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CHAGAS' DISEASE

Report of a Study Group

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STUDY GROUP ON CHAGAS' DISEASE

Washington, D. C., 7-11 March 1960

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CHAGAS' DISEASE

Report of a Study Group

The Study Group on Chagas' disease met in Washington from 7 to 11 March 1960

On behalf of the Director-General of the World Health Organization, Dr Abraham Horwitz, Director of the Pan American Sanitary Bureau, which acts as WHO Regional Office for the Americas, opened the meeting and welcomed those taking part. In his address, Dr Horwitz paid homage to the work and personality of Carlos Chagas and mentioned some of the problems posed at present by American trypanosomiasis. Although Chagas' disease is known to occur all over the continent, apart from Canada and probably Cuba, the problem of its true incidence in the Americas is far having been solved. This ignorance is the main difficulty in the way of organizing and justifying adequate control programmes in countries where other diseases are also prevalent whose morbidity and mortality are apparently much greater.

Dr Horwitz indicated that sanitation of housing and improvement in living conditions are essential prerequisites for bringing about the disappearance of Chagas' disease, and he stressed the need to study the ecological problems associated with it, so that control programmes might be organized on a practical and effective basis.

The Group elected Dr E. Dias as Chairman, Dr F. Pifano as Vice-Chairman and Dr J. L. Pedreira de Freitas as Rapporteur, and approved the proposed agenda.

INTRODUCTION

In preparing the programme of subjects to be considered, the Group emphasized the need for discussions dealing in particular with those aspects of Chagas' disease of public health importance, and drew attention to points that should be investigated in order to obtain an objective idea of the problem. The following main topics were considered :

1. Importance of Chagas' disease in public health, with special reference to the following :

- (a) geographical distribution of the disease and its vectors ;

- (b) symptomatology of the disease ;
 - (c) pathogenesis and pathology, including immunity aspects ;
 - (d) morbidity and mortality problems.
2. Evaluation of diagnostic procedures.
 3. Evaluation of survey methods.
 4. Evaluation of available methods of treatment.
 5. Control and prevention of Chagas' disease.
 6. Recommendations concerning the investigations regarded as most appropriate in the case of Chagas' disease.
 7. Inter-country coordination of the study and control of Chagas' disease.

1. IMPORTANCE OF CHAGAS' DISEASE IN PUBLIC HEALTH

Although there are so far no statistical data on the prevalence of Chagas' disease in the various Latin American countries, the Group made the rough, conservative estimate—on the basis of existing information—that the number of people exposed to the risk of infection with *Trypanosoma cruzi* is some 35 millions.

If the average of the infection rates obtained in the epidemiological surveys carried out in several countries is taken as 20%, it may be calculated that at present there are at least seven million people infected with *T. cruzi*.

1.1 Geographical distribution of the disease and its vectors

So far some 90 species of *Triatoma* have been described, almost all in the neotropical region, extending from roughly the 43rd parallel north latitude to the 49th parallel south latitude. *Triatoma* species infected under natural conditions with *T. cruzi* have been found only in the Americas. Nevertheless, only some of these species are of epidemiological importance, this being governed primarily by their density and their adaptation to primitive human dwellings.

Infection of vertebrates has been reported from all countries on the American continent, from the USA to Argentina and Chile. Human infection has also been reported in these countries. Although there are data showing the high prevalence of human infection in many areas, there have not so far been any sufficiently extensive investigations to indicate clearly the magnitude of the public health problem presented by Chagas' disease.

As regards the more important vectors, attention has been drawn to the wide distribution of *T. infestans* over extensive areas of South America, with infection rates varying generally from 20% to 30%. In the northern part of South America, the main vector is *Rhodnius prolixus*; in Panama, *R. pallescens*; in certain parts of Peru, *Panstrongylus herreri*; and in Mexico, some species of the *T. phyllosoma* group. Other species widely distributed in the Americas are of less importance as regards the maintenance of Chagas' disease.

As concerns *Panstrongylus megistus*, another important species found over wide areas, it was mentioned that in some regions this triatome is closely adapted to human habitations, while in others it is prevalent in a peri-domestic environment. On the other hand, *P. megistus* has on a few rare occasions been captured far from human dwellings, in the jungle or in trees.

A few species, for example *Triatoma spinolai*, are found in limited areas of Chile in typically sylvatic habitats. Others are partially adapted to human dwellings, such as *T. maculata*, *T. rubrovaria* or *T. sordida*. Still others are almost wholly sylvatic and consequently play no part in the transmission of *T. cruzi* to man, although helping to maintain the parasite in nature between vertebrate reservoirs.

