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**CHAGAS' DISEASE IN BRAZIL**

**A SURVEY OF CLINICAL AND PATHOLOGICAL ASPECTS**

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Table of Contents

|   | <u>Page</u> |
|---|-------------|
| Introduction . . . . .  | 1           |
| 1. Plan of Investigation. . . . .   | 5           |
| 2. Background of the Present Studies of Chagas' Disease<br>in Brazil. . . . . | 6           |
| 3. The Parasite and the Vector. . . . .                                       | 10          |
| 3.1 The Parasite. . . . .   | 10          |
| 3.2 The Vectors . . . . .   | 15          |
| 3.3 The Machado-Guerreiro Reaction. . . . .                                   | 17          |
| 3.4 Other Laboratory Tests for Chagas' Disease. . . . .                       | 20          |
| 3.5 The Epidemiological Indicators of Chagas' Disease . .                     | 21          |
| 4. Clinical and Pathological Aspects of Chagas' Disease . . . .               | 22          |
| 4.1 The Acute Phase . . . . .   | 22          |
| 4.2 The Experimental Acute Phase. . . . .                                     | 24          |
| 4.3 The Hyperacute Human Case . . . . .                                       | 25          |
| 4.4 The Latent or Indeterminate Stage and<br>its Development . . . . .        | 27          |
| 4.5 Megaesophagus in Goiania. . . . .   | 28          |
| 4.6 The Pathogenesis of the Megasyndromes . . . . .                           | 32          |
| 4.7 The Cardiac Lesions of Chagas' Disease. . . . .                           | 33          |
| 4.7.1 Frequency. . . . .  | 33          |
| 4.7.2 Cardiac Disease in São Paulo City. . . . .                              | 34          |
| 4.7.3 Cardiac Disease in Ribeirão Preto. . . . .                              | 38          |
| 4.7.4 Cardiac Disease in Goiania . . . . .                                    | 40          |
| 4.8 The Pathology of Chagasic Heart Disease . . . . .                         | 42          |
| 4.8.1 Diagnosis. . . . .  | 42          |
| 4.8.2 Pathogenesis . . . . .  | 47          |
| 4.9 Diagnosis of Chronic Chagasic Disease in the Living .                     | 49          |
| 4.9.1 Differential Diagnosis . . . . .  | 52          |

|  | <u>Page</u> |
|--|-------------|
| 4.10 Chagas' Infection and Chagas' Cardiopathy. . . . .            | 54          |
| 4.11 Machado-Guerreiro Reaction and Chagas' Heart Disease. . . . . | 54          |
| 5. The Importance of Chagas' Disease in Central Brazil. . . . .    | 58          |
| 6. Recommendations. . . . .  | 69          |
| 7. Summary. . . . .  | 71          |
| 8. Bibliography . . . . .  | 77          |
| Annexes I-IV . . . . . (See document RES 4/10, Annexes)            |             |

CHAGAS' DISEASE IN BRAZIL:  
A SURVEY OF CLINICAL AND PATHOLOGICAL ASPECTS\*

Chagas' disease has been discussed at several meetings organized by the Pan American Health Organization<sup>(1,2,3)</sup> and the World Health Organization<sup>(4)</sup>. Recommendations have been made on both the prophylaxis and the research aspects. The Advisory Committee on Medical Research of the Pan American Health Organization in its Second Meeting in 1963<sup>(5)</sup> endorsed the previous recommendations and stressed in particular the following studies:

- (a) Perfection and standardization of diagnostic procedures, primarily because of their importance in evaluating the magnitude of the problem;
- (b) A broad survey designed to evaluate the true extent and magnitude of the problem;
- (c) Ecology of vectors with a view to more radical control;
- (d) Chemotherapy, since to date no therapeutic agent has been found to be really effective against this protozoonosis;
- (e) Prophylaxis, mainly envisaging  
perfection of methods of applying insecticides, chiefly designed to discover more economical techniques;

\*Prepared for the Fourth Meeting of the PAHO/ACMR 14-18 June 1965 by Dr. J.N.P. Davies, Dept. of Pathology, Albany Medical College of Union University, Albany, New York, and Dr. Z. Fejfar, Chief, Cardiovascular Diseases, WHO, Geneva, acting as PAHO Consultants. Based upon a site visit to Brazil, on 30 November to 18 December 1964.

- (1) Report of the Advisory Group on Research in Chagas' disease (PAHO document RES 1/15, 12 June 1962)
- (2) Research opportunities in the chemotherapy of Chagas' disease in the Americas (PAHO document RES 2/21, 15 May 1963)
- (3) Regional Advisory Committee on International Classification of Diseases, Criteria for assignment of deaths to Chagas' disease (PAHO document ACC 3/3).
- (4) Wld Hlth Org. tech. Rep. Ser., 202, 1960 (Chagas' disease - Report of a study group)
- (5) Report to the Director, 1963, PAHO/ACMR, RES 2/33, pages 22-24

discovery of active substances to combat T. cruzi in blood in vivo.

- (f) Basic research on correct identification of trypanosomes similar to T. cruzi and on the nutrition, metabolism and immunological behavior of this parasite;
- (g) Research on the pathogenesis of Chagas' disease.

The Committee also urged:

- (i) The establishment of centers responsible for producing and controlling antigens for laboratory diagnosis as a means of furthering research;
- (ii) The promotion of centers to maintain strains of trypanosomes under known conditions and facilitating their exchange, also for the purpose of furthering research;
- (iii) Specifically supporting the centers of excellence already engaged in research on the various aspects of the disease.

When the Pan American Health Organization set up in 1962 an Inter-American Investigation of Mortality in 12 widely separated cities it was soon noted that the mortality attributed to syphilis and to other infective and parasitic diseases was relatively small, with the exception of Chagas' disease in Ribeirão Preto. In this city not merely was the mortality ascribed to heart disease extremely high but it was excessively high in young adults.

PERCENTAGE DISTRIBUTION OF DEATHS IN THREE AGE GROUPS BY SEX  
RIBEIRÃO PRETO, 1962

| Cause of death, groups                                | Male               |       |       | Female |       |       |
|---|--------------------|-------|-------|--------|-------|-------|
|   | Age group in years |       |       |        |       |       |
|   | 15-34              | 35-54 | 55-74 | 15-34  | 35-54 | 55-74 |
| Total deaths  | 100                | 100   | 100   | 100    | 100   | 100   |
| Total cardiovascular deaths                           | 33.7%              | 40.6% | 49.5% | 36.4%  | 48.4% | 56.2% |
| Vascular lesions affecting the central nervous system | 2.1                | 6.1   | 19.7  | 3.6    | 17.0  | 17.9  |
| Arteriosclerotic and degenerative heart disease       | 2.7                | 2.5   | 11.1  | -      | 1.9   | 14.5  |
| Hypertension  | 2.1                | 6.0   | 7.6   | -      | 4.7   | 8.5   |
| Chagas' disease                                       | 24.1               | 22.4  | 6.4   | 18.5   | 18.5  | 5.8   |
| All other circulatory diseases (excluding Chagas')    | 2.7                | 3.6   | 4.7   | 14.3   | 6.3   | 9.5   |
| All other causes                                      | 66.3               | 59.4  | 50.6  | 63.6   | 51.6  | 43.8  |

One of the Consultants (Dr. Z. Fejfar) was asked by PAHO in 1963 to review 159 case histories from the material obtained in Caracas, Ribeirão Preto and São Paulo. The purpose was to make a diagnosis of the cause of death on this available information and in particular to indicate important, reliable and acceptable criteria for the differential diagnosis of Chagas' cardiopathy from other heart diseases. Clinical history and findings, X-ray of the thorax, ECG and complement fixation test (Machado-Guerreiro) and autopsy data were the sources of information though not all of them were available in every subject. This was for the reviewer at that time his first encounter with Chagas' disease. In many instances his diagnostic conclusions were influenced by the statement of the pathologist and, where autopsy was not done, by the serological reaction. The problems of clinical diagnosis were summarized by Dr. Z. Fejfar as follows:

"Clinical symptoms and signs, as well as X-ray and ECG, when considered alone, might be ascribed to several other conditions. However, when taken together they presented a rather clear-cut 'typical' (at least for the reviewer) description of Chagas' heart disease. Here then is the picture: rapidly progressing and recurrent heart failure with dyspnea and congestion, resistant to treatment, with frequent arrhythmias. It ends very often suddenly, particularly when there is an additional burden such as infection, pregnancy, operation or other factors. Arrhythmias are very frequent and the reviewer has never, until now, seen such a high frequency of total A-V blocks especially in young subjects. Cardiac signs seemed to be absent with the exception of a systolic murmur over the left precordium. Another rather frequent finding was that of thrombo-embolic episodes. The above alterations were frequently found in young subjects of both sexes whose blood pressure was usually low with a small pulse pressure.

The picture seemed clear and when the serological reaction was positive the reviewer did not hesitate to assign the death to Chagas' disease."

Differential diagnosis from rheumatic heart disease did not present any particular problems. More difficult at that time seemed to be the differential diagnosis from ischemic heart disease in the older age groups - mainly men - and here the postmortem findings and serology appeared to be most important.

A visit of a consultant pathologist and a clinician without experience in Chagas' disease to several places with an abundance of Chagas' disease was suggested in order to study and work out criteria acceptable for cooperative studies.

At this stage in 1964, the writers were asked to investigate the status of Chagas' disease and cardiopathy in the State of São Paulo and to make recommendations which might throw further light on the situation, bearing in mind the conclusions of the previous PAHO/WHO groups mentioned above. To explain the deficiencies of this report it should be mentioned that the writers are respectively a clinical physiologist with special interest in hemodynamics and cardiopulmonary function (Dr. Z. Fejfar) and a morbid anatomist with special interests in primary myocardial diseases, studied particularly in Africa (Dr. J.N.P. Davies). Their main qualifications were their virtually complete ignorance of Chagas' disease, and at all stages they have been guided by the knowledge and advice of their hosts. Every attempt, however, was made to check and recheck every statement made and as wide a variety of opinions was sought as was possible in the time available. It was not possible to contact all authorities on the subject.

1. Plan of Investigation

A period of one week was spent in São Paulo in which as much background information as possible was sought and the views of those in the hospitals and medical schools of this large and rapidly growing city were considered. To enable a conspectus of cardiac disease in São Paulo to be gained the Consultants were permitted by Professor W. E. Maffei and Dr. C. Marigo to analyze the cardiac cases in a series of some 10,000 consecutive postmortems. The Consultants were greatly assisted in this by Dr. C. Marigo and his staff.

One week was spent in Ribeirão Preto where Professor J. L. Pedreira de Freitas was consulted on the many aspects of the disease that he has studied. Professor Mauro Pereira Barretto gave us advice on the entomological and parasitic aspects. The bulk of the Consultants' time was spent with Dr. Fritz Köberle and his staff. With their help and that of Miss Mary H. Burke of PAHO, the Consultants carried out a complete analysis of the protocols of all cases autopsied between 1960-1964 and made numerous analyses.

At the invitation of the Rector of the University of Brasilia, the Consultants then proceeded to visit other centers. Accompanied by Professor F. A. Köberle they visited Araguaia where they were shown the investigations of Dr. Calil Porto and his son Dr. Selmo Porto, general practitioners who have carried out extensive investigations on Chagas' disease. A number of homes were visited to see sites of potential infection. Goiania was then visited where the work of Professor Joffre de Rezende, Professor Jarbas Doles and their associates was seen and two hospitalized cases of acute Chagas' disease were shown by Professor Rezende. The Pemphigus



Hospital was also visited to see aspects of another of Brazil's fascinating and dreadful diseases.

In Brasilia the work of Dr. Ely Barbosa, Dr. Kelino Miseira and their associates was discussed. The Rector, Dr. Zeferino Vaz, and the Vice-Rector, Dr. Almir de Castro, made time in their heavy schedules to talk for some hours with the Consultants. Dr. Z. Vaz is a parasitologist and a one-time Secretary of Health of São Paulo. The Consultants returned to Ribeirão Preto to conclude their investigations and separated in Rio de Janeiro. A schedule of their movements and the persons consulted are shown in Section 9.

One of the Consultants (Dr. Z. Fejfar) also visited Venezuela and Santiago de Chile and there made observations which are added as illustrative of the similarity and/or differences there to those in Brazil (See Annex I and Annexes II-A and II-B to document RES 4/10).

## 2. Background to the Present Studies of Chagas' Disease in Brazil

The present position in relation to Chagas' disease in Brazil cannot be fully understood without some brief reference to the history of that country.

Unlike the rivers of Africa, the rivers of eastern South America are navigable over great distances. To the early explorers and pioneers the Amazon was a great highway to the middle of the continent. To the south the rivers of the Plate system offered only slightly more difficult access. The interior of the country was explored from the south in the period from 1530 onwards though for the 200 years from 1549 the capital was Bahia. Many cities developed on the narrow coastal plains backed by the

mountains. The expansion from the south was spearheaded by the "Paulistas", as the inhabitants of São Paulo State have been known since 1549. In 1693 the discovery of gold in Minas Gerais caused a gold rush to the area, and a further wave of immigrants was stimulated by the discovery of diamonds early in the 18th century. But despite all this effort, because of the difficulties of communications through the fringe of mountains behind the coastal plains, the coastal cities have tended to dominate the vast and sparsely populated inland uplands of Brazil. The first medical schools and the bulk of the leading educational establishments were on the coast at Rio de Janeiro and Bahia.

