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RESEARCH NEEDS IN CHAGAS' DISEASE

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In this meeting, to consider what research is still necessary to fill wide gaps in our knowledge of Chagas' disease and its etiologic agent Trypanosoma cruzi, I can't help but be reminded of a comment once made by a student when visiting our laboratory in the Canal Zone. He had come with a group of other high school students to "learn all about medical research". In my introduction, as background to our project, I explained to the group that three years before there had been a disease outbreak, which had prompted us to set about studying the problem. At this point this young man, with an incredulous expression on his face, exclaimed - "you started this three years ago, and you are still working on the same thing?"

I hope that young man is not in this audience today, because I would hate to have to explain to him that after 65 years of investigations of Chagas' disease we are indeed "... still working on the same thing".

I believe most of you are aware that Chagas' disease occurs from the United States to Argentina and Chile, with an estimated 7 million persons infected. Among this large group, the disease will exact a heavy toll in the form of disability and premature death. The ultimate goal is, naturally, to interrupt transmission, and thus to eliminate the disease. However, this goal will not be achieved for many years to come, and the immediate concern must be for what can be done for that large group of unfortunates who already have the infection. What can be done to prevent death or the crippling effects of this disease? The shocking answer is that there is currently no effective treatment which can be used to prevent death or invalidism for millions of people, and we must still look to the researcher to provide this critical need.

Despite intensive efforts over the past 65 years, only about 14 basic chemical structures have been reported to show activity against Trypanosoma cruzi in laboratory animals. Out of these 14 structures, only 8 had sufficient

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activity to warrant clinical trials in human patients. At the present time, only 3 appear to be undergoing continued testing. In Table 1, taken from a review by Dr. W. E. Gutteridge of the University Kent, it can be seen that only the 8-aminoquinolines, 5-nitrofurans, and 2-nitroimidazoles are still being considered as possible compounds for human treatment. Of these, the 8-aminoquinolines are still in the early stages of investigation, but already grave doubts have been expressed about their general toxicity and carcinogenicity. The 2-nitroimidazole, Radinil, is undergoing clinical trials, but few reports are out and I know of no one who wants to make a prediction about its future usefulness. However, the 5-nitrofuran, Nifurtimox (Lampit) is now available in South America. It is undoubtedly effective against the parasite in the acute stage of the disease, but the results of trials with chronic cases are equivocal. It is quite toxic, with sometimes severe side effects and it has no prophylactic action. Additionally, Professor Gutteridge points out that both Lampit and Radinil are nitro-compounds, and since it is now known that the mode of action of these compounds involves interaction with DNA, there must be considerable concern regarding the potential for mutagenicity and carcinogenicity of these compounds.

It is obvious then, that even the best compounds to come out of the search for a chemotherapeutic agent for Chagas' disease do not appear very promising. What appears to be even more distressing is the pronounced lack of candidate compounds for additional clinical trials. As compounds with anti-Chagas' activity are eliminated for human use, because of toxicity or other shortcomings, they are not being replaced by other candidate compounds selected by a continuing screening process in <u>in vitro</u> or animal models. A multi-step sequential system similar to that which was so highly developed in the U.S. Army Malaria Drug Screening Program, wherein a wide spectrum of chemical compounds can be screened for antiparasite activity, and those showing activity referred for testing in several models, has not been available for research on anti-Chagas' drugs. The discovery of active compounds has been fortuitous to a large degree, and drugs have arrived at the clinical trial level with a minimum of information available from testing in animal models. This is not intended to be a criticism of researchers on Chagas' disease, rather to point out a serious disadvantage under which they have had to work.

In general, only very modest resources have been applied to this field. I would venture to say that if only the level of effort expended on Chagas' disease drugs had been dedicated to research on malaria chemotherapy, we would probably still have only quinine with which to treat today. In my opinion, significant progress in Chagas' disease drug research is very unlikely to occur until an organized program can be initiated, which will promote a structured flow of compounds through a screening system to testing in several animal models. In the past, drug screening has been accomplished almost exclusively by trials against acute infections in mice. This is a good model, but initial screening *in vitro* might be even faster and cheaper. A few weeks ago at the Vth International Congress of Protozoology, I learned that trypomastigotes of *T. cruzi* can now be "stabilized" to maintain indefinitely *in vitro* the characteristics of blood stream forms, suggesting that we already have the basic knowledge to develop such an *in vitro* screen. However, there is another need which is much more acute. The only model for the chronic infection has been the dog and this has seriously impeded the study of treatment in this stage of the disease. Since little or no evidence exists that currently studied drugs have any activity against intracellular amastigotes, a means of screening drugs against this form is of great importance. The extensive knowledge of intracellular infection gained by tissue culture studies might well provide such a system if investigators can be motivated to put it to such use. An ordered processing of compounds through such screening and testing systems should eventually produce candidate drugs for clinical trials. Such a system should greatly enhance the possibility of discovering new classes of active compounds which do not have the toxic, mutagenic, or carcinogenic character of all the structures currently being studied.