In various parts of North, Central and South America, numerous vertebrate species belonging to different families of mammals have been found to be infected with trypanosomes apparently indistinguishable from *T. cruzi*; attention was drawn to the need for accurate identification of such trypanosomes found in natural reservoirs, using morphological and biological methods.

It was pointed out that, apart from the forest reservoirs, whose importance as a source of infection for man appears to be small, domestic reservoirs of *T. cruzi*, particularly the dog and cat, are of possible interest; in some areas the cavy or guinea-pig is of special importance.

Attention was drawn to the different altitudes at which vectors have been found; for example, *T. infestans*, although encountered mainly at heights of 500-1000 metres above sea level, has been reported above 3500 metres. It was mentioned that this vector has been found almost exclusively in human dwellings or near to them ("peridomestic"), but very rarely it does frequent certain typical habitats away from houses, e.g., under stones or hollows in trees used as nests by bats.

The epidemiological importance of studying the adaptation of the various vectors to human dwellings was pointed out; in this connexion emphasis was laid on the value of the precipitin test performed on the intestinal contents of triatomes captured in nature as a means of determining their feeding habits. It was, in fact, considered that knowledge gained from such studies might be very useful for the development of new and more radical prophylactic methods.

1.2 Observations on *Trypanosoma rangeli* and other trypanosomes

It was pointed out that the geographical distribution of *T. rangeli* is basically dependent on the geographical distribution of *Rhodnius prolixus*. In a few cases, *Triatoma dimidiata* and *R. pallescens* have been found to be naturally infected. So far *T. rangeli* has been found in Venezuela, Colombia, Panama, Costa Rica and Guatemala. Up till now it has not been shown that it has any pathogenic action in man. Furthermore, serological tests with the antigen of *T. cruzi* were negative in patients definitely infected with *T. rangeli*; consequently, infection with *T. rangeli* does not falsify the results of serological surveys made to determine the prevalence of Chagas' disease. *T. rangeli* has been found in man (approximately 800 cases in Venezuela and a few score more in other countries) and also in domestic or forest reservoirs.

In view of the need to differentiate between *T. cruzi* and *T. rangeli* in surveys or in xenodiagnosis, stress was laid on the importance of stained preparations in the study of the intestinal contents of triatomines. Attention was also drawn to other trypanosomes that are more easily differentiated from *T. cruzi* and are able to develop in triatomines, such as *T. myrmecophagae*, *T. diasi* and *T. conorrhini*.

Finally, reference was made to the fact that trypanosomes morphologically indistinguishable from *T. cruzi* have been found in monkeys in Asia and the Malayan Archipelago, as well as in bats in various countries. The need was stressed for more thorough investigation in order to determine the significance of these parasites and how they are transmitted in nature.

1.3 Symptomatology of Chagas' disease

Chagas' disease exhibits two basic forms, an acute phase and a chronic phase, with an intermediate phase between the two. The symptoms of the acute phase are variable and still not very well known. In accordance with established practice, it is usual to distinguish between oedematous and non-oedematous forms, with or without a visible portal of entry, but there are wide variations in the symptoms of the acute cases. Their course is also variable, with a case fatality rate of approximately 10%, the figure being higher in the first years of life. The principal signs and symptoms of the acute phase, apart from those at the portal of entry, are fever, generalized adenopathy, slight enlargement of the liver and spleen, general infectious symptoms, cardiac enlargement, and electrocardiographic changes; the latter may be pronounced but once the acute phase has passed, they often disappear completely or in part. In some cases—generally severe ones—there are signs of nervous system involvement.

The best known chronic forms are those in which the myocardium is affected, sometimes undergoing hypertrophy without any evident clinical

symptoms. Electrocardiographic changes are frequent, and serious symptoms of cardiac insufficiency may occur.

Clinical observations indicate that an as yet undetermined proportion of cases end fatally; death may be sudden or the result of intractable cardiac insufficiency. Studies among populations living in high endemic areas have not been carried out on a sufficiently large scale nor have the sample groups been carefully enough selected to allow definite conclusions to be drawn; they do seem to indicate, however, that approximately 10% of such populations suffer from serious cardiopathy associated with Chagas' disease.

Observations by some authors apparently indicate that there are regional differences in the cardiotropism of *T. cruzi*. There is some discussion as to whether these possible differences should be attributed to variations in the resistance of the affected populations, to nutritional states, or to the virulence of the various strains of parasite.

Not only are there these cardiac forms, but it has also been demonstrated that, at least in some endemic areas, certain alimentary forms particularly mega-oesophagus and megacolon, may be manifestations of Chagas' disease in its chronic phase.

