# Pharmaceuticals for Developing Countries: Conference Proceedings (1979)

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# Pharmaceuticals for Developing Countries

CONFERENCE PROCEEDINGS

DIVISION OF INTERNATIONAL HEALTH
INSTITUTE OF MEDICINE

NATIONAL ACADEMY OF SCIENCES
WASHINGTON, D.C. 1979

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The Institute of Medicine was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of the appropriate professions in the examination of policy matters pertaining to the health of the public. In this, the Institute acts under both the Academy's 1863 Congressional charter responsibility to be an advisor to the Federal Government, and its own initiative in identifying issues of medical care, research, and education.

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# PREFACE

In the summer of 1977, Senators Kennedy, Javits, and Schweiker of the Senate Subcommittee on Health and Scientific Research expressed concern that neither component of America's large biomedical research establishment -- the pharmaceutical industry's research laboratories and those in academic institutions -- was devoting enough attention to the enormous unsolved health problems of the developing countries. The Senators informally requested the Institute of Medicine, in cooperation with the Department of Health, Education, and Welfare and the Pharmaceutical Manufacturing Association, to organize a Conference on the problems associated with development and distribution of the pharmaceuticals needed by developing countries. They hoped the Conference would enable the Institute of Medicine to make recommendations that would encourage serious attention by American biomedical scientists to the health problems of developing countries.

The Department of Health, Education, and Welfare subsequently decided to sponsor such a Conference. An Institute of Medicine Steering Committee, convened in June 1978, proposed that the Conference explore four sets of inter-related issues: (1) the principal health problems of the developing world and the effectiveness, safety, and utilization of those preventive, prophylactic, and therapeutic agents now available; (2) the factors responsible for the paucity of research effort on the disease problems of developing countries by the biomedical research establishments of the American pharmaceutical industry and universities; (3) relevant scientific opportunities; and (4) policy initiatives required to strengthen incentives and overcome disincentives for industry and the academic community to do more to help solve these problems.

Knowledgeable persons from American governmental agencies, pharmaceutical firms, and academic institutions, complemented by representatives from the European pharmaceutical industry, academic science, and the World Health Organization, were asked to prepare papers and participate in discussions on these matters. The Conference was held at the National Academy of Sciences on January 29-31, 1979. Senators

Kennedy, Javits, and Schweiker all participated as did Dr. Gilbert Omenn from the Office of Science and Technology Policy of the Executive Office of the President. Their statements provided both Legislative and Executive Branch perspectives on the American government's policy concerning the health problems of the developing world.

These Proceedings contain the commissioned papers, prepared remarks of the invited speakers, and the summaries of the general discussions. A diversity of backgrounds and viewpoints is represented.

The Proceedings were used by the Steering Committee to develop an Institute of Medicine policy paper issued under separate cover, and containing an analysis of the issues and recommendations for action. That paper is entitled, "Pharmaceuticals for Developing Countries: Issues and Recommendations."

Harold J. Simon, M.D., Ph.D.
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# OVERVIEW OF THE CONFERENCE ON "PHARMACEUTICALS FOR DEVELOPING COUNTRIES"

Leighton E. Cluff

Disease has often interfered with the master plans of strategists who wish to improve the economic, social, and political development of a nation. Many historical examples show that disease has had devastating effects upon the population of a particular region, upon achievement of commercial, economic or political objectives, and upon personal and social well being.

The conquest of yellow fever, which made construction of the Panama Canal possible, was followed by elimination of this infection from the Southern United States and elsewhere, and illustrates one of the greatest practical triumphs of scientific medicine and the far reaching commercial and political consequences of controlling a single disease. Today, infectious and parasitic diseases in developing countries adversely affect social, economic, and political development. If these diseases were controlled, the consequences could certainly be as dramatic as those following control of yellow fever. The health and standard of living, particularly of the poor people in these countries, could be advanced impressively.

Poverty contributes to the occurrence and prevalence of many diseases, including those attributable to infection. Some of these diseases, however, can be controlled despite coexistent economic deprivation. For example, smallpox has now been largely eliminated from the world, including the poor and developing countries. The ravages of poliomyelitis have been eased, and death rates from infantile diarrhea and cholera have been significantly lowered in both poor and affluent segments of several countries without concomitant changes in socio-economic conditions. These and other infectious diseases were controlled by widespread application of specific, effective medical interventions. Other specific and effective interventions exist and could be used to control some important infectious diseases which are particularly prevalent in developing countries. In these instances, we must find ways to remove obstacles to and provide incentives for their use. In other instances, we must encourage and support the research needed to understand the diseases and the development of appropriate interventions.

Some specific interventions that effectively control diseases can be administered to large populations, or to particular groups of people at risk of becoming sick. Such interventions may not require continuous access to personal health services such as are provided by physicians or other health professionals. For example, a vaccine can be administered to all children in a community or population to control a particular disease, even though there is no one regularly available to care for individual children when they are sick. In other circumstances, effective interventions can be made available only to individuals who have been evaluated by a personal health professional who can prescribe a particular treatment. Then, the entire population has to have access to personal health services if the intervention is to affect signficantly the public health.

Many developing countries lack effective systems and sufficient numbers of trained providers to deliver personal health services to the population at large. In addition, the public health systems in many of these countries are ill prepared to meet the needs of the total population. Therefore, even available interventions that could be effectively used to control specific diseases cannot easily be deployed. These countries will need assistance to enlarge and strengthen their personal health care services and their public health systems to distribute and use effectively interventions that are now available or that could be developed.

The occurrence and prevalence of particular infectious diseases vary among the developing countries. Nevertheless, some infectious diseases affect poor and deprived people wherever they live. For example, infantile diarrhea and respiratory diseases occur commonly among poor children in every country. Other diseases, such as schistosomiasis and cholera, are largely confined to particular geographic areas of the world. Most diseases occurring mainly in developing countries affect the poor and rural populations. As many people move from rural areas to the cities, such diseases may become less prevalent, but the expanding urban populations suffer from diseases common to areas of poverty anywhere.

Most technology is difficult to apply under conditions of extreme poverty unless directed against specific problems. It is impossible to control all diseases, and it makes much more sense to direct efforts at the control of one or a few diseases at a time. Appropriate employment of available and effective interventions, and continuing search for weak links in the epidemiological and pathogenetic chains of specific diseases are important aspects of practical and successful efforts at disease control. Smallpox was controlled by a specific focus on it, not through efforts aimed at disease control in general. Although personal hygiene and environmental control measures would significantly reduce the burden imposed by many infectious and parasitic diseases on the people in the developing countries, the widespread application and use of specific drugs and vaccines that can effectively control the

incidence, severity, and outcome of particular diseases is also of vital importance.

Production and supply of several vaccines and drugs that would effectively control specific diseases are insufficient to meet global requirements. Without planning and investment, and without a better data base on which to gauge the need, it is not possible to meet projected rises in demand for these pharmaceutical agents. Systems for distribution and administration of agents to control a disease must be developed, and the required resources provided. Specific vaccines and drugs are needed in the developing countries, and such needs should perhaps be better reflected in their domestic budgetary priorities, but the cost of obtaining these pharmaceuticals cannot be met by these countries without help -- international cooperation and assistance will be necessary.

Multinational cooperative efforts by the more affluent industrialized countries and by the developing countries will have to be increased if the health problems of the latter are to be dealt with effectively. The populations of industrialized countries, and particularly the United States, are insufficiently aware of the health problems of people in developing countries to make positive and rational commitments in response to their need. The legitimacy, importance, and self interest of Americans in the health of people in impoverished countries should be given greater attention and visibility. Popular support is necessary to strengthen public and private institutions concerned with international health, and to expand national efforts and international cooperation to address the health needs of developing countries.

Never before in history have the opportunities for rational scientific and technologic approaches to health problems of developing countries been so great as they are now. The research, development, and production capacities of the pharmaceutical industry in the United States have achieved a commanding position in practical and theoretical efforts to perfect available drugs and vaccines, and to generate new agents for use in developing countries. Nonetheless, current constraints and regulation of the pharmaceutical industry in the United States function as disincentives to capitalizing upon such opportunities and accepting the challenge to develop new and improved drugs and vaccines which may find their greatest, and perhaps even their sole applicability beyond the borders of the United States. Furthermore, the amount of encouragement and support of research by academic scientists in the infectious disease problems of primary concern to developing countries has been less than that necessary to exploit emerging scientific opportunities and challenges. Academic scientists provide most of the fundamental information needed for the practical development of new or improved medical interventions. The pharmaceutical industry, on the other hand, has organized the multidisciplinary approaches required for development and production of these agents. Natural linkages exist between the efforts of academic scientists and

# INTRODUCTION TO THE CONFERENCE ON "PHARMACEUTICALS FOR DEVELOPING COUNTRIES"

David A. Hamburg

DR. HAMBURG welcomed the audience and speakers to the National Academy of Sciences and the Institute of Medicine. He noted that the Conference constituted a landmark both for the Institute of Medicine and for pharmaceutical development.