Of course, it should not be advocated that this empirical search for new active compounds be the only approach to the treatment problem. Such current research is based on the concept of rational design of structures based on knowledge of the biochemistry of the target organism, or of the mode of action of known active compounds. There is no reason to believe this approach would not achieve this goal as effectively as the empirical search, and it does not have the advantage of producing a fund of valuable corollary knowledge as a by-product of the search.

The possibility of treatment by means other than chemical agents is a concept which also should not be ignored. Recent research leaves little doubt that humans as well as experimental animals develop an acquired immunity to acute infections. Although the immune mechanisms in both the acute and chronic infections still need to be elucidated, several parameters of cell-mediated immunity have been demonstrated. It has been shown that macrophages play a role, in that blockage causes an exacerbation of acute infection and sensitization of macrophages with either T. cruzi antigen or BCG results in an increased ability to destroy the parasite in vitro. It is conceivable that manipulation to achieve a hyperpotentiation of the immune response could clear parasites and thus serve as an effective treatment.

A listing of the research needs concerning Chagas' disease must include elucidation of some of the most basic factors of the host/parasite relationship. The Chagas' disease picture is so complex and complicated that we have a very incomplete understanding of even those factors which influence disease outcome in man. For example, the so-called megasyndrome of Chagas' disease, the development of gross enlargements of hollow muscular organs, principally the esophagus and colon, is undoubtedly caused by T. cruzi infection, as revealed by epidemiological studies and careful anatomical research. However, megaesophagus and megacolon apparently do not occur throughout the range of distribution of Chagas' disease. This syndrome is known principally from four States in Brazil and only a few scattered localities in other countries, although Chagas' disease is widely distributed throughout the Americas. This strongly suggests differences in parasite populations. There is other evidence of regional differences in populations of Trypanosoma cruzi, such as the apparent reduced virulence in Central America and Mexico, as indicated by a much higher proportion of serologic reactors who remain completely asymptomatic. There are even pronounced differences in effect of drugs on the parasite from one region to another. However, in addition to these apparent geographic differences in the parasite, there are also differences of the same magnitude in disease manifestations within regions. The evolution of the disease normally involves

an acute phase during which some patients may be severely ill with fever, hepatosplenomegaly and heart damage, and a small proportion die from heart or brain damage. However, it is evident that other persons become infected without ever manifesting evidence of this acute phase.

After the initial phase is past, the patient continues to harbor the parasite for the rest of his life. Again, in the chronic phase some persons go for years without apparent ill effects, while others develop serious lesions of the heart, intestine, or brain and this damage leads to disability and premature death. The great disparity in disease effects cannot be explained simply by parasite numbers, and differences are seen within the same communities, or even the same houses, so it is unlikely that these are due to parasite differences. It is obvious that in both the acute and chronic phase, there is considerable variation in the host response to infection. At the present time it is not known how much these differences in degree of disease damage are due to biological diversity among the parasite populations concerned, and how much is due to differences in host susceptibility or response. It is possible that some of the variations are only apparent and not real, that they result from a lack of standardized methods and criteria. A very pressing research need is to sort out these factors and the answers to these questions will come only from research. To paraphrase the comments of Professor Lumsden of London on this subject..."basically, as long as both main components contributing to the disease outcome--the parasite and the host--are unfixed, progress in our understanding will be limited. If we are able to recognize particular parasite populations we will be able to fix one component of the picture and be the more confident in our interpretation of the effect of the other factors".

The search for means of characterizing and classifying Trypanosoma cruzi strains has recently received great impetus from the application of new parameters, other than the traditional morphologic and biologic characters. Comparison of nucleic acid buoyant densities and of isoenzyme patterns has revealed differences between strains. Continuation of studies on these, and other new parameters, should certainly be encouraged.

It is obvious that in the time allotted today, it would be impossible to make even the most cursory review of the current status of all aspects of

Chagas' disease. I have attempted to illustrate some of the research needs concerned with two of the most basic aspects--effective treatment of the infection, and understanding the disease. It is my belief that these deserve our most immediate attention. I will readily admit to a basis in selecting these priorities, since those of us who are directly faced with the problem of dealing with Chagas' disease are extremely aware of the lack of knowledge and tools with which to combat it. However, I do not suggest that there are not other areas which should receive attention; the development of a vaccine, for example. We obviously must not lose sight of the ultimate goal in the effort to achieve immediate progress. Chagas' disease presently affects millions of people over a large part of our hemisphere, and is a continuing threat to new generations. It certainly deserves major attention in our research effort against parasite disease.

COMPOUNDS WHICH HAVE BEEN TESTED CLINICALLY FOR

ACTIVITY IN CHAGAS' DISEASE

CLASS	EXAMPLE	CURRENT STATUS
Bisquinaldines	Bayer 7602 Ac	Abandoned
Arsenobenzenes	Spirotrypan	Abandoned
Phenanthridines	Carbidium	Abandoned
8-Aminoquinolines	Primaquine	Abandoned
	Others	Preclinical tests
5-Nitrofurans	Nitrofurazone	Abandoned
	Lampit	In use in South America
5-Nitroimidazoles	Metronidazole	Abandoned
5-Nitrothiazoles	Ambilhar	Abandoned
2-Nitroimidazoles	Radinil	Clinical trials

Adapted from: W. E. Gutteridge 1976.