percent of the population lives, but later also in a few inland townships. The Institute appears to work well with the control organization, SUCAM. Dr. Hipolito, of SUCAM, organized a field visit for the PAHO group to Vitoria de Santo Antão, 50 km west of Recife; Dr. Dobbin accompanied the group. BHC applications virtually eradicated Triatoma rubrofasciata in Recife and also domestic Panstrongylus megistus peripherally to the city. Other triatomid species, however, particularly T. brasiliensis and T. pseudomaculata, pose problems for control, as near as Vitoria de Santo Antão because of the recurring invasion of houses from the sylvatic environment, a situation that prevails throughout Pernambuco State and to within 50 to 100 km of the coast. There is a wealth of information in the records of INERU and SUCAM, which further supplements that from Professor Lucena's studies.

INERU also performed CF antibody tests indicating that up to 20 percent of the population had positive reactions in some areas, and proposes to undertake THA and IFA tests using technicians to be trained in Belo Horizonte. Xenodiagnosis tests are carried out.

Dr. Dobbin studied cross-matings of triatomid species to assess systematic relationships (e.g. T. lenti x T. pessoa) and has, jointly with Dr. Andre Furtado, a cytologist at the Institute of Biological Sciences, a project under consideration on the effects of gamma-irradiation on bug fertility.

Pernambuco State offers opportunities for field studies of several sylvatic bug/trypanosome situations in relation to the human population in rural areas, and in development schemes in the hinterland. Field research might be initiated at the SUCAM base at Vitoria de Santo Antão in the first instance, under the guidance of Dr. Dobbin of INERU, in collaboration with the SUCAM staff. There should, however, be a close collaboration also with the university staff interested in the problem in its different aspects, to ensure as comprehensive an understanding as possible of the significance of rural Chagas' disease in the territory. A scheme based on this pattern of collaboration, together with additional assistance of overseas workers, is worthy of support.

BRASÍLIA

29 May 1973

I. Institute of Biological Sciences, National University of Brasília

A. Dr. Isaac Roitman (Microbiology Laboratory, Department of Cellular Biology)

Dr. Roitman came recently to Brasília from the Institute of Microbiology, Federal University of Rio de Janeiro. There is still a portion of his group in that Institute. He is in close contact with Dr. Seymour Hutner, of the Haskins Laboratories in New York, who is among the most imaginative and pertinent of the present day biochemists in the field of trypanosomiasis. Dr. Hutner has been a visiting scientist in Brasília.

They are particularly interested in the cultivation of kinetoplastid flagellates in sterilizable and defined media and are using monogenetic insect kinetoplastids as models, especially "Leptomonas pessoai". They have studied the effect of temperature and drugs on those flagellates. The argument is that with a fully defined medium it is possible to determine the metabolism of the organisms. Some organisms have very simple requirements (only 3 amino acids) but the metabolism of most is more complex. However, they hope that by determining the metabolism of the simpler organisms it will be easier to design defined media for the others. They have experimented with pure populations or organisms derived by cloning from cultures of "leptomonas pessoai". There is evidence of protection of mice using these organisms as living vaccines; and they seem likely to be safe as the blood of mice is culture-negative within a few minutes of inoculation and no histological evidence of amastigote multiplication has been found. Parasitaemias in vaccinated mice were maintained at a very low level (after challenge with T. cruzi, Tulahuen strain) and mortalities, up to 30 days, were reduced. But parasitaemias caused by the challenge organisms could be demonstrated.

Dr. Maria do Carmo Moreira Souza, cooperating in this work, is in Goiania with Prof. William Barbosa, (q.v.). Dr. Nelson Alvarenga is at present working on the cycle of development of T. cruzi in the gut of triatomid bugs. Like Brener he postulates some process of syngamy between rounded amastigote forms in the stomach. The group has also discovered an endosymbiont in Crithidia oncopelti and are experimenting with the metabolism of this organism. They hope to produce an endosymbiont-free population for comparison.