Briefly outlining the history of the Institute, created in 1970 with the broad charge to study issues pertaining to the health of the public, he explained that the relatively new International Health Division focuses primarily on the health problems of developing countries, enlisting leading members of the American academic community and their overseas colleagues to work with government and the private sector to address those problems. The Institute's perspective has been that, with the enormous scientific capability of the United States and of other technologically advanced countries, even a modest increase of interest and concern from the scientific community could yield highly significant benefits for the developing world. Such efforts will prove beneficial for all nations in an increasingly interdependent world.

Several years ago, attempts to increase the interest of the Administration and Congress toward the health problems of developing countries were not very successful. Beginning in 1976, however, and under the leadership of the Executive Office of the President of the United States, several governmental agencies undertook cooperative efforts to organize and increase assistance toward improving health in developing countries. Concomitantly, and stimulated by renewed interest in the legislative branch, the Institute of Medicine undertook to identify opportunities for research and health care innovations that might receive further encouragement and support from government, industry, and the academic community.

The widely dispersed potential of diverse governmental and nongovernmental organizations must now be mobilized to increase the efficacy of work directed towards improving health in developing countries. The first major study on these issues was conducted by the Institute of

of Medicine in 1977,* and defined current opportunities to broaden program activities in international health. DR. HAMBURG expressed his belief that the principles and issues illuminated in that report have provided a useful framework for analysis, and that the Congress will act upon the recommendations contained therein.

DR. HAMBURG then cited the annual meeting of the Institute of Medicine held in October 1978, at which an entire afternoon was devoted to international health issues. Drs. Halfdan Mahler, Adetokunbo Lucas, and Sune Bergstrom contributed major addresses to the program, presenting principal aspects of World Health Organization activities. The membership reacted enthusiastically to the Institute's new international initiative, promising future interest and support.

As a sequel to this Conference, which has been sponsored by the Department of Health, Education, and Welfare, the Institute will conduct a study on "Clinical Investigation in Developing Countries." That study will be chaired by Dr. Robert Petersdorf, and is sponsored by the Office of Science and Technology Policy in the Executive Office of the President. The Steering Committee will define and analyze the principal problems and issues attendant upon the conduct of cooperative clinical investigations in developing countries, and will then develop pertinent recommendations for governments, donor agencies, academic institutions, and investigators from developed and developing countries. Continuing these activities, a study on health services research in developing countries is anticipated, which should complement the Institute's efforts in connection with this Conference, and in the study on "Clinical Investigation in Developing Countries."

DR. HAMBURG concluded by noting the long-standing commitment and contributions by Senators Kennedy, Javits, and Schweiker to solving the health problems of developing countries. He acknowledged Senator Kennedy's leadership in the Senate in providing strong encouragement to the Institute, to the academic community, and to the government toward substantively addressing the issues of increasing access to improved health care by people in developing countries. He then introduced Senator Kennedy as the keynote speaker of this Conference.

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* Strengthening U.S. Programs to Improve Health in Developing Countries. Report of a Study by the Institute of Medicine/National Academy of Sciences, Washington, D.C., April 1978.

# KEYNOTE ADDRESS
# PHARMACEUTICALS FOR DEVELOPING COUNTRIES

United States Senator Edward M. Kennedy

It is a special privilege for me to be here today to keynote the Conference on Pharmaceuticals for Developing Nations. I owe a special debt of gratitude to Dr. David Hamburg, President of the Institute of Medicine, for responding so magnificently to my request that such a Conference be convened. He and his colleagues, Dr. Leighton Cluff, Mr. David Tilson, and Dr. Harold Simon, have not assembled the top experts from around the world for just a one-shot enterprise, but have made this three-day Conference the first step in a continuing and sustained effort in this area by the Institute of Medicine.

Since Dr. Hamburg became its president, the Institute of Medicine has played an increasingly prominent role in developing national and international health policy alternatives for the United States. His compassion, his concern, his commitment to people and their problems, have made Dave Hamburg an exceptional figure on the Washington scene. The Institute of Medicine reflects his energy and skill.

Over the next three days leaders of government, industry, and academia will share their knowledge, their ideas, their problems in an effort to form a partnership to begin to address the overwhelming health problems in developing nations. Much of the talk will be technical, much of it will focus on specific problem solving. This is important and hopefully, concrete solutions will begin to emerge from the process.

But before we get into the detail, before we examine the technical problems, let us remember, in human terms why we are here. As Archibald MacLeish put it:

> "When the fact is disassociated from the feel of the fact in the minds of an entire people and in the common mind of a civilization -- that people -- that civilization -- is in danger."

We are here because one-quarter of the people on this earth -- one billion men, women, and children -- have no access to any health care whatsoever.

We are here because 15.6 million children under five years of age will die on this planet this year; 15.1 million of these children will be from developing nations.

We are here, in this International Year of the Child, because 2.6 million children will die this year from immunizable diseases because they won't have access to already-developed vaccines. There will be 72 million cases of measles in the world this year. And at a time when measles is nearing extinction in the United States, 1.2 million children around the world will fall victim to it this year. Six hundred thousand people, most of them children, will die from tetanus this year; 200,000 will die from polio, and 300,000 from whooping cough.

Measles, tetanus, whooping cough, polio -- we have vaccines for all of them.

We are here because 70 percent of the human family worldwide does not have access to clean water, and millions die each year from dysentery and gastroenteritis.

We are here because hundreds of millions of people in developing nations contract parasitic diseases each year, for which inadequate therapy exists or is not available when and where it is needed.

We are here because we know that what is a statistic to some is a face to others. Behind these statistics are the faces of millions of people suffering from symptoms we can alleviate, dying from diseases we can treat, developing diseases we can prevent entirely.

But most important, we are here because we know that progress can be made and that between us we have the skills, the energy, the compassion, and the commitment to lend a hand, to make a contribution. My brother Robert Kennedy liked to quote these lines written by Albert Camus:

> "Perhaps we cannot prevent this world from being a world in which children are tortured. But we can reduce the number of tortured children, and if you don't help us, who else in the world can help us do this?"

That is why we are here today.

Our focus for the next three days will be on the development and delivery of drugs necessary for the developing nations. Although developing nations spend 50 percent of their health budget on drugs, over 70 percent of their people have virtually no access to them at any time.

And that makes a very real difference to the quality of their lives. The current president of the World Health Organization, Dr. F. Johnson Romuald, put it very well in his presidential address last May:

> "You only fully understand the vital importance of drugs for health care when you see the long queues of the sick in front of a little dispensary out in the bush which has nothing on its shelves, not a single tablet or an anti-malarial or ... antibiotic. Yet this is the situation in entire regions of the world."

The problem of delivering existing pharmaceuticals to villages and hamlets in developing nations is indistinguishable from the overall problem of delivering primary care. We have all learned, at a tragically high price, that the industrialized model of high technology, urban-based medical care exacerbates existing problems in developing nations. We have learned that it is not a question of bricks and mortar. It is a question of building a primary care infrastructure in each country. And that infrastructure must be built by the individual country, adjusted to its particular needs. It cannot be imposed from outside. This means training local people to solve local problems. It means building a new structure of health care in the only way it can be built -- from the ground up by the people who live there.

In this effort no single nation has all the skills or answers. We must develop a partnership among nations, each contributing what it can to the common effort.

We are talking about the development of rather basic systems, by industrialized standards; but systems that can make an enormous difference to peoples' lives.

But if it is to be a simple, basic system, then it will not be equipped to handle the distribution of the 25,000 drug products currently marketed in the United States. Such a distribution system is not only out of the question from a health systems standpoint -- it is also economically impossible for the developing nations.

That is why I endorse and applaud the effort of the World Health Organization to develop the concept of an essential drug list for developing nations. Nothing could make more sense. The World Health Organization concept is a simple one. Its premise is that the first priority must be to meet basic health needs. That requires a primary care infrastructure. A myriad of competing drug products is inconsistent with that -- therefore, a relatively small <u>essential</u> drug supply is what is needed.

The list need not be, and should not be, the same from country to country. It would have to be based on individual needs. But to the extent common needs can be identified, group purchasing would reduce

the economic burden. An example of this is the recently developed South Pacific List of Essential Drugs.

Remember, we are talking about unimaginably poor countries which are already spending an unbelievably high percentage of their health dollar on drugs. The essential drug list would help, and would be consistent with the efforts to develop "bottom-up" delivery systems.

So, in my view, the delivery of drugs is linked to the development of primary care infrastructures. And the development of those infrastructures must be based on the particular needs of each country. And the role for developed nations is to help -- in a collaborative way. One of the ways they can help is to urge and provide incentives for the private sector to get involved in the effort. As industry enters developing nations and builds plants, then the health of the workers becomes of vital importance to the corporation. There are many examples of significant corporate contributions to the health of people in developing nations:

-- In Ghana, Kaiser Aluminum has helped develop a primary health care program for the area surrounding its operations.

-- In the Dominican Republic, Alcoa has, in cooperation with the government, developed an integrated primary care program.

-- In Indonesia, the Weyerhauser Company established a small hospital and has worked with the local community to control malaria, conduct immunization campaigns, and deliver other preventive services.

-- The Xerox Corporation and the Children's Television Workshop have developed mass media preventive health messages for presentation throughout Latin America.

There is a long list of private industry cooperation with local community efforts to help develop primary care systems. It is something to be built upon. In the common effort by all nations, the private sector can and should play a role.