To the southern cities particularly came the great waves of European immigrants, preferring these areas to the hotter northern areas. Between 1820 and 1889, some 880,000 such immigrants arrived, mostly in the south and from 1889-1937 a further 370,000 arrived. Some settled in the coastal cities, many passed to the interior, the movement being largely from the coast to the interior and not vice versa. Those who returned to the coast were mostly the successful and enriched rather than the poorer pioneers who tended to remain inland. On these inland uplands it began to be noted that certain unusual medical diseases occurred. From 1750 at least sudden death in young persons from heart disease was recognized and a book by a leading judge published in 1873 mentions this frequent occurrence. The frequency of dysphagia under the name of "mal de engasgo" had been recognized in Pernambuco as long ago as 1703. Langaard (1873) refers to the frequency of "mal de engasgo" in Minas Gerais and adjacent areas of São Paulo State. The novel "Innocencia" by Escregnolle de Taunay (1883), set in a farm in remote Mato Grosso, refers both to the frequency of dysphagia and sudden deaths.\*

\* Dr. Calil Porto drew attention to these references.

It was in the then remote interior of rural Minas Gerais that Carlos Chagas discovered the disease that bears his name. Though this is now recognized as one of the outstanding South American contributions to medicine it is to be supposed, and there is evidence to support this, that this discovery was not too readily accepted or appreciated by the Coastal pundits. The entomologists and parasitologists took up the subject readily, but though Guerreiro and Machado had described in 1913 their complement fixation test by which asymptomatic cases could be detected it was many years before this was widely applied and study of the clinical and pathological aspects developed only slowly.

Carlos Chagas had described acute cases and the majority of studies were concerned with the acute cases and the number of such cases remained small. Thus Strong (1944) points out that until 1937 reports were few, came only from Minas Gerais, and only 4 cases had been reported from São Paulo State. In 1937 Mazza began to report cases from Argentina. Reports followed from Uruguay (Tallice, et al, 1939), from the State of Rio Grande do Sul and from other countries including a number from Panama. Almost all these were acute cases, though in Panama, Clark (1939) had begun increasingly to diagnose cases by the Machado-Guerreiro (M.-G.) reaction.

But Brazil was increasingly turning to the rapid development of the interior with improving communication and with the development or even the founding of new cities, (i.e., Goiania(1933) and the new capital of Brasilia), at the time when the possible importance of Chagas' disease began to come to the fore. Even by 1916 Carlos Chagas had demonstrated the importance of cardiac lesions in acute Chagas' disease and had been wondering if the frequent sudden deaths and dysphagias of Minas Gerais might be manifestations of a more chronic stage of Chagas' disease.

Study of the possible chronic stages had been impeded and perhaps some were deterred from further studies by the tragic mishap by which goitrous lesions had been confused with Chagas' disease because both occurred together in certain geographic localities. This was probably a factor in delaying recognition of the true nature of the chronic stages of Chagas' disease and rendered some, especially in the coastal cities, reluctant to accept the accumulated evidence. It was, it seems, particularly to the credit of the general medical practitioners in the rural areas and in the small towns that they should have insisted on the relationship of chronic Chagas' disease to the frequent myocarditis, to the sudden deaths of young people and to the frequent dysphagias, a relation they believed in, though they lacked the techniques to prove it.

With the development of Brazil's interior and the creation of new hospitals and medical schools, the talent and techniques necessary to study the problem arrived in the interior. As a result both the clinical and pathological concepts of Chagas' disease began to alter and its potential importance as a major health hazard and as a major public health problem began to loom ominously. Meanwhile the distribution of the vectors and of the animals hosts had been studied by the entomologists and parasitologists and a vast area of possible infestation potentially affecting an enormous population had been revealed. This particularly followed the work of Dr. E. Diaz (see Chagas Krankheit, Weltseuchen Atlas, Hamburg, Volk Verlag, 1954). The potential vectors and reservoirs have been mapped in Brazil by Professor M. Pereira Barretto (1963) and others an obviously enormous number of people are potentially exposed to infection. But how serious was the risk and how serious the consequences?

### 3. The Parasite and the Vector

#### 3.1 The parasite

The possible nature and classification of the parasite has been a matter of some dispute.

Trypanosoma cruzi has been found to infect man. At least 42 animal species in Brazil have been found to be naturally infected. These animals include 8 varieties of domestic animals. New reservoirs are constantly coming to light. Among the domestic animals, the cat and dog are more frequently infected than man in endemic areas although their relative numbers are low compared with infected humans. The domestic dog seems to suffer a more severe and lethal illness from T. cruzi infection than does the domestic cat. This may indicate that the cat is a greater hazard as a long-lasting potential reservoir of infection. Infections in pigs, house mice and rats are probably not as important with respect to human disease but this depends to a great extent on the behavior of the insect vectors.

The seriousness of the widespread infection in wild animals has not been fully estimated. Many of these have little contact with man and so are not dangerous reservoirs. The marsupials may be a particularly important exception, especially the opossum which may nest either outside or inside houses. The investigation of the blood meals of infected triatomids has shown the simultaneous presence of both human and opossum blood. Wild rodents may be of importance in some areas, e.g. N. E. Brazil, because they may live in rock holes, caves, or in houses. The armadillo has been much discussed as a potential reservoir but the infection in these animals is very mild, tissue forms of the parasite are rarely found and

strains of armadillo parasites injected into other armadillos have shown little infectivity. This has led to suppositions that the parasite might be primarily an armadillo parasite, a host infection of great antiquity in South America. This is a matter of considerable importance as will be discussed later.

The situation with regard to bats is particularly interesting. Bats in South America as in Europe and Africa are naturally infected with Trypanosoma vespertilionis, which, in its morphology, differs slightly from T. cruzi, develops poorly in triatomids, and rarely infects laboratory animals. But in Brazil bats may simultaneously be affected with T. vespertilionis and T. cruzi (rather rarely) and in high endemic areas there may be a high infection rate of T. cruzi in bats. In Amazonia very high rates of infection in fruit bats are found, up to 83%, but without accompanying triatomids in what is believed to be the natural habitat of these bats, though they may sometimes be found in human dwellings. This raises the question of the vector responsible for spread in bats.

A parasite, if of great antiquity in Brazil and capable of affecting such a wide range of animal hosts, might well be expected to show considerable strain differences. Search for detectable strain differences has occupied much attention but the results so far are not clear cut. Some investigators have been unable to detect any strain differences by morphology of the parasite. However, by gel diffusion techniques, some separation by antigenic differences appear to show up. Thus Deane (1964) has divided strains into the following groups:

Group A - All human strains examined and bat strains

Group B - All strains from animals examined, e.g. opossum, monkeys, rodents, etc. with the exception of strains from the

Teyra berbera, a small carnivorous animal which differs slightly from the others in Group B and seems to be a Strain C.

While the virulence of strains of all these groups varies within the group, no differences in viscerotropism are reported. It is not known if the strains are stable, if the strains can change from one type to another, perhaps via the opossum, or if these differences can be used epidemiologically. The fact that human and bat infections are of the same strain may be of considerable importance especially as the bat strains from both endemic and non-endemic areas of the human disease are all of Strain A.

It may be that strain differences will be shown up by injecting human strains derived from patients into mice (Professor M. Pereira Barretto, 1964). In all animals it appears that young animals injected develop a severe disease with a heavy parasitemia and a high mortality. In older animals the parasitemia is brief and of low intensity and parasites are difficult to find thereafter and may completely disappear from the blood, only a few leishmania forms being found in the heart with a mild myocarditis. Some evidence of strain differences have appeared in that some human strains injected into weaned mice have not produced infection and there is some evidence that the mean nuclear index differs in some strains both human and animal. The mean nuclear index is defined as:

$$\frac{\text{Length of trypanosome}}{\text{Distance from the nucleus to the posterior end}}$$

For typical T. cruzi the mean nuclear index is 1.5 with a range of 1.2-1.7. In both humans and animals some strains have been found with very high indices or very low indices down to less than 1.0. These variations do not seem related in any way to virulence.

It would seem most desirable, in the light of the many problems to be

discussed, that much more attention should be directed to the question of possible strain differences within the species T. cruzi as well to defining the real importance of the animal reservoirs. It is now clear that a wide range of animals are affected but the relative importance of these has to be established.

Trypanosoma cruzi has a complicated life cycle which is quite unlike that of the African trypanosomes which cause sleeping sickness. The infective phase is the trypanosome stage which circulates, but never divides, in the blood. The trypanosomes are spindle-shaped with a central nucleus and a very large distinctive kinetoplast at the posterior end. The trypanosome invades the cells of certain organs in man and animals, loses its undulating membrane and flagellum becoming a leishmania form and divides by binary fission to form masses of leishmania forms which form a pseudocystic agglomeration in the invaded cell. This binary fission of leishmania forms is the only type of multiplication which occurs in the animal body. The cyst ruptures the cell and leishmania forms are liberated. These develop into the trypanosome form that circulates in the blood and invades further cells. In animals and man this cycle is believed to take about 5 days.

If infected blood containing the trypanosome form is abstracted by a triatomid, then the trypanosome form is altered into a crithidial form, that as it turns into a flagellated form, which differs from the trypanosome form in that the macronucleus which, in the trypanosome form is far from the flagellum, is in the crithidial form near the base of the flagellum. In the triatomid posterior gut, the crithidial forms multiply. Up to 99% of the parasites in this location are of this type, even if the infection was started solely with trypanosome blood forms. Thus the crithidial forms are



the only forms which multiply outside the definitive host.

In summary then, the trypanosome form of T. cruzi does not multiply at all. It only circulates in the blood and invades cells. In the definitive host only the leishmania forms multiply and this entirely intracellularly while in culture or in the insect gut only the crithidial forms multiply.

The effect of this is to impose an immense and so far insurmountable obstacle to the full study of this parasite, for all cultural work in vitro can only be done with the crithidial form which is not the form found in, and which damages, the animal cell. It must be emphasized that all cultural studies, the results therefrom, and all products of the culture of this parasite are based on cultures of the crithidial form.

A considerable amount of such cultural work has been carried out, firstly to attempt to improve diagnostic methods, secondly to attempt to grow the parasite on purely synthetic media to enable metabolic studies to be made and thirdly to provide antigens for diagnostic procedures. Culture on purely synthetic media has not been achieved. Certain basic requirements have been defined. The parasite needs hemoglobin, serum (calf, human or rat are used), adenine, uracil or uridine, but these alone will not enable continued growth to take place. Infusions of brain, liver or muscle tissue have to be added but analysis of the components of these infusions, and replacement by a great variety of substances has not been successful. It appears the parasite cannot, from simple precursors such as formate or glycine, make nucleic acids. It must have some source of ready-made purine and pyrimidine. If this is provided, growth takes place optimally at pH between 7.2-7.3 and at 28°C. Growth can take place but is slow at 20°C, is limited at 34°C and is very poor at 37°C. The optimal pH for differentiation

is 5.6.

In tissue culture, the organism will to some extent grow as in cells, leishmania developing and, on cell rupture, transforming into flagellate forms. These studies have led to attempts to kill the organisms by agents capable of blocking the formation of nucleic acids but these, while showing some success in vitro, have been unsuccessful in vivo. It seems possible that growth of leishmania is suppressed but the organisms are not killed and growth begins when the drug is withdrawn.

### 3.2 The vectors

The spread of T. cruzi from animal to animal is via various species of triatomids popularly known in Brazil as "barbeiro" because they preferentially bite on the skin of the face, eyes or lips of the sleeping human at night. Elsewhere, as in the U.S.A., they are known as the "kissing" bug, or "cone nose" bug. Many species exist in the Americas between 41°N to 41°S and other species have been described from other parts of the world. At least 37 species have been found in Brazil. The distribution of many of these, with maps and infection rates, is conveniently described by Professor M. Pereira Barretto (1963). The most important, because of their domestic or semidomestic habits are T. infestans, Panstrongylus megistus, T. sordida, T. brasiliensis and T. maculata. An additional eight species have been found infected and may play a role in maintaining natural infections with T. cruzi because of their sylvatic habits.

Triatoma infestans appears to be the main vector in Chile while in Venezuela the principal transmitter is Rhodnius prolixus.

The bite is painless but often leaves a feeling of irritation. The

triatomids are avid blood suckers absorbing up to 0.5 ml. of blood. To absorb this blood they have to evacuate fecal material which from infected bugs contains the living trypanosomes that may be inoculated into the human by scratching. Infection does not, therefore, inevitably follow a bite from an infected insect.

It appears that three infective ecological systems may occur in Brazil. (1) In Amazonia there may be widespread animal infection but the local triatomids are sylvatic and do not enter homes so that human infections are rare. (2) In Northeast Brazil, both humans and animals are infected, but the human endemicity is low because the triatomids are eclectic and live both wild or domestically according to circumstances. (3) In central Brazil the triatomids are thoroughly domestic, though recent work has demonstrated appreciable numbers in non-domestic buildings, and will invade buildings that have been sprayed.

The situation then in central Brazil would appear potentially serious because of the close adaptation of the vector to the domestic environment and providing man or animal reservoirs of infection exist there then high infection rates of triatomids would be expected.

Surveys (Professor M. Pereira Barretto, 1963) have shown extremely high rates of triatomid infection. To this must be added the fact that triatomids can survive unfed up to 2 years and infection can persist in the gut up to 1 year at least.

In some houses between 80 and 100% of captured triatomids have been found infected. Natural infection rates summarized from many publications by Professor M. Pereira Barretto (1963) have run as high as 59% with T. infestans and up to 75% with P. megistus. With the other vectors much

lower natural infection rates have been recorded. The lowest rates quoted for T. infestans were from the State of Rio de Janeiro (3.3%). Since no strain differences have been unequivocally demonstrated it would appear at present that every infected domestic triatomid represents a human health hazard.

In studies of 946 municipalities in 12 states of Brazil, Triatoma infestans and P. megistus were found most frequently (in 317 and 320 municipalities). The index of activity for T. infestans was 27.69%, for P. megistus 15.28% and less than 10% for T. sordida, T. braziliensis and T. maculata.