The Department of Cellular Biology, in common with other scientific departments briefly inspected in this Institute, is lavishly equipped, and laboratories and study spaces are very well designed.

B. Dr. G. de Freitas

An immunologist-biochemist, aiming to isolate the surface antigens of culture forms of T. cruzi, in order to study their immunogenicity. The first step is to obtain pure culture preparations of epimastigotes and trypomastigotes by stimulating or inhibiting their differentiation in culture media. So far, he has found an empirical way of doing this by adding varying quantities of haemin to a defined medium. He finds a critical "all-or-none" level, and below this, gets pure epimastigotes, above it, pure trypomastigotes. It was impossible to assess this work in a rushed 10-minute visit, but the laboratory was well-equipped, fully-staffed, and appeared to be dynamic.

II. Sobradinho Hospital

The Sobradinho Hospital, in the outskirts of Brasília, is used for the clinical training of medical students from the University of Brasília. Since there are over 100 students a year in the medical course and the hospital has only 200 beds, the facilities are not adequate to meet the student demand. Apparently there is difficulty in persuading other hospitals in Brasília, of which there are many, to associate with the University. Prof. Aluizio Prata is associated with a medical unit of 54 beds. This unit contains examples of many communicable diseases,

including Chagas' disease. Laboratories appear well-equipped and there is no shortage of technicians. The complement-fixation test for Chagas' disease is carried out. In spite of the obvious overcrowing there was evidence of a positive enthusiastic approach to medical care.

GOIANIA

30 May 1973

I. Institute of Tropical Pathology of the Federal University of Goiás

Professor William Barbosa

Professor Barbosa outlined his main work on Chagas' disease as follows:

1. Some work has been done on the characterization of antigens of T. cruzi using the agar-gel diffusion technique. Eventually he hopes to characterize different strains of T. cruzi by this method and perhaps relate these differences to differences in the clinical picture. At the moment he has shown common antigens between Brener's strains of T. cruzi and "Leptomonas pessoai". He has also been using a soluble antigen prepared by Capron and Afchain. This work is still in a preliminary phase.

2. Maria do Carmo Moreira de Souza, who wrote her thesis on "L. pessoai" and its protective effect against T. cruzi infections in mice is working in the Institute. "L. pessoai" probably originally contained Crithidia, Blastocrithidia, and Herpetomonas species, and is therefore ill-defined. It originated from the bug Zelus leucogrammus and is not wholly protective in mice. Dr. Souza is currently working on the metabolic requirements of "L. pessoai". Apparently "L. pessoai" is antigenically related also to human Leishmania and can be used as an antigen in the Montenegro test.

3. Siqueira's technique of multiple cultivation for isolating T. cruzi in chronic human infections is being evaluated against xeno-diagnosis using Schenone's technique. A further modified culture system devised by Prof. Barbosa consists of inoculating 6 ml of the patient's blood into a semipermeable sac within a liquid culture medium. This allows diffusion of medium into the blood; several flasks are set up and sampled at different times after inoculation. This work is also in a preliminary phase.

4. Dr. Sigisfredo Evangelista Rocha is working on the culture of "L. pessoai" which he passages every 48 hours. It was isolated 4 years ago. He had some good stained preparations of the organism.

Prof. Barbosa commented on the spraying programme and field entomology that had been conducted in the past by INERU and SUCAM. T. infestans and P. megistus are the main domestic vectors, with T. brasiliensis as a peridomestic species. About 70 percent of the human population is concentrated in the southern part of the state which was sprayed some years ago first with DDT to control malaria and then with BHC for Chagas' disease. This control has greatly reduced the incidence of acute cases, suggesting that transmission has been effectively interrupted. Now, less than 10 acute cases per year are seen but infected bugs are still found 180 kilometres in any direction from Goiania City. There is current evidence of active transmission in the northern part of the State.