Although the delivery of pharmaceuticals is beyond the immediate control of the scientific community and the pharmaceutical industry, the development of new drug products is not. It is here that this Conference may well make its most significant contribution.

I hope you will identify areas of great scientific promise; review areas where more basic research is needed; identify obstacles to carrying out such research. I, for one, would like to know

-- how to encourage the pharmaceutical industry to focus more attention on the development of drugs for diseases of developing nations;

-- how to build a strong scientific capability in the United States in this area;

-- how to build a scientific capability in developing nations themselves;

-- how clinical trials can be carried out if the disease exists only in countries which lack the capability to do clinical trials;

-- how the current export provisions of the Food, Drug, and Cosmetics Act affect drug industry research priorities and what differences, if any, the newly proposed Drug Reform Act would make;

-- if there is a special role for the university community in the effort to research and develop new drugs and vaccines, to carry out clinical trials, and to train personnel.

Within the next few weeks, I will introduce a major international health bill. Its goal will be to improve the ability of the United States to help solve some of these problems. It will attempt to strengthen the research capability, to improve and expand our training programs, to improve our service and technical assistance capabilities. Your work at this Conference will have an important impact on that legislation. To a large extent, it is dependent upon the answers you develop to the questions I have raised.

As Chairman of the Senate Health and Scientific Research Subcommittee, which has the jurisdiction over most aspects of international health policy, I pledge hearings on this legislation in the spring and prompt action by the Senate this fall.

There are some in this city who must wonder why so many talented people are being convened to focus their energies on the problems of faraway places. It is, after all, incongruous with the "me first" attitude, the spirit of retrenchment, so prevalent in America today. That you are together here, from all over the world, willing and anxious to help in this effort is a reflection of what is best in us. It is a recognition that in this effort, perhaps more than in any other of which we may be capable, we are all one people, harnessing our talents for the benefit of others in this struggling world we share. We cannot retreat from that responsibility without retreating from mankind itself.

The prayer for children has these lines:

> "Somewhere -- the place it matters not -- somewhere,
> I saw a child, hungry and thin of face,
> Eyes in whose pools life's joys no longer stirred,
> Lips that were dead to laughter's eager kiss,
> Yet, parted fiercely to a crust of bread."

That is why in this endeavor there is neither Jew nor Gentile, neither male nor female, neither authoritarian nor democratic nation, neither liberal nor conservative. There is only illness to be cared for, hunger to be fed, death to be driven off.

That is why you have come. I am grateful to you for it.

# HISTORICAL PERSPECTIVE

Walsh McDermott

Thirty years ago this month, on a clear and very cold January day, President Truman gave his inaugural address from a portico of the White House. It was the first inauguration covered by television and I was one of the millions who saw it in that way. As is not unusual on such occasions, the President listed a number of programs he hoped to lead to realization.

Few people can today recall points one, two, and three of his list; but Point Four has had a certain immortality. For the fourth point was the announcement of a program in which the highly valued technology of the United States would be made available for the development of the badly impoverished nations of the world.

Biomedical or health technology, if you will, was just coming into flower at that time. Its outstanding attribute was that virtually for the first time medicine was developing the capacity to intervene decisively in the course of a wide range of diseases. The diseases were some of the major ones forming the disease pattern of an industrialized society, for scientists tend to work on the diseases that are of considerable importance in their own world.

What is this interventionist technology?

In large measure it consists of medications, solutions, vaccines, and anesthetics. It also includes diagnostic and surgical techniques. For the purposes of this Conference, however, my discussion is largely concerned with drugs and vaccines.

Prontosil -- the first sulfonamide developed in 1935 -- marks the clear begining of the present era. More potent sulfonamides were rapidly developed and within five or six years we went into what I call the golden decade, from 1941 to 1951. In 1941, we had only quinine, atabrine, the arsenicals, and the sulfonamides as our antimicrobial drugs. By 1951, we had available every one of the major drug series we have today: the pencillins, the streptomycins, the tetracyclines, chloramphenicol, and isoniazid. The antifungal drug, amphotericin B, was

developed later but, except for that, no major disease has been changed to the generally drug-treatable list in over 25 years.

To say that there have been no major therapeutic breakthroughs in almost 30 years is not to say that the results of what was developed in that decade ceased when the decade ended in 1951. On the contrary, the influence has been a continuing affair and includes far greater consequences, both technologic and social, than are generally appreciated. Everyone knows the drugs transformed the disease pattern of the United States and ultimately that of the rest of the industrialized world. But it is not always realized, for example, that the drugs made possible today's lung and heart surgery. Even less consciously considered is the role of the drugs in the development of more efficient techniques for handling viruses and cell cultures in the test-tube, thereby facilitating antiviral vaccine production. Virtually the entire scientific development involving cell biology has depended on techniques that would not have been possible or would have been immensely more difficult were it not for the antimicrobial drugs.

Derivative drugs were developed, some antimicrobial, some not, as for example the thiazides and certain tranquilizers. There has been the use of antibiotics in animal feed -- an issue of controversy at this time. There have been extensive changes in the workings of the health care delivery system. And not the least of the consequences has been the creation in our country of an essentially new and greatly enlarged system for the nourishment of biomedical science and technology.

Next to the story of the genetic role of DNA (also in this decade*) this is the major biomedical event of the century. My assignment is not to tell this story, but to recall to you from it a few lessons that might help in forming a perspective for our view of the future. Because of the nature of what I am attempting, I am limiting my comments almost entirely to the United States experience.

The research support system that developed involved the federal government, the pharmaceutical laboratories, and the academic laboratories, and had mixed public and private support. Theoretically, the technologies derived from this system could be applied through either one of the two main avenues for the application of science for man's benefit. These are:

1. The public health system, in which an intervention is made that affects a number of people at once, e.g., a program to reduce the incidence of goiter by putting iodine in table salt.

2. The personal service system. This is the one most people know;

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*As were the explosion at Alamogordo and the bombing of Hiroshima and Nagasaki.

the intervention is applied not to a whole community but to an individual. This means that almost invariably it has to be applied or "delivered," if you will, by a physician or someone delegated by the physician. Irrespective of level of training, this system requires that there be one person to do something for another.

These represent two forces on our health status. A third force less easy to characterize but quite real, is the way of life permitted by the material culture.

Chemicals, as distinct from pharmaceuticals -- for example, DDT -- can be effectively delivered through the public health system. But pharmaceuticals almost by definition require some form of personal service system for delivery. Thus, when the effectiveness of that system to improve a people's health comes under challenge, it is also a challenge to the United States pharmaceutical industry. For, if its output is not having too much effect on the United States people, it might not hold forth much promise for those in developing countries.

Consequently, while considering the role of the United States industry in the developing countries, this issue of the health impact of the personal service system must be resolved. As I published just last year 1/ a detailed discussion of this issue, I shall confine myself today to only a few points that bear directly on our subject. At the outset, may I emphasize that this has become a major issue in health policy today.

Rapidly ascending costs have produced a collection of strange bedfellows, including economists who wish to invest a considerably higher proportion of the health dollar in something other, and presumably cheaper, than our present system of personal medical care -- the so-called alternative health strategies. We are interested today in only a portion of this case; namely, the nationwide health impact of the personal service physician system -- the system that consists of the physicians, their hospitals, and the therapeutic and other technologies they employ.

What is not generally understood is that we have devised no indicators to measure the effectiveness of what the doctor does on the health status of a society. For the outside critic especially, it is very easy to fail to realize when some indicator is being used to measure something it could not possibly indicate. There is a general failure to realize, therefore, that what are known as "the usual indices of health status" are indicators that have been developed through the years to measure the public health system, not the personal service physician system. These indicators are based on births and deaths. Deaths get counted as physician failures, but we have no way of measuring the successes of the personal service physician system. Everything that does show up, in effect shows up as a failure.

To be sure, if the personal physician system had an absolutely smashingly successful year -- a major epidemic of success, so to speak -- it might be picked up in the public health system indicators, even though these indicators at best can reflect only a portion of the personal physician system's influence. We would have to have a situation in which within a single year a new technology, i.e., a new drug, would be introduced that could actually prevent the deaths of large enough numbers of people to constitute a significant reduction of our annual total of two million or so deaths. To do this, the new technology, say a pill, would have to do either of two things: be effective against many different potentially fatal diseases; or be effective against one fairly common, potentially fatal, and carefuly reported disease.

These are stringent conditions to have to meet and understandably they would occur rarely, if at all. Yet they have actualy occurred at least twice in the past 30 years or so, and on both occasions there was a clear-cut fall in either the overall or the disease-specific death rate.

From 1900 to the mid-1930s, the United States death rate showed a slow but steady fall. I have presented evidence elsewhere that very little of the fall could be attributed to drugs or other therapies of the personal physician system.

In November 1936, Franklin Roosevelt, Jr., a student at Harvard and the son of the then President, was admitted to Massachusetts General Hospital with a streptococcal sore throat and treated with the hitherto unknown drug, Prontosil. Diseases with words like "streptococci" associated with them were quite generally feared by the public. For, roughly 10 years before that, the son of the then President, Calvin Coolidge, while a student at prep school, had died of "blood poisoning," a vernacular term then used to describe systemic bacterial infections such as those produced by staphylococci or streptococci.* Hence, all America followed young Franklin's course daily. And his prompt recovery was taken as the most effective of announcements to both the medical professions and the public-at-large that a new drug -- the first sulfonamide -- had been discovered. In actuality, as reported elsewhere,2/ the drug had been used for a very few patients the year before in New York City. Thus, at the start of the new year in 1937, an adequate supply of sulfonamide was put into the hands of the personal encounter physicians all over America and no advertisement of its value was needed.