Many years ago this possibility was suggested by Carlos Chagas himself, and epidemiological and serological evidence has since accumulated to support it. More recently, pathological as well as experimental studies have helped to establish a relationship between these alimentary manifestations and infection with *T. cruzi*. In some areas where Chagas' disease is endemic, particularly in Brazil, such alimentary forms are very frequent, but so far no systematic studies have been made of their true prevalence. In other countries, moreover, it has not been proved that *T. cruzi* can cause these alimentary manifestations, although in the literature isolated references are found to the association of "organomegaly" with cardiac changes or to the existence of such conditions in patients infected with *T. cruzi*. The Group stressed the importance of accurately determining the frequency of these alimentary forms, in particular by systematic radiological investigation of the population in both infested and triatome-free areas.

Some observers have reported the existence of chronic neurological forms of Chagas' disease, but there are no data to show their significance in human pathology. However, involvement of the nervous system in *T. cruzi* infection has been described in experimental work.

In view of the differences in the pathology of Chagas' disease in the various published descriptions, the Group emphasized the difficulty of comparing the data presented by the different authors. Furthermore, the need was stressed for carrying out longitudinal investigations in representative community groups in order to evaluate the chronic forms of the disease more accurately, such observations being made on a long-term basis, in view of the slow development of these chronic forms.

1.4 Pathogenesis and pathology

Under this heading were discussed factors that may affect the pathogenic action of *T. cruzi* and explain variations in this action. It was pointed out that *T. cruzi* is a parasite which multiplies mainly in cells of mesodermal or mesenchymal origin. This form of multiplication itself constitutes a fundamental biological fact in the life cycle of this protozoan and its pathogenic action.

The pathogenic effect of *T. cruzi* is regarded as being due mainly to mechanical, inflammatory, allergic and possibly toxic processes.

The mechanical action, more evident in acute or initial infections, takes the form of the destruction of muscle fibres or other cells containing the parasite.

Mention was made of recent work attributing to the disintegration of these structures in the parasitized organism a certain importance in the origin of auto-sensitization phenomena regarded as at least partly responsible for some of the symptoms observed in the cardiac forms of Chagas' disease. Although a mechanical action of *T. cruzi* doubtless exists, it is not held to play a fundamental part in the pathogenic effect of the parasite.

The inflammatory action of *T. cruzi* is intense in the acute phase of the disease, and the inflammatory processes may penetrate deep into the myocardium and other organs. These inflammatory reactions are less intense in the chronic stages, in which they are predominantly productive. It has been proved that the foci of inflammation are not always closely related to the site of the parasites.

It has been shown experimentally that suspensions of dead *T. cruzi* can provoke hyperergic reactions in animals, which would seem to indicate that this mechanism is involved in the pathogenesis of the cardiac lesions.

Many years ago the theory was put forward that on disintegrating *T. cruzi* is able to manufacture or set free a toxic substance or toxin responsible for some of the phenomena observed in the pathogenesis of Chagas' disease. More recently it has been maintained, mainly on the basis of pathological findings, that this hypothetical toxin exercises a specific effect on the cells of the nervous system, particularly those nearest to the points colonized by the parasite.

The Group recommended that more extensive studies be carried out, particularly on a quantitative basis, so as to assess accurately the importance of these nervous lesions in chronic infection with *T. cruzi*.

The Group examined the possible influence of other factors, either endogenous or exogenous, on the pathogenesis of the disease. Among these factors the significance of nutrition was considered. Some antibiotics, such as chlortetracycline, appear to aggravate *T. cruzi* infection. The same effect has been observed in the case of cortisone administered in high doses. There are some observations on the harmful effect of X-rays and

certain anaesthetics, particularly thiopental sodium, on animals infected with *T. cruzi*.

The Group recommended that investigations be continued on the role of non-specific factors in the pathogenic action of *T. cruzi*. Emphasis was laid on the possible importance of variations in the virulence of different strains of parasite and attention was drawn to the difficulty of measuring the virulence of a given strain. Some strains have shown a certain degree of viscerotropism, but this property has rarely been constant. In studies of virulence, it is important to use homozygous animals very susceptible to infection, such as the C3H strain of mice, so as to establish a standard and facilitate comparison of results obtained by different investigators.

The question of neurotropic strains warrants special attention. There is a need to define what is meant by a neurotropic strain. Various authors have found that the hind quarters of animals inoculated with strains of different origin become paralysed.

1.5 Immunity in Chagas' disease

The Group pointed out the importance of cellular immunity in the acute phase of *T. cruzi* infection. At the same time, it is necessary to take account of certain humoral factors that may be important in promoting such immunity.

As regards antibodies, high titres of precipitins and agglutinins have been reported in the initial stage of the infection. In general, as the disease progresses, the antibody titre falls more or less rapidly while, conversely, there is a rise in the level of amboceptors. So far there has been no proof that lysins are involved in the production of immunity in *T. cruzi* infections.