Prof. Barbosa has a lot of epidemiological information relating to the situation before and after spraying. Apparently there has been no BHC application in southern Goiania for the last 2 years. In Firminopolis, 150 km from Goiania, 75 percent of T. infestans are infected. The hospital in the north of the State reporting acute cases at the moment is called Unidade Mista de Porto Nacional.

The local chief of INERU is Dr. José Paulo whom the group did not have time to meet. There is no entomologist in the Institute but a Dr. Sydney Schmidt has done field epidemiology on the prevalence of T. infestans, T. pseudomaculata, P. megistus, T. brasiliensis, and the occurrence of T. maculata. Some initial work had suggested that T. infestans showed some resistance to BHC in the laboratory but this has not been followed up.

Serological surveys of patients coming from different localities put the prevalence at 10-20 percent CFT positive individuals. Serology is done in a well-equipped laboratory at the Institute.

II. Clinical Hospital, Goiania

Dr. Joffre Marcondes de Rezende

Dr. Rezende, consultant gastroenterologist, has perhaps the largest personal experience of mega-oesophagus (some 2,000 cases) and mega-colon (approximately 400 cases). With him and with Prof. Barbosa, we visited the Tropical Disease Unit: a good facility of 40 beds containing most interesting parasitic disease including a case of acute Chagas' disease.

Dr. Rezende believes in the experimental production of "mega" syndromes in animals and cited a monkey in the Oswaldo Cruz Institute in whom a mega-oesophagus of 15 years' duration was diagnosed at post-mortem examination. In spite of the remarkable incidence of "megas" in Goiás no one has worked out the capacity of the strains to produce "megas" in experimental animals. He agreed that it was difficult to evaluate "megas" in mice unless they were gross, since the colon and oesophagus can be distended with barium. Standardization of animal techniques is necessary and Dr. Rezende is obviously valuable in designing such studies.

Dr. Rezende then went on to show a remarkable series of X-ray films of mega-oesophagus (which he divided into four grades), mega-colon, mega-jejunum, and mega-duodenum. On his current service he has seen 500 cases of mega-oesophagus and 200 cases of mega-colon. Four hundred and fifty-two mega cases have cardiopathy as well. Mega-oesophagus used to be commoner than peptic ulcer in Dr. Rezende's experience. He has seen 10 cases of mega-syndrome under the age of 10 years but the onset of clinical symptoms is usually in the 3rd or 4th decade. He is still seeing 1 new mega case per week. A younger colleague, Dr. Aluizio Ramos Oliveira, has just finished a thesis on the mega-syndromes and his papers are currently appearing in the Revista de Patología Tropical. He can detect early mega-oesophagus by stasis at the lower end of the oesophagus following a barium swallow in the decubitus position.

Dr. Rezende then showed the group his four-channel electro-manometer and he is still working on the pressure recordings obtained in early cases.

As regards management, Dr. Rezende advocates the following for mega-oesophagus: (1) Initial balloon dilation of the cardiac sphincter at regular intervals. If this fails to control symptoms, (2) A Heller's operation, and (3) If this fails in grade III and IV cases, resection and substitution of a piece of transverse colon. Mega-colon is treated by resection - we saw four past resection cases with colostomies. A two-stage procedure is done. Usually it is the sigmoid colon which is excised. At a later stage the colostomy stump is anastomosed to the side of the rectal stump so that sphincter control is retained but uncoordinated peristalsis at the site of anastomosis is avoided.

Goiania is obviously an active centre for Chagas' disease research and particularly strong in the clinical area; this work should be strongly supported.

ANNEX 3

CURRICULUM VITAE

D. S. Bertram

C. E. Gordon Smith

W. H. R. Lumsden

P. D. Marsden

D. M. Minter

W. Peters

B. A. Southgate

Douglas Somerville Bertram

Birth	21 December 1913; Glasgow, Scotland
Education	University of Glasgow, Scotland, 1935 B.Sc. (1st Class Hons.) Zoology; 1940 Ph.D. (Glasgow); 1964 D.Sc. (Glasgow); 1966 F.I. Biol. (Fellow Institute of Biology).
Posts Held	Director and Professor, Department of Entomology, London School of Hygiene and Tropical Medicine, London, England.