In Venezuela infestation of R. prolixus with T. cruzi in 5 endemic states was between 7 and 64%.

In endemic areas in Chile the infestation of T. infestans with T. cruzi varied between 24.2 and 51.4%.

### 3.3 The Machado-Guerreiro Reaction

This complement fixation test was introduced in 1913 as a serological test for Chagas' disease. The original antigens used were extracts, e.g. spleen and liver from artificially infected puppies. The value of the antigen appeared to be proportional to the degree of infestation of the organ from which it was made and this was variable. The test was assessed versus the Wassermann reaction for syphilis with satisfactory results, there being no parallelism, although there appears to be some cross-reaction in cases of leishmaniasis. The test correlated well with the results of blood examinations for trypanosomes and the reaction remained positive for many years following infection. To increase the specificity of the reaction the use of cultured trypanosomes in the

preparation of the antigen began in the nineteen-thirties and this is now standard. Considerable efforts to standardize antigens and techniques have been made, notably by Dr. J. L. Pedreira de Freitas (1949, 1951, 1961) who introduced a degree of quantitation. The Davis antigen, a chloroform-benzene extract of trypanosomes cultured on blood agar is now generally used. Thus sera are divided into: (1) non-reacting; (2) reacting to a titer of over 1.4. The latter are regarded as doubtful when in the range 1.4-1.9 and over 1.9 are regarded as positive or reactive. In severe chronic cases the figure is 2.3-3 or over but usually does not go much higher and over-quantitation does not add anything to the value of the results. It is rare for a positive reactor to become negative but the longer the interval from the original infection the greater the tendency for the level to fall. Thus in 76 cases where parasites had at one time been demonstrated in the blood 80% had an M.-G. reaction of 1.9 or over; 19% were in the range 1.5-1.9 and 1% were negative several years later. It is thought that if the M.-G. reaction is positive, then live parasites are still present. The test can be done on serum, on CSF, on pericardial, pleural or ascitic effusions but not on liquor amni.

The complement fixation test appears specific for T. cruzi infection. Dr. G. A. Maekelt and Dr. Dias Vásquez (1962) found the test was positive in 93.5% of infections with T. cruzi and 12% infection by T. rangelli, while the negative complement fixation test was 6.4% for infections caused by T. cruzi and 88% for those attributable to T. rangelli.

The case for a high specificity of the M.-G. reaction seems good but some doubts creep in. First, there is no clear evidence as to exactly what is being measured by the M.-G. reaction. Secondly, the original antigen was

presumably largely composed of leishmania-derived material while culture-derived antigens are trypanosomal. Thirdly, the M.-G. reaction has always, it seems, been studied in serological and clinical terms but no strictly controlled study has been carried out in morbid anatomic terms. It may be remembered that the specificity of the Wassermann reaction was finally established when a high degree of correspondence was established between the positivity of the reaction and anatomic evidence of syphilis. Yet few clinicians would hesitate to treat an obvious case of syphilis because the reaction was negative and morbid anatomists would and do make the diagnosis of a syphilitic lesion despite negative serology.

Perhaps lack of a controlled experiment vis-a-vis the morbid anatomic evidence accounts for a curious divergence noted in opinions about the reliability of the M.-G. reaction. Everywhere serologists, parasitologists and epidemiologists spoke highly of its reliability and all deprecated the idea of diagnosing Chagas' disease if the M.-G. reaction was negative. This was to some extent supported in the city of São Paulo by clinicians and cardiologists though morbid anatomists were more dubious.

Outside the city among all clinicians, general practitioners, cardiologists and morbid anatomists there was a greatly different opinion. Seven separate opinions suggested that the M.-G. reaction was only positive in 80-90% of cases of Chagas' disease; the anatomists usually suggested 80-90%, the clinicians 85-95%. None of those consulted would hesitate to make the diagnosis in the face of clinical or anatomic evidence in a patient from an endemic area despite a negative M.-G. reaction. This is an important discrepancy which will be returned to later, and which clearly needs resolution.

Through the kindness of Professor F. Köberle, Head, Department of Pathology, University of Ribeirão Preto, the Consultants were able to review the autopsy material from the Department of Pathology in Ribeirão Preto from 1960 to 1964. There were 1,052 autopsies above the age of 10 years. The M.-G. reaction was positive in 81% of cases diagnosed by the pathologists as a Chagas' cardiopathy while 19% of these had negative M.-G. reactions. On the other hand, the reaction was positive in approximately 10% of patients where death was assigned to other heart diseases or who had no heart disease at all.

AUTOPSY MATERIAL 1960-1964  
(N = 1052)  
(including children above 10 years )

| Diseases            | M.-G. Positive (Percent) |
|---------------------|--------------------------|
| Chagas' cardiopathy | 81                       |
| Other cardiopathies | 11                       |
| No cardiopathies    | 10                       |

Dr. G. A. Maekelt in 1961 found a similar correlation between the complement fixation test and the clinical history of Chagas' disease. Out of 96 subjects with a diagnosis of chronic Chagasic cardiopathy, 78 (81%) were serologically positive and 18 (19%) negative.

#### 3.4 Other laboratory tests for Chagas' disease

It seems generally agreed that the precipitin test is useful in the acute stages of Chagas' disease but only detects some 20% of chronic cases. The "Cruzin" skin test of Meyer and Pifano (1941) was not apparently used. In the acute stages, the parasitemia is demonstrated by finding the

trypanosomes in the blood film and by culture but they are very difficult indeed to find in the chronic forms on smears or by culture. However, tragic results from transfusing blood from M.-G. positive reactors producing acute Chagas' disease in the recipient have shown that the trypanosomes do circulate in the blood in chronic cases and the use of gentian violet to obviate these tragedies is now routine.

The most useful ancillary test is the xenodiagnostic test in which non-infected triatomid bugs are fed on the suspect case and the fecal content of the bugs examined subsequently to demonstrate infection. The test can be standardized by the numbers of triatomids fed, usually 5 at a time, and by the number of repeated tests, and can be compared with the M.-G. reaction results. It would seem that about 20% of asymptomatic cases with positive M.-G. reactions will show a positive reaction to a single 5-bug test feed.

Xenodiagnosis appears to be the most sensitive of all diagnostic tests for the detection of T. cruzi in the blood during the chronic stage with a low degree of parasitemia, and a technique described recently by Dr. G. A. Maekelt (1964) using 12 bugs, instead of the usual smaller number, and examined 40 to 60 days after the last blood meal in a simplified way (homogenization in saline, separation of the chitin by cotton filter and examination of the sediment in phase contrast microscope) seems sensitive and can be performed even in small laboratories.

### 3.5 The epidemiological indicators of Chagas' disease

The foregoing discussion is merely an introduction to the clinical and pathological problems of Chagas' disease. To summarize it may be stated that there are a variety of possible ecologic situations in which



parasite and vector may combine to produce infection in human beings. These can be mapped according to the distribution of the animal reservoirs, or of the vectors and by the degree of infestation in the vectors. The human infections can be indicated by the discovery and demonstration of the parasites in the blood or tissues, by the recovery of parasites by the xenodiagnostic tests or by serological reactions of varying degrees of specificity. Finally, there are the clinical and pathological aspects of the disease in humans to which attention is now turned.

#### 4. Clinical and pathologic aspects of Chagas' disease

Acute Chagas' disease has been carefully studied and there are many reports of cases in the literature. Most of the cases recognized are in children, though adult cases occur in some numbers. It is also evident that the majority of recognized cases of chronic Chagas' disease did not have or do not remember any clearly defined acute phase. The usual sequence is described as:

Acute Stage . . . . .> Latent or . . . . .> Chronic Stage  
Indeterminate Stage

The distinction between the latter two stages is not clearcut, however, and raises the distinction between "Chagas' infection" and "Chagas' disease". In the second stage the patient may be asymptomatic but with a positive M.-G. reaction and radiologic or ECG evidence of organ involvement and the chronic stage is most easily appreciated as the time when these changes produce signs and symptoms.

##### 4.1 The acute phase

This is distinguished in many cases by the fever, facial edema,

lymphadenopathy, hepato- and splenomegaly and anemia. The conjunction of unilateral palpebral edema, conjunctivitis and lymphadenopathy described by Romana (1935) and given his name is very characteristic. The typical "chagoma," a local area of inflammatory necrosis and fat necrosis, at the site of the infected bite, is often seen. There is a high fever 38°-39°C which may fluctuate slightly and often persists for up to six weeks. Trypanosomes may be seen in large numbers and cultured from the blood. The M.-G. reaction becomes positive at about the 30th day.

Certain additional lesions are agreed. There is often evidence of severe damage to the heart involving both the muscle and conduction system, and producing lesions which vary from arrhythmias to severe heart failure. There is often evidence of infection of the central nervous system with encephalomyelitis and meningitis. The presence of leishmania in large numbers in neuroglial cells has been demonstrated. Crowel (1923) showed that C.N.S. nerve cells were rarely found invaded though in animals he did find ganglion cells of the semilunar ganglion involved.

The pathological substratum to these findings in the body in acute cases has been extensively studied. Leishmania may be found in cells in many parts of the body; they were demonstrated to the Consultants in heart and skeletal and smooth muscle fibers, in bronchial and bladder epithelial cells, in spleen, adrenal, thyroid, in neuroglial cells and in ganglion cells of the peripheral nervous system. In the heart a severe myocarditis is evident. There is no cell reaction to parasites in a myofiber prior to its rupture. It seems that the initial cell reaction to myofiber rupture in the heart is a polymorphonuclear infiltration with considerable numbers of eosinophils. The latter persists and, as more and more pseudocysts full of leishmania rupture, the reaction becomes more an eosinophilic granulomatous

reaction with lymphocytes, monocytes and the occasional giant cell. Around these lesions a moderate amount of rather loose-textured fibrous tissue develops.

It is evident that in the acute stage there is an intense generalized parasitemia with with widespread involvement of all organs in the body, and with evident rupture of many myocardial fibers. In view, however, of the intensity of the infection, the brief life cycle of the parasite and the large number of leishmania liberated it would seem, however, that many of the myofibers must reform after the rupture of the pseudocysts otherwise the cardiac deaths in the acute phase would be much more common. A mathematical model of the acute phase would almost certainly demonstrate this.

#### 4.2 The experimental acute phase

This can be studied in two ways. The conventional one is in the experimental animals. Much more valuable is the acute phase in human which results in death. In experimental animals it is common practice to introduce large numbers of organisms into animals to study the acute effects. An analogous situation arises in the occasional human case in which the acute disease develops after a blood transfusion. These rare tragic cases deserve the most detailed study and it would seem desirable to make special efforts to achieve this.

Many investigations of the acute phase in animals have been made. Dr. M. Okumura demonstrated to the Consultants the changes that develop in mice injected with large numbers of the virulent São Paulo strain. Following intraperitoneal injection the parasites were found in large numbers in serosal and then in muscle cells. There is no cell response to

the parasites while they are in unruptured cells. Following rupture there is a lymphocytic histocytic response with the development of fibrosis. Intense infection of the ganglion cells in Meissner's and Auerbach's plexuses in the gut wall is seen with large numbers of leishmania in the ganglion cells. As in the myofibers there is no cell response round the unruptured ganglion cells but with rupture there is an intense inflammatory response to rupture, and the formation of a granuloma around the cells. The nuclei of the ganglion cells themselves are not invaded, the leishmania multiply in the cytoplasm but following rupture the nuclei disappear and the ganglion cells disappear entirely until in the final stages of the acute phase in the mouse no ganglion cells can be found in many areas. Exactly similar changes are seen in the celiac plexus ganglion cells. The death and destruction of the ganglion cells in the mouse is the direct result of invasion of the cells by the parasite. Similar if less intense lesions were shown by Dr. M. Okumura (1961, 1962, 1963) in the mouse following subcutaneous injection of parasites. These lesions can be produced by parasites derived directly from human cases though some viable strains produced no lesions at all.

Similar lesions following acute infections in mice have been found by Professor F. A. Köberle and his associates. In addition, they have (unpublished) shown abnormal pharmacological responses in these animals indicating an acute deprivation of large numbers of ganglion cells in the peripheral nervous system.

#### 4.3 The hyperacute human case

In the analogous situation in which death from acute Chagas' disease in the human follows blood transfusion, it was evident that precisely similar changes occur. In one of the cases the Consultants were

privileged to see (Professor J. Doles), the usual severe myocarditis was present, with absence of cell response around unruptured cells and a cell response following rupture, and a similar invasion and response around ganglion cells in the esophagus, stomach and intestine. In some regions in this case the ganglion cells were very extensively parasitized and many had disappeared following rupture and had elicited a very heavy cellular response.

More such hyperacute human cases need to be carefully studied. The Consultants' observations do not lead them to doubt, however, that in acute Chagas' disease both in animals and humans, severe destruction of ganglion cells of the peripheral nervous system can take place. To the Consultants it would seem well worth exploring in the acute human cases the pharmacological responses to mecholyl and other sympathetic/parasympathetic affecting drugs. In Goiania steps are being taken to make such observations.

All consulted thought that acute cases were rarely seen. But from some reports acute cases in both children and adults are not so uncommon. In Goiania the Consultants were privileged to see two hospitalized acute cases at the same time, an adult and a child. Indeed in this hospital with a relatively small medical ward some 2,352 patients were admitted in two years including 9 cases of acute Chagas' disease. There are said to be areas in which an even higher frequency of acute cases was known.