In Figure 1 may be seen death rates for men and for women from our black (i.e., "all other") and from our white populations.

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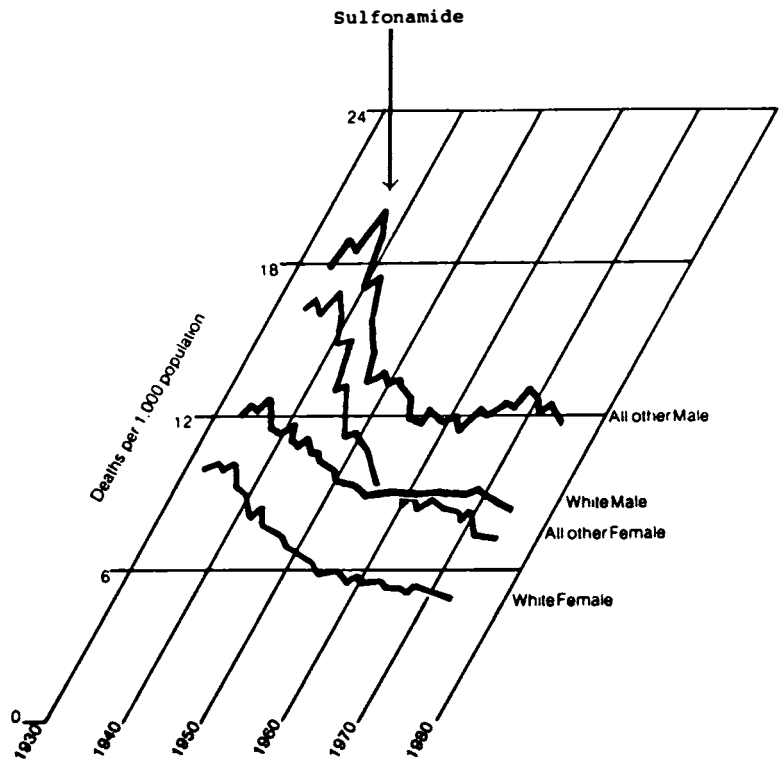
*In actuality, the infection appears to have been staphylococcal, thought to have arisen from a blister on a heel.

FIGURE 1. AGE-ADJUSTED DEATH RATES, BY COLOR AND SEX, 1933-1973 a/



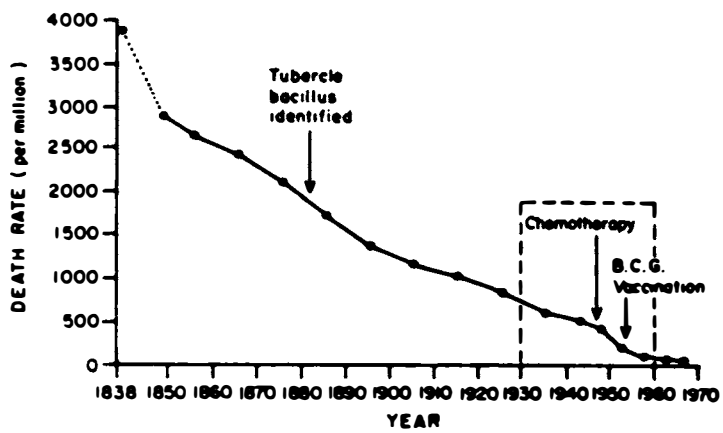

a/Source: National Center for Health Statistics (slightly adapted).

The curves start with 1935 and 1936, which were very much like previous years. In the year 1937, however, there was a sharp fall in death rate. This fall, which was sharper in the "all other" population than among the whites, started immediately with the wide use of sulfonamide. Penicillin came into wide use about eight years later, and as mentioned earlier, virtually all of the other antimicrobials were in use by 1951.

The curves are presented until the mid-70s, but it is the sharpness of the onset in 1937 that is the key point. There was no new vaccine program -- no major change in lifestyle. A new drug was introduced that was applicable to the problems of large numbers of people, young and old, and was applied only through the personal physician system.

Streptococcal disease was a major part of the disease pattern for these overall death rates. Tuberculosis was the disease for which changes in disease-specific rates may be seen. Both of these diseases have figured prominently in the studies of the British writer, Thomas McKeown.3/ In Figure 2 may be seen a graph that represents the death rate attributed to tuberculosis in England and Wales, decade by decade,

FIGURE 2. RESPIRATORY TUBERCULOSIS, MEAN ANNUAL DEATH RATE IN ENGLAND AND WALES a/



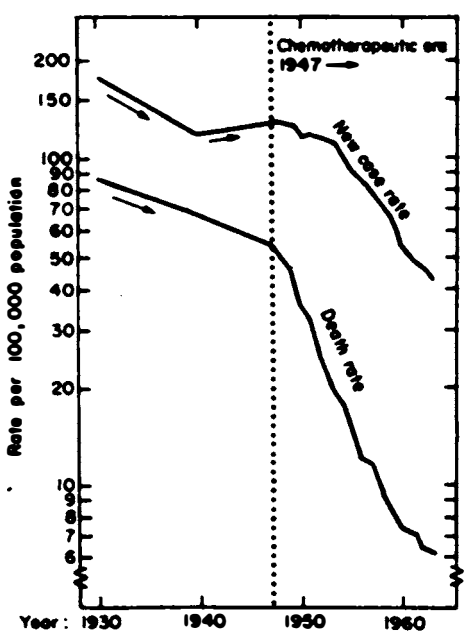

a/Dotted line square added (see reference 3/).

from 1938 to 1970. It is McKeown's graph, and a much cited one. He points out quite correctly that there is every reason to believe that the incidence of what was thought to be tuberculosis was falling throughout the 19th century. He further implies 3/ that the 20th century control of tuberculosis in Great Britain resulted mainly from a steady continuation of these same 19th century forces that occurred long before chemotherapy. While conceding that the introduction of streptomycin was accompanied by a "quite considerable decline in tuberculosis deaths in the age group 15 to 45 and over ...", he regards what occurred as "a very limited contribution" when put in perspective in

relating to the total period. This judgement is now widely cited in condensed form to the effect that the introduction of the antituberculosis drugs such as streptomycin and isoniazid have made only a limited contribution to the reduction in deaths from this disease. This interpretation of McKeown's viewpoint gets reinforced by his stated belief that even after 1935 the available chemotherapy is less effective than that of other influences against a whole spectrum of bacterial diseases. His concept thus gets projected into the future and is used extensively in support of the alternative health strategies "movement."

In Figure 3 may be seen the same tuberculosis death rates as in Figure 1. The area within the dotted line on Figure 1 has been blown up and the data placed on a logarithmic scale. This is the area that covers the introduction of the drug therapy of tuberculosis.

FIGURE 3. TUBERCULOSIS NEW CASE AND DEATH RATES IN ENGLAND AND WALES a/




a/Area within dotted square enlarged and placed on logarithmic scale showing death rates before and after onset of chemotherapy in 1947 (see reference 2/).

On this graph, the rapid fall in death rate that started immediately after the wide use of drug treatment is easily seen.

Occasions on which it would be possible to measure the effect of a new technology on a whole people are understandably rare, but these two examples certainly show that in the circumstances of the United Kingdom or the United States, the technology works.

The next point is, how did we manage to get rid of the diseases that form such an important part of the disease pattern of the developing world?

The disease pattern of the urban rich is like our own and is very much the same the world over. In some developing countries, there is an emerging middle class not yet of large size, but of whom much the same could be said. It is the others in the developing countries who form the great majority and are our concern.

Their disease pattern can be separated into an outer skin and a central core. The core consists of the diseases found virtually everywhere in the developing countries. It is useful to separate these core diseases into those of adults, including surgical conditions, and those of early childhood. This large core is covered by an outer skin of varied thickness that differs from one locality to another and thus provides distinctive local coloration to the disease pattern of a particular region. The group forming this outer layer consists principally of the helminthic or protozoan diseases -- such diseases as malaria, Chagas' Disease, hookworm, and schistosomiasis.

This then is the technologic substrate of the developing countries; for some of it we have effective technologies and for some we have not. If I were to discuss it in detail, I would be encroaching on the assignments of speakers that follow. There are a few points, however, that must be cited.

It is not always realized that malaria, cholera, yellow fever, and smallpox were all important diseases in the northeastern United States at one time -- hookworm was well known in parts of the rural South. To all intents and purposes, these have disappeared as problems.

The most important disease in the world today in terms of numbers of deaths, is the pneumonia-diarrhea complex of infants. One reason is that unlike the worms or protozoan diseases (which are certainly important, but are confined geographically) the pneumonia-diarrhea complex occurs everywhere in the conditions of poverty and can affect the same baby on repeated occasions.

Any potentially fatal disease problem of infants and young children has additional significance in terms of economic development

because there appears to be an important association between a high youthful mortality and an unwillingness to become interested in limitations of family size.

How have we managed this problem in our society?

