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**RESEARCH OPPORTUNITIES IN THE
CHEMOTHERAPY OF CHAGAS' DISEASE
IN THE AMERICAS**

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PAN AMERICAN HEALTH ORGANIZATION

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RESEARCH OPPORTUNITIES
IN THE CHEMOTHERAPY OF CHAGAS' DISEASE IN THE AMERICAS*

The urgency of furthering research in the chemotherapy of Chagas' disease was pointed out in the recommendation of the WHO Study Group on Chagas' Disease which met in Washington, D. C. in 1960 (WHO Technical Report Series No. 202) and was reemphasized and placed among the priorities in the report of the PAHO Advisory Group on Research in Chagas' Disease which met in Rio de Janeiro in June of 1962 (RES 1/15). Early last November PAHO took the initial steps to implement the recommendations of these groups and to promote a coordinated program which would take advantage of the available personnel and facilities in a number of active centers of research in the Americas.

Following discussions with the PAHO Office of Research Coordination, correspondence was initiated by the PAHO Consultant in Chagas' Disease with certain investigators in Latin America who are recognized for their competent and consistent efforts in research in the chemotherapy of Chagas' disease. In these communications and following further consultation with the PAHO staff, plans were made for the formation of a small group which could consult, advise, exchange information, arrange for clinical trials, and encourage as well as conduct research in this area. During late April and early May the Consultant visited and conferred with members of this group. The Chagas' Chemotherapy Research Group was constituted and consists of six individuals whose names and affiliations

*Prepared for the second meeting of the PAHO Advisory Committee on Medical Research, 17-21 June 1963, by Dr. Frans C. Goble, Director of Chemotherapy, Research Department, CIBA, Summit, New Jersey, acting as PAHO Consultant in Chagas' Disease.

are as follows:

Dr. Zigman Brener
Instituto Nacional de Endemias Rurais
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Dr. J. Romeu Cançado
Professor Catedrático da Cadeira de
Terapêutica Clínica
Faculdade de Medicina
Universidade de Minas Gerais
Belo Horizonte, Brasil

Dr. José Ferreira Fernandes
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Faculdade de Medicina
Universidade de São Paulo
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Dr. Frans C. Goble
Director of Chemotherapy, Research
Department, CIBA
Summit, New Jersey, U.S.A.

Dr. Tulio Pizzi
Professor de Patologia General
Universidad de Chile
Santiago, Chile

Dr. Aluizio Prata
Professor de Clínica de Doenças
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Faculdade de Medicina
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Salvador, Brasil

Of the above Group Drs. Brener, Cançado and Prata are also members of a group of seven Brazilian physicians organized at a meeting in Rio de Janeiro in the Spring of 1962 for the purpose of pooling information and resources in the study of the clinical effects of new drugs in Chagas' disease. This group of seven physicians intends to meet at approximately six month intervals, having met last in November of 1962 at Ribeirão Preto and expecting to get together again during the medical meetings of the Triângulo Mineiro at Uberaba the week of June 23, 1963. Since each investigator has only a few patients with the acute disease at any one time, the group decides which drug will be tested and a concerted trial of the same drug by all members of the group during the same period allows them, at the end of each period, to have a more conclusive opinion on the compound than would be possible if it were tested haphazardly and without coordinated effort. During the past year this group has been chiefly concerned with the testing of nitro-furan compounds but it appears likely that following the meeting at Uberaba they may be in position to try other compounds. The materials

selected will depend on the experimental data available at the time, which will allow an evaluation of the activity and toxicity and permit the establishment of priorities.

Members of this group in addition to Drs. Brener, Cançado and Prata, are:

Dr. Humberto de Oliveira Ferreira
Catedrático Interino de Clínica
Pediátrica e Puericultura
Faculdade de Medicina do
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It is expected that Drs. Cançado and Prata will act in liaison between the two groups. The resulting clinical experience will be valuable to the PAHO research program in Chagas' disease.

By mutual consent, the non-clinical investigations have been divided among the four investigators in the Chagas' Chemotherapy Research Group who are active in experimental studies, Drs. Brener, Fernandes, Goble and Pizzi.

Dr. Brener has agreed to continue his chemotherapeutic testing program in mice according to procedures he has established (1-4). There was general concurrence that his methods and criteria of activity and cure are adequate not only for screening (which can be carried out whenever it is possible to obtain compounds which have not previously been tested in experimental Chagas' disease) but also for the comparative

evaluation of substances which have already shown activity in preliminary tests. In this latter category it has been agreed that five compounds (5-11) are now in need of careful comparative study and work on these will begin in Dr. Brener's laboratory as soon as possible. These compounds are:

1. 6-methoxy-8-(5-propylamino amylamino) quinoline (WIN 5037).
2. 6-methoxy-8-(p-alkyl-piperazino alkylamino) quinoline.
3. levo-5-morpholinomethyl 3-(5-nitrofurfurylidineamino)-2-oxo-zolidinone.
4. 4,4'-dibiguanido-2,2'-disulfonamido stilbene (CIBA 22777).
5. 1-beta-hydroxyethyl-2-methyl-5-nitroimidazole ("Metronidazole", "Flagyl", "Clont").