Teaching and research appointments

1936-1938	Assistant to Professor of Zoology (Professor E. Hindle), University of Glasgow
1938-1940	Assistant Lecturer in Entomology to Professor R. M. Gordon, Liverpool School of Tropical Medicine
1940-1946	War Service, Lieutenant to Major, Royal Army Medical Corps, No. 1 Malaria Field Lab., Middle East; P.O.W., Germany 1941-45; i/e Entomology, Army School of Health, U.K.
1946-1948	Lecturer in Entomology, Liverpool School of Tropical Medicine
1948-1956	Reader in Entomology, London School of Hygiene and Tropical Medicine
1956 to date	Present appointment, London School of Hygiene and Tropical Medicine (as above).

Civilian overseas experience

Travel or periods (up to 8 months) on scientific work in Gambia, India, Ceylon, East Africa, Sudan, Egypt, Ethiopia, British Honduras, South America, Caribbean Islands, U.S.A.

Service on advisory and other committees

M.R.C. Tropical Medicine Research Board (1964-67; 1971 to date); O.D.A. Trypanosomiasis Panel (1972-) and Tsetse subcommittee, 1966 to 1972; Hon. Treasurer, Royal Society of Tropical Medicine and Hygiene (1960 to date); Consultant in Entomology, British Army (1956 to date); Regional Editor, J Med Ent (1964-71).

Research	Directing research group on triatomid bug research (cytogenetics, behaviour, juvenile hormonal and other chemical treatments) with personal concentration on hymenopteran egg parasites of triatomids; related LSHTM field team in Bahia State, Brazil.
Publications	Numerous publications on mosquitoes, ticks, bugs, insecticides, chemosterilants, repellents, and cotton rat filariasis

Charles Edward Gordon Smith

Birth	12 May 1924; England	
Education	Forfar Academy and St. Andrews University, London, England	
Posts Held	1947-1948	House Surgeon and Physician, Cumberland Infirmary, Carlisle, England
	1948-1957	HM Colonial Medical Service
	1949-1951	Clinical Appointments in Malacca and Kuala Lumpur, Malaysia
	1952-1957	Virologist, Institute for Medical Research, Kuala Lumpur, Malaysia
	1957-1961	Senior Lecturer in Bacteriology, London School of Hygiene and Tropical Medicine, England
	1961-1964	Reader in Virology, London School of Hygiene and Tropical Medicine, England
	1964-1970	Director, Microbiological Research Establishment, Porton, near Salisbury, England
	1971 to date	Dean, London School of Hygiene and Tropical Medicine, England
Publications	Over 70 papers mainly on arthropod-borne animal viruses and leptospirosis.	

William H. R. Lumsden

Birth	27 March 1914; Forfar, Angus, Scotland	
Education	1931-1938	University of Glasgow, B.Sc. with first-class honours in Zoology; M.B., Ch.B.
	1938-1939	University of Liverpool. Diplomas in Tropical Medicine and Hygiene.
	1956	University of Glasgow, D.Sc.
Posts Held	1938-1941	Medical Research Council Fellow in Tropical Medicine in the Department of Parasitology and Entomology of the Liverpool School of Tropical Medicine (Professor R. M. Gordon).
	1941-1946	On active service with Malaria Field Laboratories, Royal Army Medical Corps, as successively, entomologist, malariologist and Commanding Officer (Lieutenant Colonel), in the Eastern Mediterranean, in the North African and Italian Campaigns, and in India.
	1946-1947	Medical Research Council Senior Fellow in Tropical Medicine in the Department of Entomology of the London School of Hygiene and Tropical Medicine (Professor P. A. Buxton).
	1947-1957	On staff of the Yellow Fever (subsequently East African Virus) Research Institute, Entebbe, Uganda, as, successively, entomologist, epidemiologist, and assistant director.
	1957-1963	Director, East African Trypanosomiasis Research Organization, Tororo, Uganda. Retired 1963, on the occasion of the granting of independence to Uganda.
	1963-1964	Lecturer, Department of Bacteriology, University of Edinburgh Medical School (Professor R. Cruickshank).
	1965-1968	Senior Lecturer, Department of Animal Health, Royal (Dick) School of Veterinary Studies, University of Edinburgh (Professor A. Robertson). From April, 1968, Head, Applied Protozoology Research Department, Centre for Tropical Veterinary Medicine, University of Edinburgh.
	1968 Jan. to March and November	Visiting Professor, Department of Parasitology, School of Hygiene, University of Toronto. Professor of Medical Protozoology, London School of Hygiene and Tropical Medicine (University of London).