Thus experience of the acute cases lead the Consultants to suppose that in Brazil the main brunt of the damage in acute Chagas' disease is sustained by the myocardium and by the ganglion cells of the peripheral nervous system and that the lesions of the chronic stages would reflect this damage. Thus in the heart we might expect the consequences of a parasitic

myocarditis and in this and other organs the effect of a deprivation of autonomic ganglion cells. The relative frequency and importance of these effects need to be determined.

#### 4.4 The latent or indeterminate stage and its development

Those who have passed through a recognized acute phase, or an unrecognized phase of acute infection, can at present be assessed only by the M.-G. reaction or by various changes in the heart or organs that have not yet given rise to clinical symptoms. With the development of clinical signs and symptoms we are on firmer ground.

It is very evident that in the rural areas of São Paulo, Minas Gerais and Goiás states there are remarkably high frequencies of peculiar forms of myocardial disease causing sudden death or congestive heart failure in the young and there are extraordinary high frequencies of affections of the digestive system and other organs producing such lesions as mega-esophagus, mega-stomach, mega-duodenum, mega-jejunum, mega-gallbladder, mega-appendix, mega-colon, mega-ureter and mega-bladder. All these lesions were demonstrated to the Consultants on autopsy specimens, the common lesions over and over again, as were the radiologic changes. In a wide experience covering many countries and many thousands of autopsies on a variety of races the Consultants have never encountered such a plethora of these mega-lesions as exists in central Brazil and it is clear that some peculiar local circumstances must determine this. To encounter in one small rural town one physician who has followed 600 live cases of mega-esophagus points up the extraordinary situation which occurs in these parts.

The mega-esophagus causing dysphagia is the pathological basis for the frequent and long-recognized dysphagia of these parts known as "mal de

engasgo." In recent years with improving facilities the frequency and importance of mega-esophagus has been increasingly recognized. According to Dr. Calil Porto the radiological diagnosis of mega-esophagus and the appreciation that this was the pathological basis of the common dysphagia was first made in 1950. Rural practitioners have therefore followed with keen appreciation the demonstrations by Professor F. A. Köberle and others of the pathological basis of mega-esophagus (Köberle and Nador 1956, Köberle 1963).

#### 4.5 Mega-esophagus in Goiania

Mega-esophagus in Goiania has been particularly studied by Professor J. N. de Rezende (1959, 1962, 1963) where disorders of esophageal peristalsis were found in 11.5% of the 7,100 cases of gastro-intestinal disease studied. In 570 cases of this disorder a M.-G. reaction was determined and the results were:

|          |     |       |
|----------|-----|-------|
| Positive | 520 | 91.2% |
| Doubtful | 18  | 3.2%  |
| Negative | 32  | 5.6%  |

The patients come mostly from rural areas where a high frequency of infected triatomids had been found. In such a rural area in 1,406 unselected individuals tested positive M.-G. reactions were given by 23.5% of those tested. In 441 cases of esophageal aperistalsis it was possible to detect cardiac damage clinically in 48.5% of the cases. Conversely in the cases diagnosed as Chagasic cardiomyopathy Professor J. N. de Rezende (personal communication, 1964) found that 30% had esophageal lesions. The effect this has on hospital statistics is shown by further figures from Goiania.

Thus in 2 years, with 2,352 admissions, 33 beds, there were

diagnosed:

|                        |                      |
|------------------------|----------------------|
| Acute Chagas' disease  | 9                    |
| Chagasic heart disease | 86                   |
| Mega-esophagus         | 103 (operated on 80) |
| Mega-colon             | 65                   |
| Carcinoma of esophagus | 13                   |
| Carcinoma of colon     | 5                    |
| Carcinoma of stomach   | 14                   |

It will be noted that among the cases admitted to this hospital in Goiania the megasyndromes were more frequent than the cardiopathies attributed to Chagas' disease.

Remarkably similar evidence was presented from the small rural town of Araguaí by Drs. Calil and Selmo Porto. This is a very severely affected area. The M.-G. reaction was positive in 24% of 1,400 patients examined in the clinic. Mega-esophagus was found in 47 subjects and only 2 of these had negative or doubtful M.-G. reactions (Porto & Porto, 1962). In Araguaí 50% of 280 patients with cardiovascular diseases were diagnosed as having Chagas' cardiopathy while the second most frequent condition (arterial hypertension) was found only in 21.4%. Patients living all the time in rural zones suffered from Chagas' disease more frequently (75.2%) than city dwellers (15.6%). The Chagas' cardiopathy was found in 53.5% in the group of patients born in rural country and migrating later into the city of Araguaí.

Obviously differences of this sort indicate varying selective factors operating among the patients. The evidence is overwhelmingly clear that in parts of central Brazil mega-esophagus is extremely common and that it has a very significantly high association with positive M.-G. reactions. There seems no reason to doubt on clinical and epidemiological



grounds alone that mega-esophagus is due to Chagas' disease, as Carlos Chagas himself suggested. No area is known in which the frequency of mega-esophagus is high but in which Chagas' disease is unknown, and until such a place is discovered the association should be accepted. It is impossible to believe that this high frequency of megasyndromes has risen by genetic selection in view of the enormous migration into these parts. Furthermore, a firm pathological basis for these conditions has been established both in man and in the experimental animal. The follow-up work in the studies of Dr. M. Okumura and his colleagues (1963) has shown how frequently the acute destruction of the ganglion cells in the mouse injected with trypanosomes is followed by the production of megasyndromes. Thus Dr. M. Okumura found that 18-20% of his infected mice who survived develop megacolon and other mega-lesions have been seen in other animals. The precise mechanism by which these changes are brought about may be disputable but there seems to be no reason for doubting the fact.

Professor F. A. Köberle at Ribeirão Preto has long been concerned with the ganglion cell lesions and has emphasized their importance as the basic lesion in Chagas' disease in this part of Brazil. In a long series of papers Professor F. A. Köberle and his associates have demonstrated a profound diminution in the numbers of ganglion cells in the enteric plexuses involving the esophagus, stomach, small and large intestines, and in other organs where megasyndromes occur. The work is laborious and exacting but has revealed a consistent pattern of changes which correspond with clinical findings and these clinical findings also correspond with the positivity of the M.-G. reaction to a highly significant degree. Thus in an earlier study Professor J. N. de Rezende (1961) quoted the figures of seven authors who correlated M.-G. reactions with megacolon or mega-esophagus

with M.-G. positivities varying from 78.2% to 100% with five of these giving figures varying from 89 to 97%. While the correlation in his own initial series of 332 cases of mega-esophagus was that 7.8% were M.-G. negative, in his series of 277 cases diagnosed as Chagas' cardiopathy the M.-G. negativity was 28.5%. Thus either the diagnosis was wrong or the evidence, supported by other observations, is that there is a greater correlation of M.-G. positivity with the megasyndromes than there is with the cardiopathy. Of the megasyndromes, mega-esophagus and megacolon are outstandingly the most common perhaps as Professor F. A. Köberle (1963) has remarked because these organs have to convey a good deal of solid material. Multiple involvement of various organs and portions of the gastrointestinal tract are common and every variety of combination has been seen both with and without cardiac lesions attributed to Chagas' disease, as will be discussed later.

It should be noted that in normal individuals throughout life there is a steady loss of ganglion cells and those that die off are not replaced. Megasyndromes when they do occur in individuals in other societies tend to occur late in life, the exception being those patients born with aganglionic segments in some hollow viscus, e.g. Hirschsprung's disease. This loss during aging is never more than 50% of all ganglion cells. It is obvious from Professor F. A. Köberle's studies that the loss of ganglion cells in Chagas' disease is much more severe, takes place early in life and is accompanied by early development of megasyndromes. This corresponds with clinical evidence. The Consultants were able to see evidence of megasyndromes in young children, e.g. mega-esophagus in a boy of 12 in Goiania whence Professor J. N. de Rezende (1962) in 820 cases recorded 131 under the age of 19 years and 22 of these were under 10 years. The majority of

his cases had lesions by the third decade.

There would seem to be, therefore, every reason to accept that the main lesion in these megasyndromes is a severe deprivation of ganglion cells, that there is a highly significant correlation of these syndromes with a positive M.-G. reaction and that there is clear evidence that this loss, at least in acute cases is due to invasion of the ganglion cells by leishmania with subsequent rupture and death of the ganglion cells. There is evidence to suggest (Alcantara 1959) that up to 80% of the ganglion cells in the heart may be irreversibly damaged in the acute phase, that the ganglion cells particularly liable to damage are those in close proximity to muscle cells as in the enteric plexuses and that those distant from muscle, e.g. the sympathetic paravertebral chain ganglion cells, are little if at all affected (Brandão 1962). The consequence is, as Professor F. A. Köberle has emphasized, that the gut thus suffers a parasympathetic deprivation.

#### 4.6 The pathogenesis of the megasyndromes

The observations of an acute parasite invasion of ganglion cells in various organs in the acute phase of Chagas' disease clearly opens the way to a wide variety of clinical, pharmacological and functional studies, and to further radiological and morbid anatomic studies designed to explore many aspects of the problems raised. There may well be a variety of factors which influence the localization and progression of these lesions. There may be a potent neurotoxin which aggravates the damage though there would not seem to be any need to invoke such an agent. It may be that the arteritic lesions found in mice and other animals by Dr. M. Okumura and associates (1960) may be additional factors in the pathogenesis of lesions. It may be that the megasyndromes may be aggravated by dietary deficiencies or

other factors concerned with diet. It may be that the high frequency of megasyndromes is due to hitherto undetected strain differences of Trypanosoma cruzi in these areas of Brazil. All these aspects and many others are deserving of much more study and these investigations are of the highest scientific importance and may well provide information which may help in the clinical management of the tragic sufferers from that disease. They are deserving of the fullest support. Nevertheless in the study, and particularly in the prevention, of human disease the problems of etiology and pathogenesis must be sharply differentiated. It is evident that the etiology of the megasyndromes in these areas of Brazil is as firmly established as that of a great many other diseases. It follows that elimination of infection with T. cruzi would prevent the development of these mega-diseases and lead to an enormous improvement in the health of the population. The main activities should focus on the elimination of new infections.

#### 4.7 The cardiac lesions of Chagas' disease

4.7.1 Frequency. The mega-diseases were dealt with first in this report for three reasons: 1) the majority of studies of chronic Chagas' disease have concerned the heart; 2) if Chagas' infection is truly indicated by a positive M.-G. reaction, the association with the mega-syndromes was stronger than that with cardiopathy; and 3) if the essential pathology underlying the megasyndromes was a loss of ganglion cells, the same pathology might well underlie some of the cardiac manifestations.

The liability of the T. cruzi to invade cardiac muscle cells has long been known and Carlos Chagas devoted particular attention to the heart.

Many of the acute changes in the heart and their clinical consequences are fully appreciated, especially as regards the individual patient but less attention seems to have been paid to the public health or community importance of the heart lesions of Chagas' disease and in central Brazil this omission seems very important. Because, as has been said, this is an area where sudden cardiac deaths in young people is so common that it has sunk deeply into the public mind. These areas are the "lands of the widows," the "towns of the fatherless," an area in which sudden deaths are so common that shop notices say "no sale without payment" because not a few when shopping die suddenly before their transactions are completed. Dr. Calil Porto drew attention to a patient of his aged 99 years with mega-esophagus. Of this man's sons and grandsons no fewer than 11 have died of sudden cardiac deaths before the age of 20 years.

Cardiac disease and, in particular, sudden cardiac deaths are major problems of this area and it seems particularly important to discover the cause of this and to determine if Chagas' disease is the etiological factor because Chagas' disease can be prevented. It is to this problem that the Consultants particularly addressed themselves though they would again emphasize that they used only material and information generously made available by Brazilian colleagues. In their studies the Consultants have made personal evaluations of series of autopsy and clinical cases, have studied many autopsy specimens of hearts as well as clinical notes, ECGs and radiographs and made fluoroscopic examinations of some patients.

#### 4.7.2 Cardiac disease in São Paulo city

Dr. C. Marigo of the Santa Casa da Misericórdia Hospital made available to the Consultants the protocols of the last 10,000 autopsies

carried out by himself and his associates in this hospital.

In those autopsies on patients over 15 years of age the cardiac diseases were:

|  |           |
|--|-----------|
| 1. Non-renal hypertension, arteriosclerosis and myocardial sclerosis | 576       |
| 2. Renal hypertensive disease (chiefly glomerulonephritis)           | 131       |
| 3. Myocardial infarction   | 199       |
| 4. Rheumatic heart disease   | 280       |
| 5. Chagasic heart disease (all with congestive failure)              | 132       |
| 6. Myocardiopathy of uncertain etiology                              | 65        |
| 7. Chronic cor pulmonale   | 66        |
| 8. Other forms   | <u>58</u> |
|  | 1,507     |

It should be noted that the autopsy rate in this hospital is over 90%. In children aged 0-10 years the heart diseases were classified as:

|                                    |     |
|------------------------------------|-----|
| Congenital malformations           | 239 |
| Infantile myocarditis unclassified | 32  |
| Endocardial fibro-elastosis        | 24  |

In the adults about 13% of the 1,507 cases fell either into the category of Chagasic heart disease or myocarditis of unknown etiology. All those with Chagasic heart disease had died with congestive failure.