Besides complement-fixing antibodies, which are widely used in serological diagnosis of the disease in its chronic phase, precipitins and agglutinins have also been detected in rare cases. It has been found that these agglutinins are detected more frequently if indirect methods are used.

Laboratory animals have been successfully immunized against *T. cruzi* by inoculation with cultures whose virulence has been attenuated by successive passages or by suppressive treatment.

1.5.1 Antigenic composition of *T. cruzi*

Biochemical studies have shown that it is possible to isolate a lipopolysaccharide-polypeptide complex from *T. cruzi*. Some of the fractions isolated show antigenic activity *in vitro*. So far it has not been possible to isolate toxins from *T. cruzi*.

The Group recommended that investigations be continued on the antigenic fractions of *T. cruzi* and its possible toxins.

1.6 Morbidity and mortality

The importance of Chagas' disease can be assessed by the number of persons exposed to the risk of infection, by the infection rates, by the seriousness of the clinical forms and by the mortality rate. It is advisable for all cases of Chagas' disease to be notified to the health authorities of the country concerned.

As regards the prevalence of the disease, it is important that this should also be determined in communities that include former residents in endemic areas suffering from chronic forms of the complaint.

It was stressed that for statistical purposes it is necessary to consider not only typical clinical manifestations, but also latent cases and any less characteristic forms of the disease.

The Group recommended that studies with the aim of determining the morbidity of Chagas' disease be carried out on representative samples of the different communities in such a way as to enable the findings to be generalized and a comparative analysis made of the different endemic areas.

Attention was drawn to the importance of longitudinal studies, including study of life tables, in the evaluation of *T. cruzi* infection.

In relation to the different factors linked with morbidity, the Group noted that the majority of acute cases had been observed in the lowest age-groups, a fact that is certainly connected with greater exposure to the risk of infection. Acute cases have also been observed in adults, however, and in persons who have recently arrived in endemic areas.

Although autochthonous cases are found mainly in rural and suburban areas, they are also common in the peripheral zones of cities.

Mortality should be determined both in the acute and the chronic phase. In certain regions, the case fatality rate among acute cases has been approximately 10%, being highest in the lowest age-groups, although fatal cases in adults have also been reported.

As concerns Chagas' disease as a cause of death in the mortality statistics, it was pointed out that in the statistics for the various countries of the Americas where the disease is highly endemic, fatal cases attributed to *T. cruzi* are rare and clearly bear no proportion to the frequency of the disease. Owing to the very diverse symptoms of Chagas' disease in its chronic forms, numerous deaths are erroneously entered under different headings of the International Classification of Diseases, Injuries, and Causes of Death.

The importance was underlined of specifying on death certificates the underlying primary cause of death so that the real part played by Chagas' disease in mortality statistics could be evaluated. It was also mentioned that in mortality statistics sudden deaths, so frequent in the chronic forms

of Chagas' disease, are usually included among diseases of ill-defined or unknown origin; in these cases "sudden death" is recorded without further qualification, and without attributing it to an underlying or primary cause. The same happens with regard to uncompensated cardiac insufficiency.

In this connexion it was recommended that more extensive investigations be made to discover the real value of post-mortem examination of the heart in deciding whether cases of sudden death, or other deaths, are due to Chagas' disease. Attention was drawn, however, to the practical limitations of this method, arising from the difficulty of detecting *T. cruzi* in the myocardium.

With regard to the problem of Chagas' myocarditis, it was pointed out that, in Latin America, it is important to determine whether cases designated as "non-specific myocarditis" are due to Chagas' disease.

1.7 Economic aspects of Chagas' disease

Although no special evaluation of the economic harm caused by Chagas' disease has been made, existing data show that it must be very considerable. In the first place, the incapacitating symptoms of the chronic forms of the disease generally develop in the second half of life when the individual is making his greatest contribution to society. Secondly, the disease is found principally in rural areas where those affected are often rendered incapable of the heavy physical work demanded of them. Another factor that must be taken into account is the cost of hospitalization and subsequent rehabilitation of patients with Chagas' disease. The Group pointed out the need to assess the harm done by Chagas' disease and its repercussions on the physical development and working capacity of those affected.

2. RECOMMENDED SURVEY METHODS

To assess the health importance of a disease and organize and carry out control programmes, it is essential to have as accurate information as possible on the distribution of the disease, as well as data on variations in such distribution and frequency, and on changes it undergoes in the course of time.