One way we seek answers to such questions is to find so-called experiments of nature, i.e., situations that occur by chance but are so well recorded as to permit analysis. Such experiments on diseases that are major problems in developing countries are not too common. The reason is that two contradictory conditions must occur together. One condition is that the locality must be underdeveloped enough so that the disease is present, and present in sufficient numbers so that a change in it would be significant. The other condition is that the locality must be developed enough so that its vital statistics are believable. New York City early in this century met these two conditions.

A graph of the infant mortality in New York City from 1900 to 1930 may be seen in Figure 4. At the turn of the century (shown on the left) the infant mortality was 140 instead of today's 14 per 1,000 live births. The very large number of deaths from the pneumonia-diarrhea complex labelled Digestive and Respiratory may be seen in comparison with the number of deaths from all the other infectious diseases taken together. There was an impressive fall in the deaths from the pneumonia-diarrhea complex during the three decades shown in the Figure, and it continued steadily thereafter until it was no longer a major health problem.

The lesson from this three-decade, well-documented experience is that this impressive health gain on a disease pattern, similar to a most important part of the disease patterns in the Third World today, occurred before the time biomedical science and technology had developed specific therapies or preventives for virtually any of the diseases present. Expressed differently, this considerable health achievement, if you will, was obtained without help from our modern technology. Even the pasteurization of milk and chlorination of the central water supply seemed to have little or no influence. It was a period of considerable increase in the standard of living.

So this is how things went before we had our technology.

In another experiment of nature let us see how a disease pattern at a similar stage, but one including adults as well, was affected after the development of our contemporary drugs and many of our vaccines.

A few years after the end of that golden decade of drug productivity in the forties, my associates and I had an opportunity to suddenly apply the most up-to-date technology in conditions that in most

FIGURE 4. INFANT MORTALITY BY PROMINENT CAUSES IN NEW NEW YORK CITY (RATES PER 1000 BIRTHS) a/

a/Source: Weekly Reports of the Department of Health, New York City, Vol. XXI, no. 50, p. 396, December 17, 1932.

important particulars resemble those of a developing country. This was done as part of a large-scale project in the middle of the Navajo Reservation in Arizona and was financed in part by the tribe itself.4/

The people lived far from each other in dirt-floored, windowless, waterless log huts and maintained a very high birth rate -- 47 as compared with the general United States rate of around 14 today.

In the mid-1950s, we established a delivery system that included a well-equipped center for ambulatory care, a rudimentary satellite facility, physicians, public health nurses, bilingual allied health professionals -- even radio telephones in the automobiles. There was no question that the technology was not thoroughly delivered to the people living in the 800 square mile project area. Indeed, the community was wholly cooperative.

The conventional wisdom was that the population was disease-ridden, with about 70 percent of the disease being microbial in origin. The answer to what happened when we introduced modern technology in these circumstances was "not as much as one might think."

Of these microbial conditions, four were especially prominent. Of particular importance is the fact that the two conditions that did not require changes in household practices for their control -- otitis media and the transfer of tubercle bacilli -- were significantly influenced by the technology. By contrast, the two that did require changes in the home -- trachoma and the pneumonia-diarrhea complex -- were not affected.

The partial technologic failure was exacerbated by the high sustained fertility. The high birth rate ensured that infants and young children would comprise a large portion of the people that were sick at any one time. Our medical technology has relatively little to offer infants who are located in a virtually unprotected home environment.

The lessons thus far can be summed up: first the drugs invented for United States society have had demonstrable and major effects on its level of health; second a disease pattern of great importance in developing societies -- the pneumonia-diarrhea complex of infants -- largely disappeared from our society without the use of today's technology, but in a setting of widespread economic uplift; third attempts to substitute the drugs effective in United States society for a complete lack of sanitary barriers in the home are apt to have quite limited value in developing countries.

By the same token, impressive strides have been made by national and international groups in attacking this infant and early childhood disease pattern through splendid work on protein-calorie malnutrition and the development of practical oral rehydration.

Achievements for both adults and children have been made by WHO, PAHO, UNICEF, and other groups with: the smallpox campaign; malaria control; the tuberculosis and leprosy programs; the development of several vaccines, notably that against measles; and the programs for the provision of a protected water supply. But when one looks at this list, it appears as if most of the technologic achievements were those applied through the public health system rather than through the personal service, one-on-one system deemed necessary for use of the therapeutic drugs of the pharmaceutical industry.

Now the question we face is whether the system that has done such a superb job in producing these drugs for our society can be productively employed in the creation of drugs for the developing societies.

In attempting to judge the fitness of that system to do the job, it is appropriate to review how the system developed and what energized

it. The story could be opened at various points. Strictly speaking, it began in 1910 with Ehrlich's announcement of arsphenamine for the treatment of syphilis. This is the historic watershed. Before that time, there was some fine biomedical research, but almost without exception it led only to a greater comprehension of disease. A few vaccines had been developed, notably those against smallpox and diphtheria, but until arsphenamine, there had been no treatment that had emerged from a systematic program of research and development.

Thus, there were two big events here: there now was a highly effective treatment for syphilis; and it had been developed on purpose. Other examples occurred with insulin in 1921 and liver extract for pernicious anemia in 1926, but it was not until 1935 that the peak of the historic watershed was attained with the announcement of Prontosil.

Arsphenamine, atabrine, sulfonamide, and the early penicillin came from Germany and the United Kingdom. The United States came into the penicillin field only after World War II had started. The first penicillin made in the United States for the treatment of patients was made by Dr. Gladys Hobby working with the late Martin Henry Dawson and Karl Meyer at Columbia P&S. How rapidly have we adapted to the world of high technology. Can anyone imagine that today a therapeutic substance developed abroad would be first manufactured in this country in a university laboratory?

The principal United States contributions to this development had to do with the invention of highly imaginative manufacturing methods, notably deep tank production of penicillin, and the creation of a system of university-based clinical penicillin investigators financed by government contracts. This was done through the National Research Council of the National Academy of Sciences, which formed this government-supported system largely run by nongovernmental scientists.

Streptomycin, an American contribution, was next discovered, but was still under wartime control and was brought through essentially the same system until 1947.

At about this time, there were two important events: the instrument for the channelling of federal support was changed from the wartime Academy of Sciences to the National Institutes of Health of the Public Health Service; and the tetracycline series was developed in the pharmaceutical industry. The development of the tetracyclines is relevant to the evolution of our drug-producing system because it represented the first major antimicrobial series developed in United States industry that was not under wartime regulation and thus was the first to profit by that part of the 1938 Food and Drug and Cosmetic Act that had to do with protecting the exclusiveness of the products of one's own research and development. This served as a powerful example of the benefits that might accrue from a well-organized program of research and development on antimicrobial drugs in a company that had a complete

system, i.e., sales and full marketing capability in addition to the research and development. The lesson did not go unheeded.

Indeed, there are those who mark this development as the model on which the present-day structure is organized. Be that as it may, it represented a turning point in the arrangement of roles among the three institutions all necessary for the development of new drugs and preventive technologies. Until this point, sometime in 1948, there was considerable blurring of the lines separating the scientific investigators and administrators in the government, in industry, and in the universities.

What was special about the situation that melded the three sets of participants so closely together at the outset of this highly successful effort?

One answer is that the United States entered World War II as the decade began. In short, it was wartime. This is true, but in my judgment there was more to it than that. For, it was also one of those times when there was a coincidence of motivations only partly attributable to the war; those from industry, from the university laboratories, and from the government all shared a common goal. We were not then so much looking for new drugs, as for additional diseases to conquer. For various understandable reasons, this has not always been true since. But for the brief period of some four or five years, it was the case.

Each success in bringing one more disease under control registered high on the scale of values of everyone concerned. Whether in industry, the university, or government, we had that wonderfully exalting self-image that we were saving lives.

The last diseases to be brought under control (except for certain fungal diseases) were typhoid fever and the rickettsial diseases. This was done by chloramphenicol and by the tetracyclines (except for typhoid). From this point on, the bonds between university and industrial investigators gradually loosened. By the time of the Truman inauguration in 1949, the irregular but functionally almost unified system had given way to the more formally structured, functionally separate, but intellectually-linked system of today.

Although I have been telling the story only in terms of antimicrobial drugs, I believe it was much the same for the others.

In effect, we have two parallel systems. One consists of the research and development effort in industry; it is paid from earnings. The other is supported by the federal government, through revenues obtained by taxation. It is administered chiefly through the National Institutes of Health and is conducted there and in a country-wide network of other laboratories in universities and research institutes.

(In state-operated medical schools the state governments also contribute by providing laboratories and some salaries.)

Broadly speaking, the research in the university/National Institutes of Health system leads to our greater understanding of various diseases -- usually diseases to be found in the United States. The most vulnerable links in the pathogenetic chain may get identified.

The research workers in industry carefully follow this research and indeed have made valuable contributions to it. Their primary concern, however, is to develop the interventionist technologies, most of which have come from industry. They too have tended to focus on the diseases of our society.

As noted earlier, using this system the actual inventions or discoveries of research and development in the pharmaceutical industry have almost exclusively been therapies (or contraceptives) that fit the United States disease pattern and require some form of personal service system for their administration.