The racial composition of these groups (where known) was:

| Groups   | Myocardial Infarction | Chagas' disease | Non-specific myocarditis |
|----------|-----------------------|-----------------|--------------------------|
| Negro    | 12                    | 31              | 5                        |
| White    | 77                    | 60              | 18                       |
| Mestizo  | 13                    | 33              | 7                        |
| Japanese | 2                     | 2               | 0                        |
| Total    | 104                   | 126             | 30                       |

Mortality below and after 50 years of age was:

| Group                                    | Under 50 years |         | Over 50 years |         |
|--|----------------|---------|---------------|---------|
|  | No.            | Percent | No.           | Percent |
| Myocardial infarction                    | 33             | 31.4%   | 72            | 69.6%   |
| Chagas' cardiopathy                      | 112            | 88.2    | 15            | 11.8    |
| Cardiopathies of un-<br>specified origin | 20             | 66.6    | 10            | 33.3    |

It was noted that all cases diagnosed as Chagas' disease not only died in congestive failure but had lived in endemic foci of Chagas' disease. An analysis of the non-specified myocarditis group confirmed that they differed in a number of respects from those diagnosed as Chagas' disease; some had died acutely, and they differed in respect of a wider range of heart weights, a different sex distribution and to some extent a different racial composition. No attempt was made to apply more specific labels either to the myocarditis cases nor to those in the category of "other forms". It is probable that some of the myocarditis cases were Chagasic but in the absence of either the finding of the parasite or of specific lesions or of positive serology due caution in respect to calling these Chagasic was certainly justified. In other cases lesions were seen similar to those elsewhere attributed to a viral myocarditis and in São Paulo and elsewhere it was found that both clinicians and pathologists were well aware and appreciative of forms of myocarditis and cardiomyopathy other than Chagasic. The Consultants were shown instances of these in all areas, including endomyocardial fibrosis, fibro-elastosis and other lesions. There did not appear to be any tendency to overdiagnose Chagas' cardiopathy on

pathologic grounds.

Subjects with Chagas' cardiopathy in this series differed from those with myocardial infarction. The majority died below the age of 50 years and their hearts were heavier.

| Heart weight<br>in grams | Chagas' cardiopathy |         | Cardiopathies of unspecified origin |         | Myocardial infarction |         |
|--------------------------|---------------------|---------|-------------------------------------|---------|-----------------------|---------|
|                          | No.                 | Percent | No.                                 | Percent | No.                   | Percent |
| -450                     | 20                  | 16.4%   | 8                                   | 26.6%   | 64                    | 61.6%   |
| +450                     | 102                 | 83.6    | 22                                  | 73.4    | 40                    | 38.4    |

Nearly all cases with Chagasic cardiopathies had heart weights of more than 400 g. The heaviest hearts were seen in young people and there was a very particular grouping of cases between the ages of 25-40 years, with heart weights of 500-700 g. Obviously the heavier the heart the shorter the life expectancy. In terms of racial groupings and age the negroes and mestizos seemed to have a poorer prognosis in that far fewer of them were found among those in the older age group, but the total number is too small for definite statement. One particularly interesting finding in this series was that the sex ratio was males 110 to females 17. This was explained by social factors. Only 6 instances of mega-diseases were found, 3 mega-esophagus, 2 megacolon and one with both lesions.

Irrespective then of etiology and specific lesions, parasites were found in the hearts in only 18 of these 132 cases.

It was evident that in São Paulo city there was an unusual type of heart disease, compared to our knowledge from other continents, causing



death from congestive cardiac failure in young people who had very large hearts. The series was selected in that it was mostly male and represented largely city dwellers who had left their rural environment.

#### 4.7.3 Cardiac disease in Ribeirão Preto

A further assessment of heart disease at autopsy was made at Ribeirão Preto. Every autopsy protocol from 1960 to 1964 (first six months only) was examined. There was a total of 1,064 autopsies above the age of 10; 732 males and 332 females. Diagnoses in the 1052 cases with completed records are shown in the table below (see page 39).

Chagasic heart lesions were diagnosed in 36.5% of all males and in 25.2% of all females autopsied. A wide range of cardiovascular diseases came to autopsy and were found in 63.7% of all males and 54.5% of all females and of those dying from cardiovascular disease 46% of the men and 39% of the women had Chagasic cardiopathy. While of those with abnormal hearts the lesions were those of Chagasic type in 55% of the men and 44% of the women. There was no special distribution regarding the ethnic group.

The age of death in Chagas' disease and in other cardiovascular diseases is summarized in the table (p. 40). The majority of patients with Chagasic cardiopathy died below the age of 50 in contrast to coronary heart disease, a similar finding to that from São Paulo.

See Table on page 40.

AUTOPSIES, RIBEIRÃO PRÊTO, 1960-1964 (first six months)

ALL CASES 10 YEARS AND ABOVE

| Cause of death - diagnosis                | No. of males                       | No. of females                   |
|---|------------------------------------|----------------------------------|
| A. Chagas' cardiopathy only               | 215 (46% of all CVDs)              | 73 (39% of all CVDs)             |
| Chagas' cardiopathy - plus other disease  | <u>42</u><br>257 (55% of all CVDs) | <u>9</u><br>82 (44% of all CVDs) |
| B. Other cardiovascular diseases          |                                    |                                  |
| Rheumatic heart disease                   | 30                                 | 35                               |
| Hypertensive ht. disease                  | 68                                 | 24                               |
| Syphilis                                  | 19                                 | 5                                |
| Coronary heart disease                    | 52                                 | 18                               |
| Congenital ht. disease                    | 2                                  | 3                                |
| Chronic cor pulmonale                     | 8                                  | 3                                |
| Cerebrovascular accidents                 | 3                                  | 0                                |
| Other                                     | 27                                 | 15                               |
| All cardiovascular diseases (A + B above) | 466<br>(63.7% of all deaths)       | 185<br>(54.5% of all deaths)     |
| Chagas' disease other than in the heart   | 8                                  | 3                                |
| All other diseases                        | 257                                | 133                              |
| TOTAL                                     | 731                                | 321                              |

ETHNIC GROUPS IN AUTOPSY MATERIAL FROM RIBEIRÃO PRÊTO

| Cause of death - diagnosis | Males    |            |       |           | Females  |            |       |           |
|----------------------------|----------|------------|-------|-----------|----------|------------|-------|-----------|
|                            | Afri-can | Cauca-sian | Mixed | Japa-nese | Afri-can | Cauca-sian | Mixed | Jap- nese |
| Chagas' cardi-opathy       | 60       | 167        | 30    | 0         | 19       | 56         | 7     | 0         |
| Other CVDs                 | 44       | 150        | 15    | 0         | 24       | 67         | 12    | 0         |
| No CVD                     | 45       | 190        | 24    | 6         | 34       | 82         | 17    | 3         |
| TOTAL                      | 149      | 507        | 69    | 6         | 77       | 205        | 36    | 3         |

AUTOPSIES - RIBEIRÃO PRÊTO

| Diagnosis                                    | Males   |         |                | Females |         |                |
|--|---------|---------|----------------|---------|---------|----------------|
|  | -50 yrs | +50 yrs | % below 50 yrs | -50 yrs | +50 yrs | % below 50 yrs |
| Chagas' cardiopathy as a cause of death      | 146     | 69      | 68%            | 52      | 21      | 71%            |
| Chagas' cardiopathy as an associated disease | 19      | 23      | 45             | 4       | 5       | 44             |
| Coronary heart disease                       | 7       | 45      | 13             | 1       | 17      | 5              |
| Hypertensive heart disease                   | 29      | 39      | 43             | 12      | 12      | 50             |
| Other cardiovascular diseases than Chagas'   | 71      | 138     | 34             | 45      | 58      | 44             |
| No heart disease                             | 140     | 118     | 54             | 84      | 49      | 63             |

4.7.4 Cardiac Disease in Goiania

The high percentage of cardiovascular deaths and in particular deaths caused by Chagas' cardiopathy is surprising and contrasts sharply with the series from São Paulo city. Any autopsy material is necessarily selected and the series from Ribeirão Preto is probably inevitably selected in respect to Chagas' disease by staff interests.

But firstly consideration should be given to whether 46% and 39% respectively of all cardiovascular deaths are impossibly high figures. In

Brasilia, 35% of all heart disease is attributed to Chagas' disease. In the Medical School of Goiania, Professor Joffre de Rezende made a breakdown of the etiology of heart failure in clinically diagnosed patients admitted to his medical wards during the past two years (see table below). These are clinical diagnoses only and the series excludes 40 cases which came to autopsy.

ANALYSIS OF HOSPITAL ADMISSIONS FOR CARDIAC FAILURE  
OVER THE PAST 2 YEARS - GOIANIA

| Etiology  | Males            | Females                           | Total |
|---|------------------|-----------------------------------|-------|
| Chagas' cardiopathy                               | 33               | 26<br>(1 x Ch. +<br>rh. ht. dis.) | 59    |
| Rheumatic fever and<br>rheumatic heart<br>disease | 4                | 4                                 | 8     |
| Myocardial sclerosis                              | 2                | 1                                 | 3     |
| Arterial hypertension                             | 2<br>(1 x anem.) | 2                                 | 4     |
| Chronic cor pulmonale                             | 1                | -                                 | 1     |
| Not decided                                       | 15               | 15                                | 30    |
| Anemia  | 1                | 4                                 | 5     |
| Hyperthyroidism                                   | 0                | 1                                 | 1     |
| Bacterial endocarditis                            | 0                | 1                                 | 1     |

  

| Age and Sex         | Chagas' disease |         | Other or undecided |         |
|---------------------|-----------------|---------|--------------------|---------|
|                     | No.             | Percent | No.                | Percent |
| Males, - 50 years   | 25              | 76%     | 8                  | 24%     |
| + 50 years          | 8               | 32      | 17                 | 68      |
| Females, - 50 years | 16              | 62      | 23                 | 82      |
| + 50 years          | 10              | 38      | 5                  | 18      |
| Total               | 59              | 100%    | 53                 | 100%    |

The actual mega-diseases seen in these patients were:

|                | <u>Male</u> | <u>Female</u> |
|----------------|-------------|---------------|
| Mega-esophagus | 10          | 6             |
| Mega-colon     | 3           | 1             |

This series demonstrated three things: the very high frequency of a heart disease attributed to Chagas' disease in Goiania (57% men, 48% women admitted with cardiac failure) and the frequency with which it affects young people; the high association of this heart disease with megacolon and mega-esophagus, and thirdly the fact that the high percentage of cardiac disease at Ribeirão Preto attributed to Chagas' is not an impossibly high one out of line with all local clinical experience. The experience in relation to the association of megasyndromes with alleged Chagasic cardiopathy is also not out of line with experience in Goiania. Thus:

| Area           | Male          |                      |         | Female        |                      |         |
|----------------|---------------|----------------------|---------|---------------|----------------------|---------|
|                | Mega-syndrome | Chagas' cardio-pathy | Percent | Mega-syndrome | Chagas' cardio-pathy | Percent |
| Goiania        | 13            | 33                   | 39 %    | 7             | 26                   | 27%     |
| Ribeirão Preto | 47            | 257                  | 18.2    | 15            | 82                   | 17      |

It can therefore be assumed that the autopsy findings at Ribeirão Preto are not far out of line with the clinical findings in a similar area where Chagas' disease is endemic.

#### 4.8 The pathology of Chagasic heart disease

##### 4.8.1 Diagnosis

The above conclusions were based on the assumption that a

clinical and pathological entity exists which can be diagnosed as Chagasic heart disease and which can be distinguished from other forms of heart disease. This is a crucial matter. The Consultants were able to examine upwards of 40 hearts in which such a diagnosis had been made. Almost all of these had exhibited evidence of congestive cardiac failure in life.

Certain features were common to all these hearts: almost without exception they were considerably heavier than normal, and exhibited severe degrees of hypertrophy and dilatation - these changes were seen in all the heart chambers. In a few there was severe hypertrophy without marked dilatation. Some hearts were of monstrous size, 1,000 g. or more.

The visceral pericardium frequently showed evidence of a past pericarditis in the form of irregular white patches. There were two frequent changes in the configuration of the hearts. First there was often a most marked dilatation of the pulmonary conus in the absence of any lung disease, the dilatation at times being almost aneurysmal. Secondly the apex was often bifid presenting two swellings at the apices of the right and left ventricles or a bulging of one or other apex which presented beyond the apex of the other ventricle.

It is well appreciated that relative to other portions of the ventricular walls the apical portion is distinctly thinner but in many of the hearts examined the apical thinning was remarkable and of a most peculiar type. Two sorts of lesion were seen. In one type there was a deep narrow "V" shaped cleft rather resembling a square root sign ( $\sqrt{\quad}$ ) in that the endocardium on the two sides was at slightly different levels. In other cases the swelling had broadened out and become spherical so that what at first sight seemed a large aneurysm, up to 3 cm. across, had

developed. The extreme apical portion of this was often white in color, almost paper-thin and very translucent and the muscle fibers in this part had either disappeared or were represented by a few sparse fibers. Some inflammatory cells might be present but were not seen in sections from a number of cases. There might or might not be some superimposed blood clot and there might or might not be some fibrosis but they were often not present and it seemed as if the endocardium had fused with the epicardium in many of these lesions.

(In hearts opened by the usual conventional methods these lesions may not be easily seen and located; so Köberle uses the technique of slicing the heart from apex to base to open both ventricles at their apices. This is an excellent method for demonstrating these lesions though it is not advised in other forms of heart disease).

Apart from these apical lesions, fibrosis may be seen in a few areas of the myocardium but was not very evident and when present is small-scale as were microscopically visible collections of inflammatory cells which were not usually evident to the naked eye. In many cases, however, there were some curious changes visible in the cut surface of the interventricular septum. There seemed to be a subendocardial layer of lighter muscle tissue which contrasted with the darker muscle in the middle of the septum. It seemed as if there was some differentiation going on between muscle layers.