The possibility was considered that comparisons between compounds, even of the same chemical group, may not be adequate if only a single dose level is selected, and it was agreed that the inclusion of several dose levels might result in the determination of an optimum level which might most accurately indicate the potentialities of a compound. Differences in rates of absorption and excretion between different materials are recognized along with the necessity for trying various regimens in evaluation tests.

Dr. Brener will continue his studies on prolonged administration of selected compounds and will explore methods of testing drugs against chronic infections in mice. It is considered desirable to make a comparison of the activity of one or two selected compounds against several virulent strains of the parasite. It is proposed therefore that comparative studies be initiated by Dr. Brener using, in addition to the

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"Y" strain with which he has most experience, the "Brasil" strain used by Dr. Goble, the "Tulahuen" strain used by Dr. Pizzi, and a virulent Peruvian strain obtained from Dr. Felix Naquira.

Dr. Fernandes is continuing his work on the effects of various compounds on the leishmanial and trypanosome forms as they occur in tissue cultures of monkey heart (12-19). In this system he is able not only to discover which drugs act against the intracellular or the extracellular forms or both but also to study nucleic acid syntheses and the factors which influence them. During the next several months Dr. G. C. Mueller of the University of Wisconsin will be working with Dr. Fernandes in this field.

Dr. Pizzi intends to pursue the subject of nucleic acid metabolism (20-21) of the parasite under the influence of drugs, with special reference to the blood forms, thus complementing those studies of Fernandes on the tissue forms. Dr. Pizzi will do other fundamental studies, particularly those related to the rate of parasite reproduction during drug treatment and the effects of chemotherapy on the immune response of the host. He does not plan to carry out any program of broad screening but would be interested to examine more closely a number of compounds of a particular series. He is most interested at this time in compounds of the metronidazole ("Flagyl") type and in trying combinations of drugs with different modes of action.

The necessity and urgency of employing both rational and empirical approaches to the search for better chemotherapeutic agents is well recognized and it is in connection with the latter that Dr. Goble's research efforts have been directed (22-23). He is at the present time

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supervising a screening program in which from 750 to 1000 compounds are tested each year. It is not known whether this number is above or below average for like programs in similar laboratories although it might be conjectured that comparable efforts are being made in perhaps a dozen other industrial laboratories.

Inasmuch as it is felt that the empirical approach may lead to the discovery of useful chemotherapeutic agents as quickly as the rational approach, every effort will be made to keep in touch with the organizations doing this kind of testing so that new substances with promising activity may be evaluated early. In addition it seems possible that if the Chagas' Chemotherapy Research Group can publicize its aims and activities, other sources of compounds which would not normally be tested in Chagas' disease might become available for testing, possibly in Dr. Brener's laboratory.

In addition to encouraging and developing investigations along these lines Dr. Goble will endeavor to collect all pharmacological and toxicity information concerning compounds of interest, and to outline criteria to be considered in preclinical programs for proof of safety. Special toxicity problems in the treatment of infants are recognized, together with the potential effects that such drugs may have on the fetus.

Two items which were thought to be worthy of later consideration are related to the development of studies on the chronic state in Chagas' disease and the possibility of its treatment. In addition to the investigations of this subject in mice which Dr. Brener is pursuing it was felt that other species might be found in which the chronic disease would simulate the conditions which are found in man. It was thought that if

further work in dogs was to be done this might more effectively be pursued in the United States where facilities and expense might be less a problem than in Latin America. It was also recalled that information on the disease in monkeys is not extensive, that more studies in various simian species would be interesting and might be best carried on in South or Central American laboratories. Both these lines of endeavor were considered to be only in exploratory stages and to be areas which should not be forgotten if opportunities develop to encourage further work.

The financial and equipment needs of the members of the Group who are engaged in basic or experimental studies have been surveyed. Support for Dr. Fernandes' work is already available through grants. Dr. Pizzi has the personnel and equipment for the basic metabolic studies which he contemplates but if his animal work is to be expanded to provide for his study of a series of compounds or combinations of drugs he will need support, particularly in the area of animal cages and rations. Support could be obtained from a number of sources and he has experience in applying for grants. It seems possible that he can at least get his studies under way without substantial assistance from PAHO at present. Dr. Brener has personnel and space for the studies he contemplates but will need additional animals, cages and feed if his work increases. He has not previously had experience with governmental grants (such as from NIH) and it would be desirable if he could be assisted in the preparation of applications for these or other funds.

It should be pointed out that although the Group has not yet met together as a body almost all of the points touched on above were discussed by Dr. Goble with each member of the Group during his recent trip

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and remarkable accord was found in most of the feelings expressed by the individuals visited. No difficulty was encountered in dividing the responsibilities and little divergence of opinion was found. It is planned to arrange a meeting of the Group in Rio de Janeiro in early September, 1963, at which time most of the members will be attending the Seventh International Congresses of Tropical Medicine and Malaria.

In conclusion it should be pointed out that the Group feels that, short of embarking on a synthetic chemistry program (the directions of which could probably not be determined any more effectively than is already being done by commercial interests), the projects discussed above, which are already under way or will soon begin, comprise a program which adequately covers the areas of chemotherapeutic research which should be explored.

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