Honorary positions

Member of the World Health Organization Panel of Experts, participating in four Expert Committees: Trypanosomiasis, Geneva, 1962 (WHO Technical Report Series, No. 247, Geneva, 1963); Immunology and Parasitic Diseases, Ibadan, 1964 (WHO Technical Report Series, No. 315; Geneva 1965);

Scientific Group on Comparative Studies of American and African Trypanosomiasis, Washington, 1967 (WHO Technical Report Series, No. 411; Geneva 1969); African Trypanosomiasis, Geneva, 1968 (WHO Technical Report Series, No. 434, Geneva, 1969).

Publications

Editor, Surgo (Glasgow University Medical Journal) 1937-38.
Editor, Uganda Journal, 1951-55.
Chairman, European Editorial Board, Experimental Parasitology, 1968-1971.

Philip D. Marsden

Birth

7 January 1933; London, England

Education

1956 University College Hospital Medical School, London, M.B., B.S.
1956 University College Hospital Medical School, London, L.R.C.P., M.R.C.S.
1958 London School of Hygiene and Tropical Medicine, London, D.T.M. & H.
1958 University of London, Academic postgraduate diploma in Applied Parasitology and Entomology
1959 Edinburgh, M.R.C.P. With tropical medicine as a special subject
1960 London, M.R.C.P.
1965 London, M.D.

Posts Held

Hospital appointments

1956-1957 House Physician, Dreadnought Seaman's Hospital, Greenwich, England.
1958-1959 Medical Registrar, Hospital for Tropical Diseases, London, England.
1959-1964 Assistant, Medical Unit, Hospital for Tropical Diseases, London, England.
1964-1966 Assistant Attending Physician, The New York Hospital, U.S.A.
1966 Assistant, Medical Unit, Hospital for Tropical Diseases, London, England.

Academic appointments

1959 Junior Lecturer in Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine, London, England.
1960-1962 Visiting Worker, Medical Research Council Laboratories, Gambia, W. Africa.
1962-1963 Visiting Lecturer to the Department of Medicine, Mulago Hospital, Kampala, Uganda.
1963-1964 Lecturer in Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine, England.
1964-1966 Assistant Professor of Tropical Medicine, Cornell Medical Center, New York, U.S.A.
1966- Lecturer in Clinical Tropical Medicine, London Schoo of Hygiene and Tropical Medicine, London, England.
1966 Appointed Recognized Teacher in the University of London.

Research

1960 Hampshire - Nigeria (fascioliasis, amoebicide).
1960-1962 Gambia, W. Africa (ascariasis).
1962-1963 Uganda - Mulago Hospital (sickle cell, hookworm, and splenomegaly diseases).
1965 New Guinea (relationship between splenomegaly and malaria).
1966 South America (Trypanosoma cruzi).