The actual inventions or discoveries used in the public health system have largely come either from the university/National Institutes of Health system in the case of vaccines, or from the chemical industry in the case of water disinfectants and vector controls. Hilleman's work in industry on respiratory vaccines is a notable exception.

To be sure, once the effectiveness of a vaccine has been demonstrated by government or university investigators, the pharmaceutical industry has done fine work in making it suitable for mass administration.

What are the prospects that the United States twin system that has proved so bountiful in meeting our own disease problems can be expanded as it stands to serve also in a productive attack on major problems in the developing countries?

Simply to expand it as it stands would not look like the road to success. And I am talking about both arms of the system -- the universities and the industry. In part, the judgement reflects the constraints both economic and biologic that characterize the situation. In large measure, however, it is based on another example from our history.

Almost 20 years ago, an effort was started in the President's Science Advisory Committee to develop an institution to link the worlds of science and technology in industry and in the universities to the foreign aid effort. A system was set up along the National Institute of Health-university pattern, within the Agency for International Development; there was a first-class and hard-working Advisory Committee from outside the government, and a grants and contracts program that

included health, though not limited to it. After almost a decade of trial, the effort was judged a failure. The whole story is an illuminating chapter in the long annals of science and public policy. I do not propose to tell it here, but there was one very important lesson that came from the experience.

The lesson is that in attempting to aim the weapon of research and development at a problem, it is absolutely essential that the institutional framework devised to organize, support, and monitor or manage the effort be carefully tailored to fit the key characteristics of the problem.

A system of research support effective for the Department of Defense may be quite ineffective for the Department of Agriculture. The huge success we have had in mobilizing our biomedical research and development effort by inventing the twin National Institutes of Health-university and industry systems has tended to blind us to how beautifully the components of that system fit the key elements of the problem.

But the problem to be addressed by this Conference is different. The question is no longer whether a treatment for X disease can be developed; it becomes changed to: can one be developed that can be purchased and delivered for one United States dollar per capita, per year, when the total budget for all health services is only two dollars per person, per year? Neither arm of our present system has such capability, so that the plea that they do more becomes meaningless. The most needed invention is not a new drug, but a new system for their development -- a new system especially tailored to both the financial and biologic needs of the problem.

Does this mean there is little ground for hope -- that, to use an American phrase, "there is no way to the Post Office from here"?

Certainly not, but it does make it seem most likely that the problem areas suitable for attack through the pharmaceutical industry will represent a far smaller portion of the total problem than is the case in our society. The hope comes from the fact that there is a considerable variety in the specific mechanisms by which microbial diseases cause illness in one person or spread to others. Hence, they present different points of potential vulnerability to attack. Some are controlled by putting a chemical, i.e., chlorine, in a central water system used by millions of persons; for some other disease it might be necessary to have someone inject a chemical intravenously into each sick person every day. Thus, a series of trade-offs is involved between two key issues: one trade-off is the probability of significant drug toxicity versus the degree of expertise needed to staff the personal service system. For some drugs little is needed; for others the physician must be visible at least on some days, even if only in the background. The other trade-off is between whether the desired

effects can be produced by the drug alone or whether some significant change in household habits is also necessary.

To recall the Navajo study, two of the problem diseases were tuberculosis and trachoma; both of which are clearly susceptible to antimicrobial drugs. The chain of spread of tubercle bacilli involves the contamination of the air within a dwelling space. This can be stopped easily by the infected person taking a daily pill. But trachoma can be spread by the momentarily contaminated fingers of small children, and how to decontaminate them is quite another matter. Two different diseases -- for both there are effective drugs -- but in the conditions of a developing society, one worked and one did not.

What I am saying here goes quite against the conventional wisdom, for that wisdom has it that if a disease is characteristically bred, or greatly facilitated, in the conditions of poverty, it is foolish to try to attack it with a technology -- one must do something about the conditions in which it is bred. As a general law, that is not a bad one. My point is that it is not always so. Occasionally, the poor get lucky.

The classic example is the chemotherapy of tuberculosis. In Figure 5 may be seen the tuberculosis death rates among blacks and whites in New York City in the period before and after the drug treatment for tuberculosis was introduced in 1947. At the start of the drug era, the rate for whites was slightly less than 35, while the rate for blacks was an appalling 150, roughly four times as high.

Once the drugs were introduced, however, the fall in death rate was at least as rapid, if not more so, among the black population as among the white.

Whatever it was that was responsible for that difference between 35 and about 150 tuberculosis deaths per 100,000 people each year, obviously was no constraint on the effectiveness of the technology. There is reason to believe the marked pre-treatment differential reflected the living conditions of the black poor in New York City in the 1940s.

In Figure 6, a graph based on New Zealand data shows the same thing. The top curve is for the Maoris, the bottom for those of European birth or descent. Some indication of the general level of health conditions of the Maori is the infant mortality of 51 they had about that time. But as in New York City, the rapid reduction in death rate was as great or greater among the Aborigines as among the European or those of European descent.

And with that I come to my close. In that inaugural address President Truman said that the material resources that could be used for the assistance of other peoples are limited. "But our imponderable resources in technical knowledge are constantly growing and are

inexhaustible." The central truths in that statement for the industrialized societies have been gloriously affirmed.

To what extent it is possible to find ways so that they have meaning for the developing world is the challenge before us. And if success comes, there will be many more a day than there is now in which one can say with some satisfaction, "Sometimes the poor get lucky."

FIGURE 5. TUBERCULOSIS MORTALITY FOR BLACKS AND WHITES, NEW YORK CITY, 1905-1955

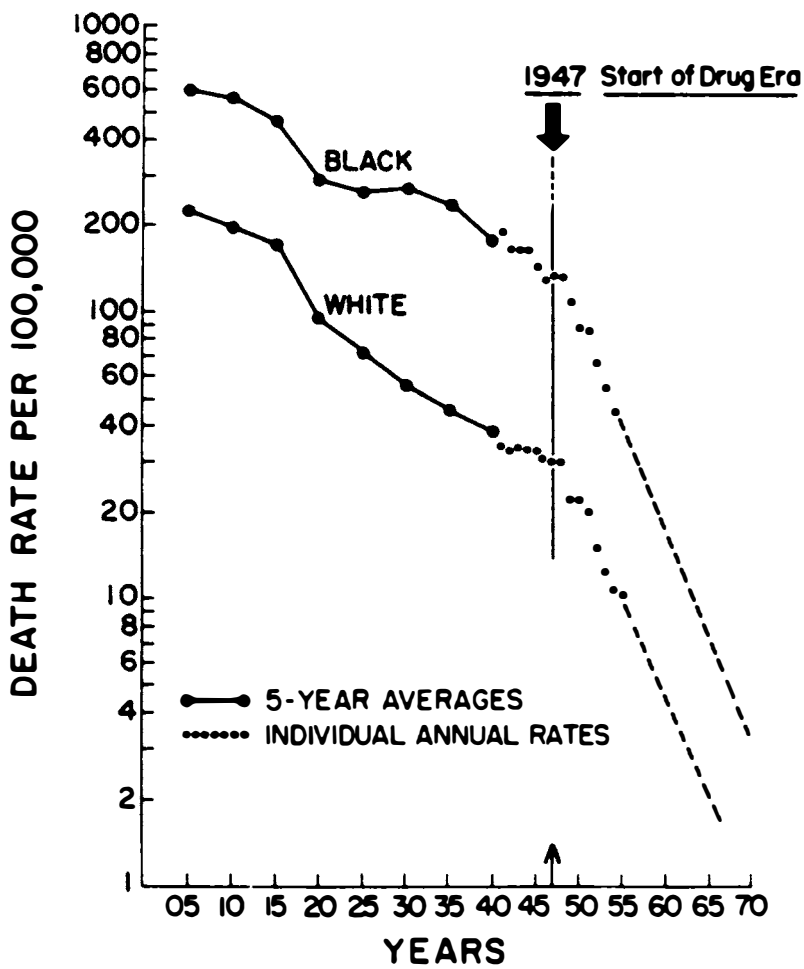
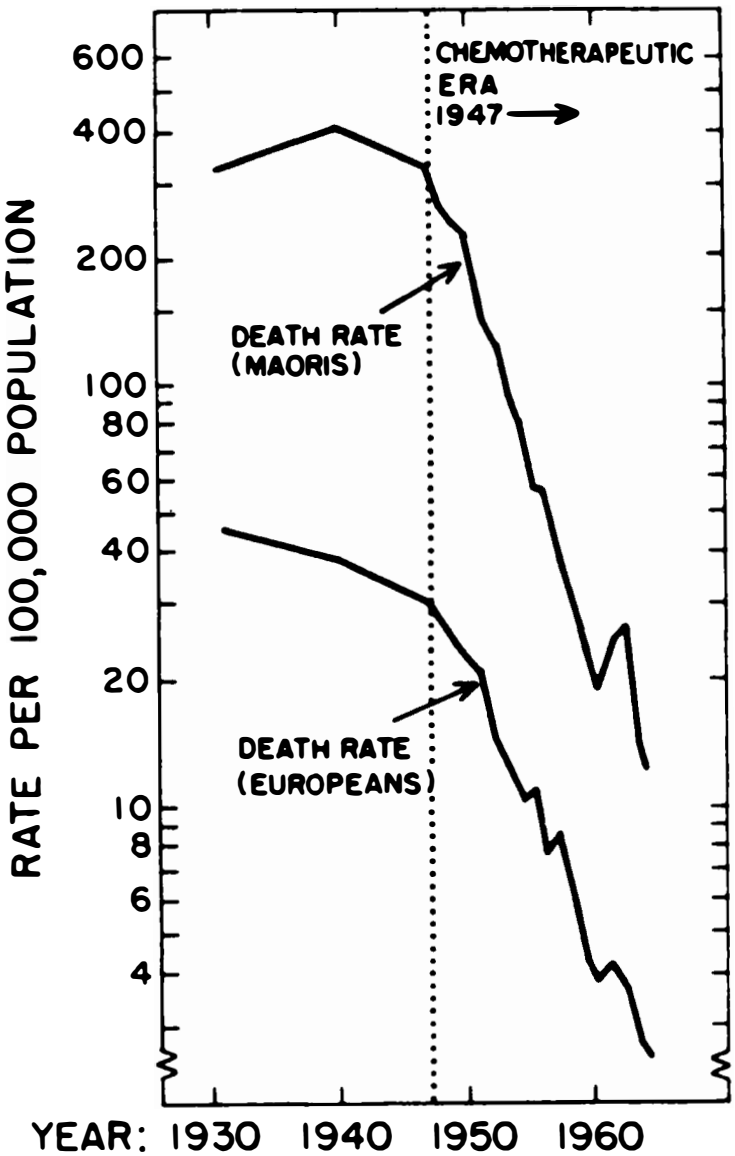