In this way, a picture is built up of the natural history of the disease, with all the factors that may affect its epidemiology. As *T. cruzi* is a parasite of man and of many animal species and its transmission in nature depends mainly on *Triatoma*, when evaluating the problem of Chagas' disease it is necessary to take into account all three of these links in the epidemiological chain, as well as the associated climatic, geographical and

social conditions. It is therefore advisable to establish triatome and trypano-triatome rates, for both human infection and infection of reservoirs, particularly in regions that are possibly endemic and in which no adequate surveys have so far been carried out.

The polymorphism of Chagas' disease in man and consequently its faulty notification and the rareness with which it appears in mortality statistics clearly show the need to carry out epidemiological surveys in endemic areas.

These surveys should aim at accurately determining the distribution and density of *Triatoma* species in different regions, their habits, and the degree to which they are adapted to human dwellings and their immediate neighbourhood (peridomestic). The *T. cruzi* infection rate for triatomes captured in human habitations is particularly valuable and constitutes a kind of "natural xenodiagnosis". It is also useful to have information on the presence of *T. cruzi* infection in domestic, peridomestic and sylvatic reservoirs, and in this connexion special attention should be paid to the exact identification of the parasites found.

The Group pointed out that in order to evaluate human infection it was important to establish both the incidence, determined by long-term longitudinal observations on population groups, and the prevalence rates, obtained by assessing the amount of infection present in the community at a given moment. The need also emerged for the establishment of life tables.

In clinical surveys on human population groups, use should be made of suitable serological methods, xenodiagnosis, and clinical examinations supported by electrocardiograms and radiological examinations. As concerns the main criteria for selecting sample population groups, the Group recommended that in general the recommendations summarized in the WHO Technical Report on Immunological and Haematological Surveys should be followed.¹

3. EVALUATION OF DIAGNOSTIC PROCEDURES

In evaluating diagnostic procedures for Chagas' disease, etiological and clinical diagnosis were considered.

Etiological diagnosis in the acute stage is based on the detection of *T. cruzi* in the peripheral blood. This should be done by methods employing direct examination of blood or of stained smears; the Group stressed the advantages of the thick film and the need to repeat the tests. Although the percentage of acute cases of Chagas' disease in which the parasite

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1959, 181

can be found in the blood by direct methods is high, nevertheless in a few cases it can be detected only by using more sensitive techniques. Among these were considered xenodiagnosis, inoculation of laboratory animals, and blood cultures.

The precipitin test, using the fraction extracted from *T. cruzi* by means of formamide, is positive in a high percentage of cases during the acute phase. Also in this phase the agglutination titres of cultures are high, particularly if live *T. cruzi* cultures are used.

Once the acute phase has passed, methods for the direct detection of the parasite almost always fail, since there is a smaller number of parasites in the blood in chronic cases.

Post-mortem diagnosis is made possible by detection of trypanosomes in the tissues. Xenodiagnosis constitutes the best method known so far for demonstrating the presence of *T. cruzi* in patients with chronic forms of the disease. In a few cases the presence of the parasite can be demonstrated by inoculation of laboratory animals. The best results have been obtained with puppies and mice of the homozygous C3H strain. So far, blood cultures have rarely been positive in the chronic forms of Chagas' disease.

The indirect methods that give better results in the chronic stage are those for the detection in the blood of antibodies dependent on the presence of *T. cruzi*. Of these, the complement fixation test is the one that has given the best results, since it is very sensitive and specific. The Group recommended the continuance of investigations already commenced with the aim of preparing more uniform and more stable antigens and evaluating the possible variations in antibody titre in patients' serum. Attention was called to the fact that the application of the complement fixation test to corpses could be of great value in determining the primary cause of death.

The need was stressed for co-ordination of efforts directed towards standardization of the antigens and techniques for this test. The precipitin and agglutinin tests are rarely positive and are difficult to read in the chronic stages of Chagas' disease.

With respect to clinical diagnosis, it was emphasized that while some cases exhibit characteristic symptoms of the disease, there are many others in which only laboratory tests can establish a diagnosis.

In the acute phase, the fever and other symptoms previously mentioned serve as pointers to the diagnosis in many cases. Nevertheless, it was pointed out that differential diagnosis is often very difficult, and sometimes the problem is only solved by a chance finding during autopsy or routine laboratory tests.

Attention was drawn to the great diagnostic value of supplementary examinations, particularly the electrocardiogram, radiological examination and, to a less extent, blood tests.

The electrocardiogram frequently shows different changes in the acute and chronic phases of the disease; in both, however, there may be considerable alterations in the formation and conduction of the stimulus, so that an electrocardiogram is one of the most valuable aids to the diagnosis of this disease.

Radiological examination in the acute phase frequently reveals cardiac enlargement. It is also very valuable in the chronic phase, since in addition to revealing the size of the heart it enables morphological and dynamic changes in the oesophagus and intestines to be studied.