Publications

Over 20 papers mainly on clinical tropical medicine

Donald M. Minter

Birth	22 December 1928
Education	B.Sc., Ph.D., M.I. Biol., FR. Ent. Soc. 1953 Graduated First Class Hons., University of London
Posts Held	Project Leader Senior Lecturer, London School of Hygiene and Tropical Medicine with main interests in entomology and epidemiology
Research	Fourteen years of leishmaniasis/trypanosomiasis research in Africa Two years of Chagas' disease research in Brazil
Publications	Author and coauthor of 31 publications, largely on trypanosomiasis and leishmaniasis (1965-1973)

Wallace Peters

Birth	1 April 1924; London, England
Education	St. Bartholomews' Hospital, University of London, London, England; 1947 M.B., B.S. (Hons.); 1948 L.R.C.P., M.R.C.S., 1950 D.T.M. & H.; 1966 M.D.
Posts Held	1948-1950 Military service in West Africa. 1951-1953 Medical Officer, Tanganyika. 1953-1955 Scientist Entomologist and Malariologist, WHO in Liberia and Nepal. 1956-1961 Organizer and Director of malaria service in Papua, New Guinea. 1961-1966 Pharmacological research into the mode of action of antimalarial drugs with CIBA Pharmaceutical Company in Switzerland; Lecturer in pharmacology of anti-parasitic chemotherapy at Swiss Tropical Institute, Basle. 1966-to present Professor, Head of Department of Parasitology Liverpool School of Tropical Medicine, Liverpool; Hon. Director, WHO Regional Malaria Reference Centre for Screening of Potential Antimalarial Compounds; Hon. Director, MRC Research Group on the Chemotherapy of Protozoal Diseases and Drug Resistance. Honorary positions Member of Expert Advisory Panel on Malaria, WHO. Member of Council, Royal Society of Tropical Medicine. Member of Editorial Panel, Annals of Tropical Medicine and Parasitology. Member of Reviews Panel, Tropical Diseases Bulletin. Member of Swiss Society of Tropical Medicine (corresponding member). President of British Society for Parasitology. Vice-President of British Section of Society of Protozoologists.
Publications	Numerous publications on malaria, medical entomology, epidemiology, chemotherapy of malaria, biochemistry and physiology of malaria parasites, chemotherapy of helminth infections, drug resistance in parasitic infections.

Brian Andrew Southgate

Birth	17 June 1930; Hartlip, Kent, United Kingdom	
Education	1948-1953	St. Bartholomew's Hospital Medical College, University of London, M.B., B.S.
	1954	RAF Institute of Tropical Medicine and Pathology, Halton.
	1961-1962	London School of Hygiene and Tropical Medicine, Rockefeller Foundation Fellowship.
	1964-1965	London School of Hygiene and Tropical Medicine, WHO Fellowship.
	1965	University of London, passed diploma in Applied Parasitology and Entomology, (with distinction).
Posts Held	1953-1954	Resident hospital appointments in Medicine, Surgery, and Obstetrics and Gynaecology in the United Kingdom.
	1954-1957	Service in Royal Air Force Medical Branch; officer i/c at Medical Division in RAF Hospital, Aden, with rank of Squadron Leader.
	1957	RAF Hospital, Nocton Hall, U.K. Brief periods of service in Egypt, Cyprus, Iraq, Bahrain, Jordan, and Sharjah.
	1957-1958	Resident registrar posts in hospitals in U.K.
	1958-1968	Clinical appointments in the Kenya Government Medical Service.
	1969-to date	Senior Lecturer in Tropical Hygiene, Ross Institute of Tropical Hygiene, London School of Hygiene and Tropical Medicine.
	Consultancies	
	1964-1972	Official delegate of the Government of Kenya to the 17th World Health Assembly, Geneva; WHO consultant on African Trypanosomiasis, Nairobi, Kenya; Schistosomiasis, Geneva; Parasitic Diseases, Kampala, Uganda; Leishmaniasis, USSR and Geneva; Filariasis, Geneva; Immunology of Parasitic Diseases, Geneva, Lausanne, Stockholm, and Paris; Filariasis, Fiji and Western Samoa; Tropical Medical Research, West German Government in Togo; Chairman of the section on leishmaniasis of the VIII International Congress on Tropical Medicine and Malaria.
Publications	About thirty, mainly on the epidemiology of parasitic diseases.	