The Consultants' observations were fully in accord with the previous descriptions of many Brazilian workers which are summarized in the detailed monograph of Professor C. Mignone (1958). There are certain aspects of these ventricular "aneurysms" to which Mignone has drawn particular attention. In other countries, ventricular aneurysms other than those

resulting from myocardial infarction are extremely rare and single cases are considered worthy of report (Dubb et al 1964), but aneurysms resulting from infarction do not resemble in the least these clear-cut, smooth-edged, non-fibrosed "aneurysms" as seen in Chagas' disease. Even more surprising is it that no one had ever seen one of the ventricular apical aneurysms rupture despite the many hundreds of cases examined. The Consultants were informed that Carlos Chagas had seen one rupture but none of the individuals consulted had personally seen such a case or heard of one. That ventricular "aneurysms" should be so abundant and yet never rupture suggested to Mignone that some unusual pathological reaction underlay this lesion. He made most detailed studies of the anatomic location of lesions in these hearts (Mignone 1958) by studying multiple transverse slices involving the myocardium of both ventricles and these showed that the lesions at the ventricular apices differed in distribution from those of other parts. Thus, in most parts the fibrosis and cellular infiltration were mostly in the inner two-thirds of the myocardium; at the apex it was in the outer third. He further noted that the initial myocardial apical lesion was not a localized myocarditis but a clefting of the inner portion of the myocardium in which the muscle bundles are dislocated rather than destroyed and that dilatation of the heart increases the dislocation and stretched out the muscle so that endocardium and epicardium come into proximity. What Mignone showed was that the apical lesion is in strict terms a lesion of the vortex of the heart as defined in classical anatomy, and that the muscle fibers and bundles of the vortex as it were unwind.

This ingenious concept of Mignone's has been the subject of further study by Pedro Raso (1964) who has provided superb photographs of hearts



in which the sino-spiral and bulbo-spiral muscle bundles have been dissected. It would seem quite evident that the explanation of the ventricular thinning and "aneurysms" lies in the separation of the muscle bundles at the vorticular region at the apex of the ventricles and this contributes to the peculiar configuration of the heart. It was therefore not surprising that at Ribeirão Preto investigators demonstrated to the Consultants that the pulmonary conus dilatation was part of the same process involving the same muscle bundles that were connected with the apical lesions. It was also demonstrated that section of this particular muscle bundle in a Chagasic heart led to an immediate dilatation and herniation of the endocardium at the apex which was not apparent in the gross intact specimen.

It was thus apparent that the main lesion in these hearts was a slackening or loosening of the normal muscle bundles so that the pulmonary conus was bulged out, the vortex had unwound and protrusions of endocardium took place at the apices. It was equally obvious that in the dead heart these lesions were more strikingly obvious than in the living and that the lack of rupture of the "aneurysms," so contrary to expectation, was due to the fact that they were protected from the full force of the ventricular eject pressure by the coming together of the muscle bundles in systole to produce the eject pressure. While morphologically "aneurysms", functionally no such localized weakness of the ventricular wall existed, which is why they did not rupture.

In the cases of Chagasic cardiopathy at autopsy at Ribeirão Preto such endocardial apical protrusions were found in 50% of both sexes by Köberle and his associates. Raso in 40 dissected Chagasic hearts found apical lesions in 65%, the left vortex was involved in 92%, both left and right in 38% and an

isolated right vortex lesion was found in 7%. If the conus dilatation is, as it appears to be, part of this same lesion the frequency of this type of lesion will be higher than the figures given.

These discoveries of the true nature of these cardiac lesions of chronic Chagas' disease are so recent that they can only be discussed by the Consultants in a speculative way and doubtless much more will soon be learned about them. But based on considerable experience of many types of myocardial disease and myocarditis the Consultants can say that this lesion is unique to this condition regardless of its pathogenesis and etiology. The Consultants know of no other condition in which such a loosening and unwinding of the cardiac muscle bundles occurs and this suggests it is due to some highly specific mechanism operative in this region.

#### 4.8.2 Pathogenesis

From the pathogenetic viewpoint the various theories have been described by Raso (1964). Three obvious possibilities exist, that it is due to an inflammatory process, that it is a vascular lesion, or that it is nervous in origin. From specimens of Professor Mignone and of Professor Köberle it is obvious that neither dilatation nor hypertrophy is a necessary accompaniment though these are present in the majority of cases seen. It is difficult to conceive of any vascular lesion which could produce a combination of muscle defects in affected muscle bundles in such a way that they unwind in this fashion over such considerable areas of the myocardium. The careful studies of Mignone (1958) on the distribution of cell infiltration and fibrosis and the mechanical consequences of such lesions make a case for the lesions being a direct result of the myocarditis of Chagas' disease. The objections to this lie in the fact that similar

lesions are not known to arise in any of the many other forms of myocarditis or myofiber destruction with which the Consultants are familiar or in any form of myocardial fibrosis. This suggests that the distribution of the lesions described by Mignone may be a secondary phenomenon rather than a primary lesion or may be epiphenomenal.

The idea that seems more attractive, as Raso suggests, is that this cardiac lesion is due to the destruction of the ganglion cells in the heart described by Köberle and his associates. Their conclusions of the loss of ganglion cells of the heart are based on studies of the area between the superior vena cava and the inferior vena cava in 100 human hearts. Block area counts of serial sections of this area have revealed a severe diminution in the number of ganglion cells in Chagasic hearts and it appears that when the reduction reaches 25% then such lesions as have been described develop as judged by such clinical criteria as sudden death or the onset of congestive cardiac failure. Moreover, the diminution in general correlates well with heart size, the greater the diminution in cases of congestive failure the greater the heart size.

The evidence that the bulk of the destruction of the ganglion cells takes place in the acute phase has previously been mentioned. It is also evident that in hyperacute cases cardiac lesions as well as mega-diseases can develop quite rapidly though usually these lesions do not appear till the teens. It would seem however that the ganglion cell losses do not correlate closely with the ECG changes, nor with the frequent AV blocks seen and the pathology responsible for the lesions of the conduction system is not well understood.

The relationship of all these lesions to sudden death is also not

well understood. It appears that death occurs suddenly and unexpectedly in about 70% of all patients with congestive failure from Chagasic heart disease and about one third of the cases found at autopsy to be Chagasic heart disease have died suddenly without previous congestive failure. There is thus evidence in at least 50% of Chagasic hearts that there is the loosening and unwinding of the muscle bundles, that there is loss of ganglion cells, and that there are in these and in many other cases areas of myocarditis with muscle fiber destruction. The nature of the pathologic changes in the conduction system is not known, the precise significance of the various lesions in respect to the signs of cardiac disease is not known and the chain of events that so often conduces to sudden death, with or without heart failure is not known. Much further study of the cardiac pathology in Chagas' disease is needed.

#### 4.9 Diagnosis of chronic Chagasic disease in the living

It has been mentioned above that there are no difficulties in diagnosing the acute Chagas infection where the heart may be affected to a varying degree. The problem becomes more difficult when we seek signs of the chronic Chagasic cardiopathy with a positive M.-G. reaction and without symptoms of the disease or when one attempts to evaluate the prognostic significance of some alterations of cardiac function.

As for the diagnosis of the chronic Chagasic cardiopathy it has been shown that at autopsy the heart in the great majority of cases shows typical changes and that the diagnosis can justifiably be made even in the absence of the positive complement fixation test. Progressive diminution of the contractile elements in the heart and typical localization of the lesions are reflected in the diminishing working capacity of the heart ending in

clear-cut cardiac failure and in frequent alterations in the excitability of the heart and conductivity of the heart beat. Some of these alterations may lead to sudden death. When the lesions involved more the conductive systems of the heart, arrhythmias and sudden death may occur without great enlargement of the heart. At the other extreme are subjects with progressing enlargement of the heart and sooner or later apparent signs of cardiac insufficiency.

The heart may be enormously dilated so that the apex can be localized in the axilla. One rarely sees a similar enlargement of the heart in hypertensive or coronary heart disease. The low output of such heart can be assumed from the low pulse pressure in the periphery, frequent absence of marked hypertrophy of the left ventricle (by physical examination as well as ECG) and by the soft, weakly audible heart sounds in the mesocordium. The great enlargement of the heart contrasts with the small sometimes invisible aortic arch and normal vasculature of the lungs. The absence of marked nocturnal dyspnea typical for hypertensive heart disease corresponds well with this x-ray finding suggestive of global myocardial weakness. The heart on skiascopy looks flaccid and has been described sitting on the diaphragm as an "iceberg" and sometimes even showing the respiratory movements corresponding to changes of the intra-thoracic pressure.

Pulsations of the heart are diminished and sometimes absent. The unaccustomed person might be misled into making the diagnosis of exudative pericarditis. The anatomical lesion at the apex, in the pulmonary conus, and sometimes on the dorsal part of the left ventricle near its base (Dr. K. Brass, 1964), may alter the usual contraction wave of the ventricles. The paradoxical pulsation at these areas may be seen on skiascopy and even

proved by x-ray kymography (Dr. J. J. Puigbo, 1964). One is able to recognize them in a subject with enlarged heart and without clinical symptoms of heart failure.

An arrhythmic heart beat is caused most frequently by ventricular extrasystoles and different kinds of conductive defects (heart blocks). Auricular flutter and fibrillation occur less frequently. Pinto Lima, Spiritus and Tranchesi (1956 - 1958) analysed the ECGs in 103 patients in whom the autopsy confirmed the diagnosis of Chagasic cardiopathy. Normal ECGs were found in 2 patients only. Extrasystoles were found in three quarters of the patients, AV blocks of the 1st or 2nd degree in 22 cases, and total AV block in 23. Complete right bundle branch block was diagnosed in 37, incomplete in 12; and left bundle branch block was found in 29 cases, 5 of whom were aged 12 to 23 years. Auricular flutter and fibrillation was found in 13 cases only.

Focal damage of the myocardium finds itself expressed also in deformation of the repolarization phase on ECG in different localities and may indicate subepicardial fibrosis. Many studies confirm that a combination of right bundle branch block with ECG signs of the loss of usual spread of electrical impulse in the apical or septal part of the heart is typical for Chagas' cardiopathy.

The picture corresponds well with the anatomical features described above. The enormous enlargement of the heart seems to be relatively seldom associated with marked signs of ventricular hypertrophy.

A similar clinical and electrocardiographic picture was described by Dr. J. E. López and Maekelt (1960) in Venezuela in patients with directly proven chronic Chagasic infection either by xenodiagnosis or myocardial

biopsy, and seemed to apply to chronic Chagasic cardiopathy in other areas (Rosenbaum, 1964).

#### 4.9.1 Differential diagnosis

The marked enlargement of the heart and the absence of damage to the valves with the exception of signs of relative mitral and tricuspid incompetence enable one to differentiate the syndrome from chronic rheumatic heart disease. Syphilitic and hypertensive heart disease can also be distinguished reasonably well.

The clinical differential diagnosis between coronary heart disease and chronic Chagasic cardiopathy may sometimes cause some problems. Both conditions, however, differ in several aspects. It has already been mentioned that Chagasic cardiopathy occurs in young age, is more or less equally distributed in both sexes, the enlargement of failing heart is greater and is not accompanied by chest pain characteristic for ischemic heart disease; arrhythmias and conduction defects are more frequent in Chagas' cardiopathy than in atherosclerotic coronary heart disease in which one encounters more often auricular fibrillation than multifocal ventricular extrasystoles or heart blocks. Moreover, we were told repeatedly and had demonstrated to us that extra-muscular branches of the coronary arteries are usually open and without obliterative atherosclerosis or thrombosis. The possibility has been raised (Torres, 1941) that anatomic features of progressive myocytolysis with little or no inflammatory reaction may be the consequence of primary vascular damage of small coronary vessels. Vascular alterations have been described in experimental Chagas' disease but the histological picture of the human chronic Chagasic cardiopathy shows more damage of the muscle fibers than of the vessels.

It is felt, however, that coronary arteriography in autopsy material could easily provide information about the coronary vascular bed. The Consultants are pleased to know that steps have been taken to apply the techniques suggested at the WHO meeting on cardiomyopathies in Geneva in 1964.

Greater difficulties might arise in differential diagnosis of the cardiopathy ascribed to Chagas' infection from the other parasitic infestations of the heart or from the primary disease of the heart of other infectious, toxic, metabolic or unknown etiology. In the description of the anatomical picture it has been stated that no similar condition is known to the Consultants from personal experience. Keshan Disease from North-east China, as described in 1959 (Tung and T'ao 1959) looks to some extent similar anatomically and also the clinical description of rapidly progressing heart failure with arrhythmias may resemble the cardiopathy caused by the American trypanosomiasis. The character of Keshan Disease, which appeared as an epidemic, with a fairly rapid course, seemed to indicate the virus etiology although at that time no specific virus had been discovered. The pathogenesis of the condition is not known but it is fair to assume that a similar clinical and anatomical picture may be made by varying etiological agents affecting the same structure of the heart, e.g. the nervous cells in the auricles. It is not known whether Keshan Disease also involves the gastrointestinal tract and other tissue apart from the heart.

Chronic toxoplasmosis in the heart as described by Niedmann et al (1959-1962) may look similar clinically but diagnosis is possible from the serology and from the heart biopsy. Moreover, only a very small number of



cases with toxoplasmosis of the heart has been described compared to the great frequency of cardiopathies ascribed to American trypanosomiasis.

Summing up personal experience with all they were able to analyze from discussion and published papers, the Consultants feel that the morphological and functional picture of chronic Chagas' cardiopathy in people with symptoms may be considered very suggestive. The diagnosis in the great majority of cases can be corroborated by the positive complement fixation test; further confirmation comes from the epidemiological evidence of birth and stay in the endemic area or being bitten by the triatomid bugs or having passed through an acute Chagas' infection phase.