As regards the haematological aspect, mention was made of the existence during the acute phase of leucocytosis with a high percentage of lymphocytes, mainly of atypical appearance.

4. EVALUATION OF AVAILABLE METHODS OF TREATMENT

As regards evaluation of the methods of treatment available for Chagas' disease, the Group recognized that so far there is no effective curative therapy. Some drugs have shown an intense trypanocidal action in laboratory animals and, even if their clinical value has not been thoroughly assessed, appear to reduce the case fatality rate in the acute phase of the disease. No drug so far tested has a radical trypanocidal action in the chronic forms of the disease. Various quinoline derivatives have shown some chemotherapeutic activity. In the 8-aminoquinoline group, pentaquine, isopentaquine and particularly primaquine have been found to possess a curative action in experimental infections, particularly among mice. The results in man have in general been rather unsatisfactory: although these drugs do have an action on parasitaemia, xenodiagnosis has usually given positive findings after treatment. Certain sulfonated arsenobenzenes have shown some activity in experimental infections, as have also certain phenanthridine derivatives. The latter have been tried in clinical cases as well, with results very similar to those reported above.

With regard to the antibiotics, some references are made in the literature to a favourable action of stylomycin in experimental infections, but not in man. More recently, an aminonucleoside has been isolated from stylomycin which is active not only against intracellular forms in tissue cultures but also against mouse infection. A few other compounds, such as the nitrofurans and 2-acetamido-5-nitrothiazole have also shown some degree of effectiveness.

The Group stressed that the action exhibited by these drugs in experimental infections requires doses that are too high for the treatment of human cases. Attention was also drawn to the importance of keeping a check on treatment by means of xenodiagnosis and of improving quantitative serological techniques for evaluation of the results.

5. CONTROL AND PREVENTION OF CHAGAS' DISEASE

The persistence of endemic Chagas' disease is due primarily to the poor construction of the dwellings and to the primitive sanitary practices of the population, which together create conditions favourable for the breeding of triatomines with domestic habits. Consequently, in the prophylaxis of Chagas' disease the fundamental need is to improve housing and to promote better hygiene among the people, which will entail a complete transformation in economic and social conditions. However, this is a process that can be carried out only gradually and the economic and cultural factors are difficult to overcome in a short space of time.

On the other hand, some of the modern residual insecticides have been shown to be effective against triatomines. Of the various insecticides at present in use, the gamma isomer of hexachlorocyclohexane (lindane, gamma-BHC) and dieldrin have proved to be the most effective. DDT has been found less active, particularly against the nymphs of the insect. There is insufficient field experience to evaluate other insecticides, such as organic phosphorus compounds. Dieldrin, which in some areas has shown a considerable residual effect, has disadvantages that cannot always be overcome in the field, on account of its toxicity for man and domestic animals. Consequently, its use calls for carefully selected, trained and supervised personnel who must be made aware of the dangers of poisoning and provided with adequate means of protection.

The highly toxic effect of this insecticide on domestic animals prevents its use in hen runs and farmyards which are important breeding places for some *Triatoma* species. Furthermore, in some areas it has been proved that dieldrin is not sufficiently effective against certain vectors. BHC has been found to have satisfactory triatotoxic effects on most species and it does not have the drawbacks of toxicity mentioned in the case of dieldrin. The length of its residual action has not yet been determined with sufficient reliability. None of the residual insecticides so far tried has a lethal effect on *Triatoma* eggs.

To ensure that the selection and application of insecticides should be as effective as possible, careful attention should be paid to the ecological peculiarities of the different species of *Triatoma* in each region. Sprayings should be very extensive and thorough, covering not only the internal and external surfaces of houses, furniture and implements, but also the annexes immediately adjacent to or near houses, since the vectors frequently reproduce in such places. The importance was emphasized of pursuing ecological studies on the refuges utilized by the various species of triatomines, particularly peridomestic ones, in order to render spraying more effective.

Insecticides are usually applied in suspensions or solutions, in a minimum concentration of 0.5 g per square metre in the case of BHC and 1.0 g per

square metre in the case of dieldrin. A single spraying with dieldrin or BHC has generally proved insufficient to exterminate all the triatomines in a locality. It was therefore recommended that a second or even a third spraying be carried out, with intervals of 30-180 days between sprayings. Some workers prefer to limit subsequent spraying to residual *Triatoma foci*, provided that these are located by means of thorough searches.

A factor of considerable importance is that changes made by residents in their dwellings after spraying may provide new, untreated hiding places for the insects. Furthermore, careful consideration should be given to the possible migration of triatomines from untreated areas.

