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CHAGAS' DISEASE CHEMOTHERAPY RESEARCH GROUP

REPORT OF THE SECOND MEETING

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PAN AMERICAN HEALTH ORGANIZATION

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CHAGAS' DISEASE CHEMOTHERAPY RESEARCH GROUP

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Two sessions of the Chagas' Disease Chemotherapy Research Group were held in 1966, one in July at the time of the III International Pharmacology Congress in São Paulo and the other in August at Belo Horizonte where round tables on parasitic disease control had been arranged by the Departamento Nacional de Endemias Rurais. The First Meeting of the Group took place in September 1963. At that time it was felt that it would probably not be necessary to get the Group together oftener than every 12 to 18 months. Since there were tentative plans to have the first Latin American Congress of Parasitology meet in Santiago in 1965, it had been recommended that the Group convene again at the time of that gathering (RES 3/8, June 1964) or during the III International Pharmacology Congress to be held in São Paulo in 1966. As it turned out, the first Latin American Congress of Parasitology was postponed until 1967, and it was thought desirable to get the Group together before that time.

The following members of the Group were present at the first session (July 27) in São Paulo: Dr. Z. Brener, Prof. J. Romeu Cançado, Prof. J. Ferreira Fernandes, and Dr. F. C. Goble. Attending as an invited guest was Dr. Julian Jaffe (19) of the University of Vermont who, along with three member of the Group (Brenner (5), Fernandes (9), and Goble (22)), had taken part in a symposium on the Mode of Action of Antiparasitic Drugs organized, with the assistance of Dr. Goble, as a part of the International Pharmacology Congress.

*Prepared for the Sixth Meeting of the PAHO Advisory Committee on Medical Research, 12-16 June 1967, by Dr. F. C. Goble, CIBA Research Department, Summit, New Jersey. Previous reports appeared as RES 2/21, 15 May 1963; and as RES 3/3 and Annex 4 to RES 3/3, 15 May 1964.*
At the second session of the Group (August 1) in Belo Horizonte, the following members were present: Dr. Z. Brener, Prof. J. Romeu Cançado, Dr. F. C. Goble, and Prof. A. Prata. Through these two sessions, all of the members of the Group were reached except Prof. T. Pizzi (Chile) who had also not been able to attend the 1963 organizational meeting.

In view of Dr. Jaffe's activity and interest in the field (1, 17-21, 26) it was decided at the second session to invite him to join the Group to which he subsequently agreed.

During both sessions, the entire program of the Group was reviewed and the successes and short-comings discussed under the following six headings, which are those used in a previous report.

1. **Organization**

   It was decided to continue along previous organizational lines keeping the Group small (the addition of Dr. J. Jaffe not actually increasing the Group since Prof. Pizzi has been essentially inactive) with Dr. Goble continuing to serve as informal secretary and in a liaison function.

2. **Clinical Studies**

   Three of the members of the Group (Brener, Cançado, and Prata) are still members of the Brazilian group of physicians interested in Chagas' disease which continues in existence although it has been less active than before because of the conclusion of the studies on nitrofurans (6, 12, 25) and 8-aminoquinolines and the lack of compounds for clinical trial. It was the consensus that, although a few possible cures had been obtained with the above mentioned compounds, they were not
really satisfactory agents and the need for more active and less toxic substances is still pressing.

At both Belo Horizonte and Salvador, special courses on Chagas' disease have been given to local physicians by members of the Group (Cançado and Prata) in order to make them more conscious of and knowledgeable about the malady so that more acute cases might reach the clinic and be available for drug trials. The Group felt that, in Brazil and Central America, sufficient new cases have been found annually to make satisfactory drug evaluation possible whenever a promising candidate substance is developed. Maintaining the Group would insure rapid transition from the laboratory to the clinic, if and when interesting compounds are found.

3. Screening and Experimental Evaluation

In addition to empirical screening of new compounds, a number of older preparations which had shown activity were studied more extensively in order to answer certain questions which arose during earlier discussions.

Dr. Brener (2, 4) completed a comparative study of selected chemotherapeutic compounds against a variety of strains of T. cruzi to determine whether there are significant strain differences in sensitivity. The investigation of six strains, each treated with four different drugs, indicated that, in general, there were no great differences in sensitivity between strains. Only with one compound (which had already been discarded as clinically unsatisfactory) did differences occur.

Dr. Goble re-evaluated certain other compounds which had been suggested earlier as possible therapeutic agents for Chagas disease. CIBA 22777 (13) and metronidazole (previously mentioned in RES 3/3, Annex 4),
CIBA 32644 (14), and emetine (24), all having shown activity in preliminary laboratory tests, were eventually declared unsuitable as candidates for clinical trials. Because of the questions which had arisen concerning the use of tetracyclines in patients with Chagas' disease, Goble and co-workers (16) made an extensive study of the effects of chlorotetracycline, oxytetracycline, and tetracycline in mice with *T. cruzi* using various routes of medication and various regimens. They concluded that, contrary to certain earlier reports, no enhancement of the disease occurred and that warnings against the use of tetracyclines in patients with Chagas' disease, which had found their way into the literature, were unwarranted.

4. **Basic Studies**

Dr. Fernandes (7-12) continues his studies on *T. cruzi* in tissue culture and in culture medium demonstrating the effects of amethopterin, mitomycin C, and 5-fluorouracil desoxyribose on the morphology of culture forms and the ability of actinomycin D to interfere with the incorporation of thymidine into DNA. These basic observations may lead to the development of attenuated non-infective forms of *T. cruzi* which, although avirulent and unable to establish an infection, retain antigenicity and might be used in vaccines (Dr. Goble is also engaged in some immunological studies; 15,27). Dr. Jaffe intends to extend studies on the metabolic pathways for nucleic acid substances in the various developmental forms of the parasite, and is attempting to discover factors which can modify the proper function of these pathways. He also proposes to isolate the DNA from the crithidial form of *T. cruzi*, unwind it and recombine the single strands with comparable strands isolated from the
5. **Procurement of Compounds**

It is felt that it is probably not necessary for untested compounds to be screened by the Group, inasmuch as testing programs for agents against Chagas' disease are in effect in at least nine major commercial laboratories in the United States, in at least four in Britain, and in several on the European continent. Hence, thousands of new preparations are being examined each year and promising ones can be made available to the Group. In addition, innumerable preparations are also being tested in a program sponsored by the United States armed forces.

6. **Future Activities**

The course of the Group's future program can be inferred from the above discussion. In general, investigations will continue along the lines mentioned, being adaptable to any changes indicated by new discoveries and additional information. Correspondence will maintain the integrity of the Group during the period between formal meetings and permit the sharing of all important new information pertaining to the problem. No definite time for a future meeting was suggested but the principles originally adopted (RES 3/3, Annex 4, page 28) remain acceptable.
REFERENCES