FIGURE 6. TUBERCULOSIS DEATH RATES IN NEW ZEALAND



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# MAJOR DISEASE PROBLEMS OF DEVELOPING COUNTRIES —THE CURRENT STATUS OF PREVENTIVE, PROPHYLACTIC, DIAGNOSTIC, AND THERAPEUTIC AGENTS

# MAJOR DISEASE PROBLEMS IN THE DEVELOPING WORLD

C. E. Gordon Smith

It is customary to address the problem of which are the major disease problems in terms such as that of the WHO estimates in 1971 that in the world then there were 650 million people with ascariasis, 450 million with ancylostomiasis, more than 400 million with trachoma, 350 million with amebiasis, 350 million with trichiuriasis, 250 million with filariasis, 180 million with schistosomiasis, 100 million with malaria (causing 1 million deaths annually), 20 million with tuberculosis and more than 10 million with leprosy.36/ Impressive figures and designed to be so -- probably underestimates by now in view of population growth. But on what real evidence are these guesstimates based when most of the populations to which they refer have highly defective census data, access only to the most rudimentary of health services and certainly little or none to the diagnostic laboratories which could provide the necessary evidence? There is evidence from surveys but, collated, they often give more information about the distribution of parasitologists or microbiologists than of the diseases. Moreover, health statistics are usually very focal in origin: in Kenya 40 percent of patients attending a health center came from within a five-mile radius and 70 percent from within a ten-mile radius;14/ and one Indian study showed that the proportion of patients attending a dispensary decreased by 50 percent for each additional half-mile they had to travel; another that over 60 percent of patients at a health center came from within a one-mile radius.35/

There is no doubt that these infectious diseases are widespread and that at least some of them cause disease in very large numbers of people. What these figures conceal are the great differences both between and within developing countries.

The gaps between rural, peri-urban (squatter) and urban populations are far greater than between similar population groups in industrialized countries. The health problems of rural and peri-urban populations are dominated by the diseases characteristic of poverty in warm temperatures, and by parasitic diseases, while the diseases of affluence (alcoholism, coronary heart disease, degenerative and malignant diseases) are of rapidly increasing relative importance among urban

populations in some developing countries. The differences between countries in geography, climate, ecology, population density and distribution, stage or direction of economic development, etc., have a profound influence on the causes, incidence, and distribution of diseases.

## Major Diseases Throughout the Tropics

Certain diseases are characteristic of poverty and deprivation throughout the tropics -- the lethally synergistic combination of gastroenteritis, malnutrition, and respiratory infections which is the main child killer and probably an important barrier to wider acceptance and implementation of birth control. Moreover, these diseases are often most prevalent at the season most demanding on agricultural labor or at which the roads are impassable and health services particularly inaccessible. They are a dominant health problem of much of southern Asia, the Caribbean, Latin America, and parts of the western Pacific, 37/ widespread among poor rural populations and in the vast peri-urban slums which are a particular problem in Latin America, India, and parts of Africa. This shanty town phenomenon was called "semi-urbanization" by Jacoby 21/ and is now apparently called "peri-urban marginality" by WHO 37/ -- neither term doing much to describe the appalling squalor and deprivation combined with lack of social structure, employment, health services or political influence which it represents. The percentages of the rural populations which migrated to towns and cities between 1950 and 1960 were about 25 in Argentina, 19 in Brazil, and 29 in Chile;21/ and WHO 37/ expects this to continue while the population of Latin America doubles before the end of the century. Already it is estimated that more than half of the population of Lima, Peru, lives in shanty towns. In India, migrants make up 64 percent of the populations of Bombay and Delhi and 53 percent of that of Calcutta.9/ These problems are aggravated by refugees in many parts of the world: between 1961 and 1968 more than 800,000 people in Africa are estimated to have taken refuge in other countries,7/ and the series of wars in recent years can only have aggravated this.

Because of the extreme lack of accurate data in most developing countries -- particularly on the least healthy sectors of their populations -- it is very difficult to assess the relative importance of various diseases in different parts of the world. In 1970, WHO reported the result of asking 112 tropical and subtropical countries to list their major health problems.10/ These, collated by WHO Region (Table 1), show that all Regions listed malaria and diarrheal diseases, and all except the Eastern Mediterranean listed malnutrition. This collation is useful to that extent but because of the great variation within Regions it also conceals a great deal. For example, only the African Region listed schistosomiasis, although this is a major problem in the Philippines and it is estimated that there are as many as six million cases in Brazil.37/ It is certainly also a major and increasing problem in Egypt (Eastern Mediterranean Region).

TABLE 1. MAJOR HEALTH PROBLEMS OF DEVELOPING COUNTRIES NOMINATED BY AT LEAST THREE WHO REGIONS 10/

| Problems | Regions | | | | |
|---|---|---|---|---|---|
| | African | American a/ | S. E. Asian | W. Pacific b/ | E. Mediterranean |
| Malaria | + | + | + | + | + |
| Diarrheal diseases | + | + | + | + | + |
| Malnutrition | + | + | + | + | |
| Tuberculosis | + | | + | | + |
| Leprosy | + | | + | + | |
| Sexually-transmitted diseases | + | + | | + | |

a/Excluding North America.
b/Excluding Australia, New Zealand, Japan.

The latest report of the Director General,37/ suggests that the present-day picture is not very different. He says that malaria continues to be a major problem in the majority of tropical countries -- microscopically diagnosed and reported cases increased from 3.2 million in 1972 to 7.5 million in 1976. Most of Africa south of the Sahara is holo- or hyper-endemic. Reported cases in the South Asian Region increased from 1.9 million in 1972 to 6.5 million in 1976; malaria has re-established itself at its former endemic levels in several areas of Bangladesh, India, and Sri Lanka and has worsened in Thailand. There has been a recent epidemic of over 100,000 cases in south-eastern Turkey. Plasmodium falciparum resistant to chloroquine now occurs in areas with a population of over 45 million and populations of 90 million are at grave risk. And one-third of all malaria control programs are facing problems of insecticide resistance.

The American Region regards infantile gastroenteritis, with respiratory tract diseases and malnutrition, as one of the principal causes of death in Latin America and the Caribbean. The South East

Asian Region describes gastroenteritis as the major killer of children, and the Western Pacific Region nominates diarrheal diseases along with sexually transmitted diseases, arbovirus diseases, schistosomiasis, filariasis, malaria, and leprosy, as its major problems. Tuberculosis is estimated still to be causing more than 0.5 million deaths each year -- 74 percent of them in Asia. In a study of 88 countries, acute respiratory infections were found to account for 6.3 percent of all deaths and for more than 20 percent of deaths in children. Sexually transmitted diseases affect 10-20 percent of the population in some countries (which, if correct, must indicate at least twice these figures at sexually active ages) and the proportion of penicillin-resistant gonococci is increasing substantially annually.

From all this it is clear that certain diseases -- malaria, diarrheal diseases, malnutrition, acute respiratory diseases, and sexually transmitted diseases -- are common and important in most tropical countries, particularly in impoverished rural or peri-urban populations.

Bryant estimated that 92 percent of the deaths attributed to diarrhea in Colombia occur in children under five years of age.8/ In some Central American communities half the children will have had at least 10 attacks of diarrhea before their fifth birthday, some five or six attacks in a single year.36/ Both diarrheal and respiratory infections of children are caused by a multiplicity of organisms, varying in relative importance from place to place but a particularly serious cause of death in overcrowded populations. However, the occurrence or severity of diarrhea may depend as much on nutritional status, particular foods eaten, environmental conditions, behavior or chemical factors as on particular pathogens -- viruses (especially rotaviruses), bacteria of several genera, and parasites: giardiasis is probably especially important in young children, at least in some areas; amebiasis is widespread, neglected by research, and difficult to assess in relative importance. The mortality and morbidity of diarrheal diseases can at least be sharply reduced by prompt oral rehydration (provided that vomiting is absent or can be controlled) -- and this administered locally by a health auxiliary is likely to have a larger impact on the mortality, especially among rural and peri-urban populations, than belated but sophisticated parenteral rehydration in a distant hospital. But can the parents find time to attend to the child's needs when they have only a few days to plant the maize before the ground hardens?