The application of insecticides against triatomines should be directed towards as radical a control as possible of the vector species, in particular those most adapted to human dwellings. The Group recommended that thorough investigations be continued within limited areas of the different zones, so as to examine the possibility of eradicating certain species and to compile data for assessing the cost of such programmes.

Resistance to insecticides has not so far been found in any species of triatomines. With respect to the programme for the production and evaluation of insecticides to be sponsored by WHO during the next four years, it was stated that the investigators concerned will receive technical facilities and assistance for carrying out these studies with the triatomines found in their respective countries.

Although there has been a decrease in the number of triatomines in areas where antimalarial spraying is carried on, it cannot be hoped that more permanent results in the fight against these insects will be obtained as the result of such programmes. This is due partly to the type of insecticide employed and partly to the fact that the methods used for the control of *Triatoma* differ in certain fundamental respects from those used for mosquitos, a number of additional measures being needed, such as peri-domestic spraying which is not used in antimalarial campaigns.

Taking into account the magnitude of the public health problem presented by Chagas' disease and the need to initiate control programmes against this endemic disease as soon as possible, the Group was of the opinion that it was not advisable to await the end of the active phase of malaria eradication programmes before commencing this work. Nevertheless, the Group recognized that *Triatoma* control programmes should be carried out in such a way as not to prejudice malaria eradication campaigns.

Although recognizing the technical and administrative difficulties involved, the Group recommended that a study be made of the results obtained when *Triatoma* control and malaria eradication programmes are carried out side by side, a method that is at present being employed in some areas. It was recommended that in countries where malaria eradica-

tion programmes are most advanced, the services responsible for these programmes should gradually take over responsibility for the control of *Triatoma*.

With regard to the housing question, the first aim, both on the periphery of the towns and in the rural areas themselves, should be to repair the existing dwellings so as to create better conditions for spraying. This may be done by manual labour, with the collaboration of the occupiers, and on a larger scale using mechanical methods. It was stressed that both simple repair work and more extensive programmes for the renovation or construction of rural dwellings should be carried out as part of a general plan, taking into account the economic and social aspects of the problem, so as to obtain more lasting results.

As regards health education, the Group pointed out that the best way to guarantee a lasting preventive action consists in arousing an aversion to triatomes among persons living in endemic areas by disseminating knowledge of the harmful role of these insects and convincing the population of the importance of exterminating them.

It was recommended that health education be intensified, particularly in rural schools and other population groups. This educational work should include not only technical information on the problem, but in particular should encourage people to make an active personal contribution to official programmes for the control of *Triatoma*.

Since it has been proved that Chagas' disease may be transmitted by blood transfusion and also that *T. cruzi* infection is highly prevalent among blood donors in some countries, the Group drew attention to the need to intensify investigations on the importance of this problem with regard to blood banks receiving blood from persons coming from endemic zones. The need was mentioned for systematic application of the complement fixation test to donors, not only in endemic areas but also in areas where persons coming from endemic regions have settled. In view of the difficulty in many cases of applying this test as a routine measure, attention was drawn to the advisability of adding trypanocidal substances to the blood. It has been shown that gentian violet is a drug that can be used for this purpose. The need was emphasized for continuing studies with the aim of discovering other substances with a trypanocidal action on blood intended for transfusion.

The Group stressed the desirability of assessing the degree to which transmission of Chagas' disease takes place from mother to child. The prevention of congenital transmission offers great practical difficulties; it is therefore necessary to study the conditions that may favour such transmission.

It was also recognized that it is important to study the role played by milk in transmission in the case of lactating mothers suffering from the chronic form of the disease.

6. RECOMMENDATIONS REGARDING THE MOST SUITABLE INVESTIGATIONS

For a more precise understanding of the problem of Chagas' disease, it is evident that epidemiological surveys are of fundamental importance and that it is also necessary to have a knowledge of the pathogenesis, chemotherapy and immunology of the disease, the ecology of the vectors and their susceptibility to residual insecticides, as well as the factors governing endemicity. It must be recognized, however, that in the present state of our knowledge, even these basic questions call for more thorough investigation.

These considerations emphasize the urgent need to carry out basic scientific research so that the techniques and measures demanded by the magnitude and seriousness of the problem will become available in the future.

The Group was of the opinion that any organized programme of action should include measures for the effective promotion of scientific investigations. Analysis of the problem suggests that work in the following fields is most urgently needed at present, bearing in mind that the order of priority of the programmes may vary according to the country and allowing for the advances that have already been achieved in various parts of the world, as well as their importance from the viewpoint of practical application.

6.1 Biology and pathology

Investigations are needed to clarify many questions relating to the organic changes caused by the invasion of the parasite during the different phases of the disease—from the structural as well as from the physiological, biochemical and pathological points of view—with the object of discovering the mechanism of such changes and providing new bases for diagnosis and treatment.