#### 4.10 Chagas' infection and Chagas' cardiopathy (heart disease)

While it appears that the clinical diagnosis of chronic Chagas' cardiopathy is not difficult in patients with manifest heart failure, the problem did not seem clear as to when one can make the diagnosis of chronic Chagas' disease in subjects once infected but without signs of cardiac failure. The problem, in the opinion of the Consultants, concerns mainly the diagnostic and prognostic value of the M.-G. reaction and of the most common clinical signs of cardiac damage, that is, alteration of the excitability and conduction of the heart beat and enlargement of the heart.

#### 4.11 M.-G. reaction and Chagas' heart disease

Evidence has been presented above that the M.-G. reaction is almost specific for infection with T. cruzi and that the positivity remains so during the whole life in most cases. It has also been shown that in the parts of Brazil visited by the Consultants heart disease very commonly occurs which has certain features which are unique and would indicate a

highly specific etiology. In only a small proportion of cases can leishmania be demonstrated in the heart muscle but we can use this cardiac lesion to assess the reliability of the M.-G. reaction. In Ribeirão Preto, where possible and indicated, an M.-G. reaction is done, either in life, or entirely separately at autopsy using serum or pericardial or other fluid. If a positive reaction is ever obtained, either in life or at autopsy, it is recorded in the table as positive. Thus from 1960-1964 in 300 cases diagnosed as Chagasic heart disease the percentage of negative M.-G. reactions was 18.9 and the reaction was positive in 81.1%, in other forms of heart disease it was positive in 10.7% and in those without any heart disease it was positive in 10.8% of those tested (see table page 20). The figure of about 10% M.-G. positive reactions was about the level of positive reactions in the community according to information given to the Consultants. This figure has remained very stable at autopsy in the years 1960-1964 but the percentage of positive M.-G. reactions in the cases diagnosed as Chagas' heart disease has never risen above 90%.

Personal examination of a series of hearts in which the M.-G. reaction was negative, even after several repeat tests, showed that they were in all respects identical with those in whom the M.-G. reaction was positive. In several cases the M.-G. reaction was negative, (in one case after 5 repeat tests in life and one at autopsy) yet parasites were found in the heart muscle.

One may conclude that the diagnosis of Chagas' disease by the pathologist can be made in cases where the M.-G. reaction is negative on the basis of specific lesions - hence a pathological diagnosis of Chagas' heart disease can be made without the M.-G. reaction.

This corresponds with the views of morbid anatomists elsewhere and with the evidence regarding the mega-diseases in which the positivity rate is higher, and from the evidence of clinicians in the inland regions. None would hesitate to make a positive diagnosis in the presence of typical clinical evidence in a patient who came from an endemic area despite a negative M.-G. reaction which several independent estimates agreed was seen in 10-15% of cases.

The high correlation between the positive M-G. reaction and the characteristic clinical and anatomical picture of the described chronic heart disease is highly suggestive of the same etiology and this is further confirmed by positive proof of the parasite in some of them. It does not seem therefore necessary to look for another etiological agent associated with the trypanosoma infection for the pathogenesis of this type of chronic cardiopathy. The question remains, however, as to how many subjects with positive M.-G. reaction, that is those who once had been infected, will develop Chagas' cardiopathy and what are the early signs of damage to the heart - in other words, what is the prognostic value of the M.-G. reaction, of ECG and X-ray of the heart.

Ramos, Pedreira de Freitas and Borges (1949) surveyed 500 people from a population of 4,000 in one area of the State of São Paulo. 337 had positive M.-G. reaction; 37 of them had clinical and ECG alterations suggestive of Chagas' cardiopathy. Right bundle branch block, multifocal ventricular extrasystoles, altered AV conduction, and primary alteration of the T waves, were most frequent. The ECG was not altered in 111 subjects with negative M.-G. reaction. Some subjects with positive M.-G. reaction had evidence of hypertensive and rheumatic heart disease respectively. Nine per

cent of persons in the highly endemic area presented therefore signs of cardiac damage.

Laranja et al (1951) found ECG alterations in 29 out of 101 subjects with positive M.-G. reaction from the State of Minas Gerais. Rosenbaum and Cerisola (1959) described several abnormalities on ECG in 146 out of 504 subjects with positive M.-G. reaction from several endemic areas in Argentina. A survey of the population in the Belén area (State of Carabobo, Venezuela) revealed cardiovascular damage in 27% of subjects with positive M.-G. reaction and in about 90% of these it was ascribed to chronic myocarditis.

These examples taken from different areas demonstrate that 10 to 30% of the people with positive M.-G. reaction have some signs of alteration in the heart. So far we have not been able to find enough data from longitudinal studies. The evidence presented above that the great majority of subjects with Chagas' cardiomyopathy die below the age of 50 suggests the more favorable prognosis for those with Chagas' infection who did not develop the Chagasic cardiopathy before this age. A longitudinal study of a population sample from endemic areas is badly needed and the 3-year follow-up of more than 1,000 subjects from the Belén area in Venezuela should, in the Consultants' opinion, continue for several years and similar studies should be organized elsewhere.

The prognostic value of ECG alteration has been assessed by C. C. Porto (1963), who observed 503 cases of Chagas' disease (246 males and 161 females), from several municipalities of the State of Minas Gerais for six years. Ninety-six of them (71 males, 25 females) died during this period. There were 36 sudden deaths, 53 died from cardiac decompensation and 7 from extra-cardiac causes (once as a consequence of mega-esophagus, 4 times following

abdominal surgery, once malignant tumor). Sixty-three deaths were in subjects younger than 50 years and 23 between 51 and 60. Those with normal ECG at the time of the examination had apparently a better prognosis although 11% of deaths were from this group.

Chronic Chagasic cardiopathy was diagnosed in more than half of the patients with cardiac failure, its evaluation sometimes being interrupted by sudden death. The normal ECG in general points to a good prognosis. The electric alterations indicating possible fibrotic lesions, such as multiple extrasystoles, RBBB with the left axis shift, LBBB, or signs of apical fibrosis, paroxysmal ventricular tachycardia and in particular total AV block have a worse prognosis than RBBB without shift of the axis, primary changes of the T wave or even low voltage of QRS complex. It seems also that the latter signs are more frequently found in the initial stage of the cardiac damage.

The Consultants did not encounter prognostic studies of unselected population groups in whom the full clinical ECG and radiological picture would be compared with the complement fixation tests; with the exception of the study in Belén. In their opinion such studies are urgently needed.

##### 5. The importance of Chagas' disease in central Brazil

The purpose of the Consultants' visit was to assess the present situation in central Brazil as regards Chagas' disease, and to make recommendations.

It is evident that triatomid vectors of T. cruzi are abundant in the rural areas and in the small towns especially in houses made of mud and wattle (pau-a-pique) which are so common. These often develop cracks and

crevices most congenial to the thoroughly domesticated local triatomid vectors. However, some of these local vectors live in non-human buildings and walls and will invade houses which may have been previously cleansed by spraying (Pereira Barretto, 1964). Many potential animal reservoirs of the trypanosome exist though the exact importance of these in relation to the actual situation in Brazil is not clear. It may be that the most important practical reservoir is man himself.

Very high rates of infestation of the local triatomids with the trypanosomes are recorded and the overall rates include focal areas and houses where the rate may be 100%. Opportunities for being bitten by infected triatomids are obviously abundant and this is a major hazard of the region particularly to children.

Most available data refer to the prevalence of infection, but less to human disease. High rates of infestation and infection of triatomids correlate with high rates of positive M.-G. reactions in humans and with the development of disease conditions attributed to infection with T. cruzi. The only reported exception to this was in Rio Grande do Sul, an area the Consultants did not visit, where they were told that high rates of triatomid infection, up to 64%, were not associated with high M.-G. positivity rates nor with human disease. Substantiation of these reports would seem necessary.

In the areas visited by the Consultants, the percentage of M.-G. positive reactors was reported as from 10-23% of the population tested. If a rate of 10% is accepted, on a population basis between four to five million people at least would be affected. The evidence seems sound that the M.-G. reaction, if positive, does indicate infection with T. cruzi, that false

positives are rare and there is evidence to suggest that a positive M.-G. reaction indicates the presence of living parasites in the human host. There is also evidence that once the M.-G. reaction becomes positive it rarely reverts to negativity in the human.

On the other hand both clinical and morbid anatomical evidence exists, resisted by those in other disciplines, that the M.-G. reaction may be negative in 10-15% of those dying from Chagas' disease, indeed perhaps up to 20%, and that some cases in which living parasites can be demonstrated are persistently M.-G. negative. As the M.-G. reaction is the best method of community survey currently investigated it would appear necessary that the exact position be established as quickly as possible. It should be easy to set up an investigation of the kind in which the serological results and the morbid anatomical findings are studied in isolation and the results correlated by an independent observer. For the moment it would seem safer to assume that the M.-G. reaction underestimates the true frequency of infection by 15-20%. This would considerably increase the number of infected persons who are at risk. In view of the correlation between the M.-G. reaction and positive xenodiagnostic tests and of the evidence of the hazards of spreading the disease by blood transfusions derived from infected donors it is evident that this large pool of infected persons is a major health hazard to others so long as the vectors are widespread. This points to the necessity of providing an efficient trypanocidal drug if one can be discovered and it is possible that this will be the major use for such a drug, i.e. the sterilization of infected humans as regards the trypanosomes.

An overall rate of 10% of M.-G. positive reactions includes houses and other local areas with very much higher rates. Thus in one region where

4,000 individuals randomly selected were surveyed 55% of them were M.-G. positive and 9% of the population showed evidence of Chagasic heart disease. There are areas of even higher M.-G. positive rates. Where the rates are very high, triatomids abundant and their infestation rates high, it would seem impossible that some people would avoid getting bitten by infected bugs, yet some always seem to escape. Perhaps there are difficulties or special circumstances which prevent their getting infected and some may possess a natural immunity or develop sub-clinical infections without becoming M.-G. positive. Studies of the normal people in very heavily infected areas may be rewarding.

No cases of a second attack of acute Chagas' disease seem to have been seen or recorded yet the victims under existing circumstances must often be repeatedly bitten by infected bugs. There is considerable divergence of opinion as to whether repeated re-infection is important. Rural practitioners are strongly of the opinion that repeated re-infection aggravate the lesions and conduce to more severe lesions and earlier death. Big city opinion does not consider repeated re-infections important. Both agree that the best treatment for Chagas' disease is a "well-lined pocket" which enables the individual to live without severe exertion or great stress or strain. From the public health aspect, however, the importance of repeated re-infections must be established or refuted and this could be done by a longitudinal study of those who have moved from endemic areas to non-endemic areas.

As stated above, the risk following infection seems not to have been established by longitudinal and follow-up studies of subjects with positive M.-G. reactions and these are obviously necessary. An ethical dilemma here



protruded itself in that clinicians do not like to inform individuals of the M.-G. reaction as positive because of the emotional reaction; for many regard this as a death warrant and believe they are in constant danger of sudden death. This may be so but the available evidence does not warrant this. It may be that an appreciable proportion live out a normal life span without any disabilities or only minor disabilities. The whole question does need a full investigation because it is of vital importance to several million people. The question is if this can be answered in a timely manner, by a series of small-scale investigations. The Consultants believe that Chagas' disease is such a major public health hazard in this area that small-scale investigations to this end would not be profitable.

For it is obvious that all investigations are hampered by an utter lack of adequate statistics. Chagas' disease is not a notified or registered disease. The first step is to set up the machinery to notify the disease to some central organization because at every stage information currently available is inadequate.

Thus the frequency of acute Chagas' disease is unknown. Most think it is rare but it is evidently not rare in Goiania and may not be so rare in other areas. The acute cases are very important because the start of the illness can be dated accurately and follow-up studies based on these known dates. It is equally evident that these cases can be studied, within the accepted code of medical ethics, to provide the badly needed information in humans as to whether the acute attack is the period of maximal tissue damage. It is equally obvious that if an efficient trypanocidal drug is produced, the acute cases will be the ones likely to benefit individually most from the drug and an efficient method of bringing these cases to light

by notification at the earliest possible moment will be necessary. The Consultants have reasons for supposing that an efficient notification system would bring to light many more cases of acute disease than are currently believed to exist.

Cases of infection from blood transfusion are the human equivalents of the experimentally infected animals and careful study of these may show if the maximal damage is indeed only in the acute phase. That the hazard of the transmission of infection by the blood of subjects not having positive M.-G. reactions is recognized and as far as possible prevented only emphasizes the importance of the most detailed study of such cases that occur. It is suggested that special steps be taken to set up such studies.

While it is generally accepted that most acute infections occur in young children, adult cases were also observed. However, the cardiac lesions of chronic Chagas' disease are not commonly seen before 17 years of age. Study of subjects in the latent interval is obviously necessary. There is at present no drug that will kill the parasite in the host and there is evidence that were such invented the effect upon those now infected might be negligible save that they might be rendered non-infective. All that can be hoped for is to slow down, ameliorate or perhaps prevent the lesions of the late stages from developing. If this is to be done, then much more detailed functional investigation must be made of young Chagasic patients in the latent stage of Chagas' disease

All this to be truly effective will require the notification and registration of cases of Chagas' infection. The Consultants consider this should include all acute cases of Chagas' disease however the infection is acquired, all patients who have positive M.-G. reactions and all who show

evidence of lesions of chronic Chagas' disease. Notification will be essential to adequate public health control.

The evidence would suggest that Chagas' disease is a major public health problem of these areas in Brazil. It also suggests strongly that steps should be taken as quickly as possible to prevent new infections from occurring. This can be achieved by the spraying of all dwellings with gammexane (benzene hexachloride) as quickly as possible. Pilot experiments have been carried out and much important data are now available (see Pedreira de Freitas, 1963). The insects are highly susceptible and thorough careful spraying should eliminate the vectors from infected dwellings and cause a rapid reduction in the numbers of infected children as judged by the M.-G. reaction.

The Consultants consider that it is of the highest importance that control measures should start as soon as possible. They were informed in São Paulo State that the apparatus, equipment, personnel and maps are available in the Department for National Services against Malaria and Rural Endemics - and that the staff and officers are eager to undertake this work if the insecticide can be provided. They have not started because the importance of Chagas' disease as a public health problem has not been realized. Despite current anxieties about the malaria situation in Brazil it would appear that in central Brazil Chagas' disease is the major problem. The Consultants hope there will be no obstacles to starting a campaign against domestic triatomids as soon as possible.

Close entomological and parasitological control will be needed both to assess the results and to prevent reinfestation. There seems no doubt that an adequate campaign of gammexane spraying against the domestic vectors

would reduce the new infections with Chagas' disease.

This would leave the sad army of those now infected for whom there is no effective treatment and over whom may hang the constant menace of sudden death, of the development of megasyndromes and of congestive cardiac failure. The whole problem seems not to have been adequately studied.

To this end the Consultants consider that the first step must be notification and registration of acute and chronic cases. This is both a local and an international problem, in that the I.C.D. list provides only the place and the 4th digit under trypanosomiasis - for Chagas' disease, (Category 121.1). But in advance of such agreement the Consultants would suggest that the appropriate local and Federal authorities in Brazil and possibly in other countries with endemic Chagas' disease should set up an efficient system of notification and registration if only to get an indication of the size of what obviously constitutes a major national health problem and to enable the risks of Chagas' infection to be assessed more accurately. Current knowledge is based on small surveys and investigations based on the work of devoted and much-to-be-admired single-handed or small-group investigators. It is their work which has drawn the outlines of this major public health problem and these outlines need to be filled in by national action.

In suggesting this the Consultants are not insensible to the existence of other major public health hazards of national concern in Brazil and which must be considered. Of these probably the most important is schistosomiasis. This is a problem of major importance to many countries, it is under investigation in many of them and unhappily at present efficient control measures are not possible.

But Chagas' disease can be controlled. It can be expected that hookworm disease will diminish with improvements in diet and in sanitation which are taking effect in the rapid development of Brazil. Malaria is being controlled for the most part in Brazil and though resistant strains of parasites are causing concern the matter is being efficiently handled and cure is possible by conventional methods. There is, however, no cure for Chagas' disease.

The economic grounds for preventing Chagas' disease are very strong. The frequency of Chagasic heart disease causing death in young people has been shown. Much attention has been paid to the tragic high death rates of young children in many tropical and subtropical countries. Regrettable as this is, it is not economically so catastrophic as the loss of young fathers and mothers in the age group 20-45, in the peak of working life. When to the pure economic loss caused by invalidism and death of so many in this age group are added the family losses, the emotional effects and disruption of family life and the cost of rearing so many fatherless, one realizes the immense economic strain imposed on the community. The follow-up study of 503 patients of Dr. C. Porto has been mentioned. During a period of 6 years there were 96 deaths (19%) and of these only 7 were not due to Chagas' disease. One area has been alluded to in which 9% of the total population had evidence of heart disease believed to be in the main Chagasic. The bulk of all these patients are young adults under the age of 45. When to these are added those with megasyndromes it is obvious that Chagas' disease is a major public health problem.

Even if new infections are stopped, several millions of infected persons in Brazil will for many years pose major medical problems. The

follow-up will be much easier if indeed a notification and registration system is set up. But both in relation to the megasyndromes and to the cardiac lesions there are a variety of problems needing investigation. While the heart lesions were considered merely a parasitic myocarditis the problem was simply one of local interest and of mere curiosity to the rest of the world. The labors of Brazilian pathologists have shown that this is not the case. The lesions are a myocarditis but in addition with denervation of the heart by destruction of ganglion cells and separation of the muscle bundles. This is of immediate importance to cardiologists in all parts of the world for it seems to be a unique type of heart diseases. Studies of every aspect of the structure and function of these hearts including hemodynamic, electrical and metabolic changes, as well as their pharmacological behavior now becomes of immediate concern to all interested in cardiac pathology and heart disease. So does the study of the structural changes in the conductive system, of the pathogenesis of these lesions and their functional consequences. Central Brazil thus is a natural laboratory for the study of the consequences of cardiac denervation, a subject which previously could only be studied by various laborious and complicated experimental procedures in animals. If the Consultants do not suggest more precise detailed studies in this field it is only because the need for them and the type of studies needed is well understood in Brazil and will be obvious to those interested in heart disease in other countries. It is hoped that such studies may also provide information immediately useful in the clinical management of the many sufferers from Chagas' disease.

It is equally obvious that much more fundamental work requires to be

done on the parasite, on its pathogenic and antigenic components, its metabolism and serology. The fact that the growth of the parasite in cultures stops at a temperature of 39°C calls for further trials on whether prolonged fever would also kill the parasite in the living organism as this might provide a logical approach for treating subjects with a positive M.-G. reaction before they will reach a stage of irreparable damage to the heart or other organs.

There would seem to be need for more specific indications of infection than the M.-G. reaction. The ramifications of this are enormous but it is clear that the infection in Brazil is of such a nature as to make it necessary to continue to search for possible strain differences, for possible antigenic components which might enable efficient serological protective substances to be elaborated and above all to provide the avenues to efficient chemotherapy.

Reference laboratories storing and distributing standard strains would seem to be very useful as well as uniform antigen and procedures for complement fixation tests (M.-G. reaction) so as to ensure a comparable screening test for Chagas' infection.

Although some individual studies, such as that by Pedreira de Freitas (1963), produced adequate evidence that proper care of the infected house can considerably reduce the frequency of human infection, the present situation in the areas the Consultants were able to visit is not satisfactory. Chagas' disease is a very serious public health problem deserving of national attention and of international cooperation as soon as possible to stop fresh infections and to provide new information for the care of the millions of people now affected.

6. Recommendations

- 6.1 That the importance of Chagas' disease as a major public health problem in Brazil and in other countries should be recognized by the creation of a separate category (Rubric) for this disease in the International Classification of Diseases.
- 6.2 That steps be taken to register all cases of the disease by a system of notification and registration in each area, to include all cases showing evidence of infection by positive responses to diagnostic tests as well as those diagnosed clinically, radiologically or by morbid anatomic evidence as infected by Trypanosoma cruzi.
- 6.3 That immediate steps be taken to reduce the number of new infections occurring on repeated exposures to infection by a campaign directed against the triatomid vectors by insecticidal spraying at the earliest possible moment utilizing all facilities now available in affected areas as well as by the creation of facilities in areas where they do not exist.
- 6.4 That steps be taken to enable special studies to be made of any cases developing acute Chagas' disease by infection from transfused blood, particularly in relation to the early destruction of ganglion cells.
- 6.5 That longitudinal studies be conducted in affected areas to assess the prognosis and the significance of a positive complement fixation test in otherwise asymptomatic cases and to assess the prognosis and the rate of progression of the disease in cases exhibiting clinical evidence of Chagasic disease, and to determine the effects of repeated exposure to infection by triatomid vectors.



- 6.6 That studies be conducted to assess the reliability of the Machado-Guerreiro complement fixation test in relation to morbid anatomic and radiologic evidence of Chagas' disease lesions.
- 6.7 That studies be conducted on acute and chronic cases of Chagas' disease to assess the responses to drugs and other agents in patients with varying degrees of loss of ganglion cells.
- 6.8 That studies be conducted on the pathology of the cardiac lesions of Chagas' disease with special reference to:
- a) loss of ganglion cells and the results therefrom
  - b) the lesions of the conductive system
  - c) the pathogenesis and consequences of the vortex lesions
  - d) the extent and consequences of the myofiber rupture from the formation of leishmania pseudocysts.
- 6.9 That further studies should be carried out in an attempt to determine strain differences within Trypanosoma cruzi and to see if these are of importance in determining the onset and severity of the various lesions.
- 6.10 That further studies should be carried out to determine the importance of animal reservoirs of the disease in relation to the human disease.
- 6.11 That further steps be taken to educate the general public in the importance of Chagas' disease and to the means of preventing the disease.

## 7. Summary

- 7.1 The history of Chagas' disease in Brazil has been briefly reviewed and the reasons for the recent development of interest in the disease, particularly in the late chronic stages, is discussed.
- 7.2 The large number of animal reservoirs, the number and ubiquity of the vectors, means that a large population over a vast area is potentially exposed to infection. However, the relative importance of the animal reservoirs, the relative importance of the vectors and the existence of strain differences of Trypanosoma cruzi in the various areas has not yet been established.
- 7.3 Community infection and the potential hazard can to some extent be estimated from:
- a) the numbers and frequency of infection in animals, domestic and wild, and their reaction to infection
  - b) the numbers, frequency of infection and habits of the vectors
  - c) by the Machado-Guerreiro complement fixation test
  - d) by the xenodiagnostic reaction
  - e) by the clinical, radiologic and anatomic evidence of infection
- 7.4 None of the above modes of estimation is yet entirely satisfactory. Much entomological and parasitologic work has advanced knowledge in these fields more extensively than it has advanced on the clinical and anatomic sides in relation to the disease in the community. A major difficulty is the assessment of the M.-G. reaction. While the specificity of this reaction vis-a-vis other infections is high there is clear evidence that the reaction is negative in many cases with anatomic evidence of infection. The situation in this respect needs to be clarified.

- 7.5 The infection in the human being can be recognized by:
- a) the clinical signs and symptoms in the acute stage
  - b) the demonstration of parasites in the blood
  - c) the Machado-Guerreiro reaction
  - d) the xenodiagnostic test
  - e) clinical and electrocardiographic evidence of heart disease
  - f) clinical and radiologic evidence of damage to hollow viscera
- e) and f) having been established as due to Chagas' disease, by:
- 1) the coexistence of parasites in the blood and affected organs
  - 2) high rates of correlation with the M.-G. reaction
- 7.6 The acute stage is recognized in only a minority of individuals but is probably a more common disease than is generally accepted. The hyperacute cases which follow transfusion of infected blood are very important and deserve the fullest clinical, functional and pathologic study.
- 7.7 The lesions of the mega-type are extremely common in inland central Brazil, occur particularly in areas where there is a high frequency of community infection as estimated by all the measures indicated by 7.3 above; the M.-G. reaction is positive in well over 90% of those with evidence of mega-esophagus, the pathology has been demonstrated as a great diminution of the parasympathetic ganglion cells of the enteric plexuses with comparable lesions in other organs and there is an accompanying cellular infiltration around dead and dying ganglion cells.
- 7.8 It has been established both in acute human cases and in experimental animals that ganglion cell invasion and destruction by leishmania is a common occurrence and experimental animals who survive an acute infection will develop such mega-lesions later on.

- 7.9 In the light of the available evidence there seems no reason to doubt that the mega-syndromes in this area of central Brazil are due to Chagas' disease. Whether these lesions occur with such profusion elsewhere, or are due to some specific local factors, strain differences in the parasite or intensity of infection has yet to be determined.
- 7.10 There is considerable overlap in this area between the mega-syndromes and cardiac disease believed Chagasic on the basis of the evidence in 7.5. The clinical and electrocardiographic changes enable a diagnosis of Chagasic heart disease to be made with a fair degree of confidence. There are a great many cases in which sudden death from heart disease occurs in young adults with or without decompensation and there is much evidence that these acute deaths are mainly due to Chagas' disease.
- 7.11 The pathology of the heart in Chagas' disease is a myocarditis which has been repeatedly described. Conduction defects are extremely common and the exact basis of these has yet to be ascertained. However, the most striking lesions are thinning of the apices of the ventricles with the formation of large aneurysms which do not rupture. The basis of these remarkable lesions seems to be a slackening of certain muscle bundles, especially the bulbo-spiral and sino-spiral muscles, which leads to an unwinding of the vortex region of the apex.
- 7.12 This lesion seems to be unique to Chagas' disease and does not occur in other forms of myocarditis and cardiomyopathy so it seems that it must be due to some highly specific pathogenetic mechanism.

It seems that the most likely explanation at present is that it is due to the demonstrated loss of ganglion cells in the auricles and hence has a similar pathogenetic mechanism to the mega-lesions.

- 7.13 The pathologic lesions in the heart and other organs seem to be diagnostic of Chagas' disease and are so specific that a positive diagnosis can be made even if the serology is negative.
- 7.14 The evidence seems conclusive that in these regions Chagasic heart disease is responsible for an enormous amount of invalidism and many deaths and is therefore a major public health problem.
- 7.15 The epidemiologic evidence would suggest:
- a) that several million people in the area are affected
  - b) that the figure is probably under rather than overestimated by the Machado-Guerreiro reaction
  - c) that when electrocardiologic changes develop in conjunction with a positive M.-G. reaction the prognosis is poor but
  - d) it has not been established that an M.-G. positive reaction in an asymptomatic person necessarily means that the individual will eventually develop clinical Chagas' disease.
- 7.16 The extent and severity of the disease justifies the immediate application of steps to diminish the numbers of triatomid vectors at the earliest possible moment. Efficient insecticides and the staff, apparatus, equipment, maps, etc., are available to take up this problem.
- 7.17 However, the first step necessary is to register the disease and to make it notifiable. Lack of epidemiologic and longitudinal study data is the present major deficiency.

- 7.18 If the basic essential pathology is the destruction of ganglion cells and if, as seems likely, the bulk of this damage takes place during the acute phase, any chemotherapy is likely to be effective maximally in the acute phase which makes notification necessary and would also permit the required follow-up studies.
- 7.19 That the public health importance of Chagas' disease be recognized as an important remedial problem in the area, that the degree of infestation can be reduced by the use of insecticides and that fresh infections can be prevented by improvement in housing and living conditions and by education of the public in the importance and prevention of Chagas' disease.

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