The following problems were considered most important:

- (a) the factors that determine the appearance and development of chronic cardiopathy, both under experimental conditions and in clinical medicine;
- (b) systematic investigation of alimentary "organomegaly" in endemic areas, and in particular the study of oesophageal dysfunction;
- (c) investigation of congenital Chagas' disease, with a study of its causes and a search for factors liable to influence this phenomenon;
- (d) transmission by blood transfusion and study of methods for preventing this.

6.2 Immunology and immunochemistry

It is indispensable to carry out investigations on the immunological and immunochemical aspects of the problem, directed towards increasing our knowledge both of the reactions of the host and of the antigenic composition of the parasite.

The object of immunological research is to determine as far as possible the role of immunization processes in the various phenomena connected with the disease, and to study the antibodies involved in these phenomena, paying special attention to immunity mechanisms in the chronic forms.

The aim of immunochemical studies is the extraction, isolation and identification of the macromolecular components of the parasite, as well as the determination of their biological activity in the host and their behaviour in *in vitro* reactions.

If it were possible to work with homogeneous components of the parasite this might lead to basic knowledge of its pathogenic action and constitute the most logical way of establishing simpler and, above all, more specific diagnostic methods.

6.3 Biochemistry of the parasite

The aim of biochemical research is, firstly, to extend our knowledge of the chemical factors affecting the growth of *T. cruzi* and, secondly, to investigate its intermediate metabolism in the various stages of its life cycle.

Increased knowledge of the chemical factors affecting the growth of *T. cruzi* will enable methods to be developed for the large-scale production of trypanosomes for use in research work and epidemiological surveys, and, at the same time, will contribute to the study of the nutritional requirements of the parasite. Complete knowledge of these requirements may supply helpful data in relation to new drugs.

Investigation of the intermediate metabolism of the parasite constitutes a fruitful field of study, and it is to be hoped that the findings will enable some form of treatment for Chagas' disease to be developed.

6.4 Treatment

The urgent need to find a drug that is really effective against Chagas' disease demands large-scale trials of all compounds believed to have some therapeutic action, as well as of substances that are active against *T. cruzi* in the blood *in vitro*.

6.5 Vectors and anti-vectors

The importance of research on vectors is self-evident and needs no further comment. This naturally applies also to research on substances able to destroy the vectors.

It was considered that the following problems are those which are most in need of investigation :

(a) studies on the physiology and the biochemistry of vector species of Hemiptera to provide information useful for their control, bearing in mind the mechanism of acquired resistance to insecticides ;

(b) systematic tests of new insecticides or compounds already known but not yet tried out.

It would be very desirable for such work to be done in collaboration with WHO.

6.6 Ecology and control

It was considered very important to carry out research on these questions, in accordance with the ideas expressed in the chapter on control and prevention.

7. INTER-COUNTRY CO-ORDINATION OF THE CONTROL OF CHAGAS' DISEASE

Chagas' disease affords considerable scope for international sanitary collaboration between the countries of Latin America. As has been mentioned, Chagas' disease is closely connected with low living standards, poor housing, and ignorance of hygiene, all of which indicates the need for a programme of general improvement of the primitive dwellings commonly found in the rural areas of the Americas. This should form the basis of an international co-operative programme in which regional health protection bodies would take part.

In order to organize a plan for the control of Chagas' disease, it is necessary to know the extent of the problem in all its ecological aspects ; this indicates the urgent need for extensive epidemiological surveys and pilot plans for the control of *Triatoma*. To facilitate these studies it was suggested that the international organizations supply technical advice and study the possibility of using regional laboratory diagnosis centres, which could be established on the basis of those already existing in some countries or set up in scientific institutions in others.

It would be very desirable to standardize the epidemiological methods and techniques employed in the surveys so as to obtain comparable results from the different areas where the disease is endemic. Similarly, better registration of known cases of the disease and of deaths should be encouraged, in order to improve vital statistics.

Governments should be encouraged to supply the resources necessary for control of the disease on a wide scale. The respective programmes are the responsibility of each particular government, but the international organizations could supply technical advice to those governments requesting it. The Group suggested that the international organizations should study the possibility of offering the fullest facilities for the technical training of the professional and auxiliary staff who would participate in the epidemiological surveys and the control programmes, and should encourage interchange of experience between those engaged in these activities.

The Group urged WHO and the Pan American Health Organization (PAHO) to arouse the interest of national or international institutions or foundations, whether official or private, in giving their support to projects for research on the biological, medical and public health aspects of Chagas' disease with the aim of extending knowledge of the disease and its control. It was also recommended that WHO and PAHO promote and co-ordinate projects for scientific investigation and facilitate interchange of bibliographical information.