The widespread use of antibiotics, even by quite poor people in poor countries, must be discouraged by controlling their availability, as individual benefits are likely only by chance and disadvantages to the health of the community are a certainty. To take only one example, 76 percent of enterotoxogenic Escherichia coli isolates from the Philippines, Korea, Taiwan, and Indonesia were resistant to one or more antibiotics, 44 percent to four or more antibiotics.12/ Antibiotics are available without prescription in the Philippines and only 80 of 1,000 children admitted to hospital with gastroenteritis had not received

antibiotics before admission. Antibiotics are also frequently used for pediatric gastroenteritis in Indonesia and Taiwan.

General improvements in nutrition, housing conditions, etc., could all substantially reduce mortality and morbidity from at least the majority of acute respiratory infections which include measles, meningococcal meningitis, etc. Apart from existing vaccines and the few infections important enough in industrialized countries to make vaccine development economically attractive (e.g., respiratory syncytial virus infections) there are really no current realistic hopes of controlling these important and widespread diseases by vaccination.

There is a very large amount of disease in these same populations which we already know how to prevent, but do not because of the widespread deficiencies in financial and trained manpower resources, because of the paucity of reliable data and hence of effective planning, and because of the lack of trained and able management personnel in the middle and lower echelons of health ministries and services. WHO estimates that about five million children in developing countries die each year from one or another of diphtheria, measles, pertussis, poliomyelitis, tetanus, and tuberculosis; and that 80 million chlidren born each year in thse countries are not immunized against these common diseases. To demonstrate the difficulties, an assessment of the 1972 immunization program in Yaounde, Cameroon, showed that because of poor timing, and poor quality vaccine poorly handled in the field, an estimated 83 percent of the measles vaccine used was wasted and no significant benefit to the population achieved.2/ With the advent of a revolving fund from which the cost of vaccines can be obtained, it is hoped to rectify these problems over the next few years. But a much better planned and executed immunization program in Yaounde in 1975-6 showed that one or more doses of DPT, poliomyelitis, BCG, measles, and smallpox vaccines each reached only about a third of the largest population during the first nine months. Inadequate publicity was blamed -- only 18 percent of parents attending had heard of the program through radio or posters. 16/ And it is interesting to note that 10 percent of a sample of children attending had arrived in the city within the previous month. The cost of immunizing one child against the range of infections mentioned was estimated at U.S. $1.90 -- greater than the total per capita health services expenditure of perhaps 40 percent of developing countries, of which only 12 of 65 studied were spending more than $5 per head in 1975 35/ -- averages which ignore the uneven distribution of health services, with a bias against rural and peri-urban populations. It is probable that the oppressive health problems of such populations (and the associated severe deprivation) cannot, in many countries, be widely improved without a corresponding improvement in the economic status of the affected populations. This is not necessarily measured by the rate of national economic growth, as the failure of most tropical countries to distribute improved wealth (and, more important, health and social services) at all equitably means that the condition of rural and peri-urban populations can be seen to deteriorate in the face of large

improvements in GNP. It is generally accepted, however, that unless galloping population growth can be brought under control the prospects for general improvement are very poor -- and these lethal diseases of babies and young children must make acceptance of birth control more difficult for the worst affected populations.

But the incidence of many tropical diseases could, at least theoretically, be greatly reduced by relatively simple measures, and considerable successes are reported from China and Cuba -- countries which have the necessary political determination and which have engendered a disciplined will among their populations to solve their own health problems. The risk of some mosquito-borne infections could be greatly reduced by the use of mosquito nets, care about exposure to snail-infested waters could reduce the rapidly growing problem of schistosomiasis and the wearing of shoes that of ancylostomiasis. "Man-made" malaria can result from excessive reliance on insecticides and the neglect of elementary and often well-tried mosquito control measures.7/ In Karachi, much malaria arose from increased Anopheles stephensi breeding in shallow pools, borrow pits, and puddles left by uncontrolled building operations in the rapidly spreading urban periphery.32/

Expensive drugs and vaccines cannot be the only answer and must be supplemented by simple but effective hygienic and behavioral changes. To take an example chosen by the World Bank,35/ vaccination against cholera gives about 50 percent protection for four to six months and costs U.S. 15 cents per head. "In admittedly favourable conditions in the Philippines, rudimentary privies were built at a cost of under $1 per privy, excluding self help labor. This is equivalent to a per capita cost of about 15 cents. Such privies, if properly maintained and used, cut cholera rates by about 60 percent .... Even when the cost of privies is three times that of immunization, the privy program will be cheaper after the sixth year .... Where diseases whose incidence can be reduced through improved water supply or improved sanitation are many, and account for a very large part of the total disease pattern ... privy facilities which are properly used and maintained would be far more economical than personal curative care."

Unlikely though it may seem that these behavioral changes can be induced in large impoverished and illiterate populations (and it may be necessary first to achieve some as yet undefined level of basic education) -- it probably is no more likely that they will receive modern vaccines or drug treatment for the multitudinous infections. Few (if any) really serious efforts have been made to assess the requirements or to use the unquestioned powers and skills of the media and the advertizing industry to induce desirable behavioral changes for health in developing countries -- even less has the problem of how to evaluate such efforts been seriously tackled. These approaches must surely justify a substantial investment at least in experiment and evaluation.

## Major for Where?

The importance of geography and of the contrasts of urban and rural ecologies can be illustrated by consideration of one of the most widely distributed parasites, Wuchereria bancrofti, which is transmitted by a variety of mosquito species in different areas, which has no animal reservoir other than man (perhaps explaining its wide distribution), and which causes disease (elephantiasis, chyluria, lymphadenitis, lymphangitis) only after prolonged exposure to infection. In rural areas the disease may be very focal with wide differences in prevalence within relatively short distances. The intensity of foci depend on (a) the presence of an efficient mosquito vector in large numbers, (b) close contact between the vectors and the human population, and (c) the proximity of vector breeding sites to human habitations and places of work.20/

Filariasis occurs in high density in many parts of Asia stretching from India to Korea. India alone contains more filarial subjects than all of the rest of the world: in Uttar Pradesh, where an estimated 33 million are at risk, 20 percent of populations studied were infected and disease rates among them ranged from 2 to over 30 percent.17/ Over recent decades, the infection has become increasingly prevalent and important as an urban disease in India: Hyderabad and Bangalore, for example, were free of filarial transmission until the early 1960s but Culex fatigans now breeds profusely and filariasis is being transmitted in both cities.26/

In the Pacific, the infection is highly focal but some islands have the highest intensities in the world.20/ In Africa, information is particularly incomplete but prevalence is higher in East than West Africa. The disease is still almost entirely rural but seems likely to become a major urban disease with the increasing prevalence of C. fatigans in such cities as Lagos, Freetown, Accra, and Luanda; in East Africa, too, C. fatigans is spreading widely with urbanization.33/ In coastal Tanzania, estimates of adult male infection rates range from 6 to as high as 70 percent, and elephantiasis rates are as high as 1.6-2.4 percent (and hydrocele rates even higher) in some villages.18/ In the Americas, information is uneven but the disease is mainly urban (except in Guyana) and common only in Brazil, Guyana, and Haiti. Its prevalence in South America appears to be decreasing due to improved mosquito control and special campaigns.19/ Thus, Bancroftian filariasis is a good example of a rural endemic disease which has become a major problem of squalid tropical cities because of the spread and profuse breeding of C. fatigans in latrines, cesspits, and sewage-polluted waters.

During the second half of the 19th century and the first two decades of this, dengue fever was similarly transformed from a rural disease to become an important cause of urban epidemics 27/ transmitted by Aedes aegypti, which breeds readily in any sort of container --

particularly the prevalent urban litter of tin cans, automotive tires, and the like. There have been recurrent large epidemics of the classical type of disease in South America and the Caribbean in recent years. In 1958, its haemorrhagic/shock syndrome form appeared in Manila and remains a serious cause of childhood mortality in Bangkok and more recently in cities in Burma, India, and Indonesia.

Many other notable geographical differences could be cited. Holoendemic malaria in Africa is a serious cause of deaths in children; unstable malaria (e.g., in the Punjab) seasonally disables whole populations. Schistosomiasis, except for one tiny focus, is absent from the whole of the Indian subcontinent. Tsetse-transmitted trypanosomiasis is confined to Africa; triatomid-transmitted Chagas' disease to America. The vast majority of these infections affect rural, not urban populations; and within countries their distributions depend on those of their arthropod or snail hosts.

The importance of most major diseases in the tropics thus varies widely both between and within countries, depending on geography, ecology, etc. To reach any sort of assessment of which of them are "more" or "most" major one must face the questions: major for whom? ... or what?

## Major for Whom?

At the extreme, the major disease (or, in the tropics, more often diseases) for the individual is the one (or several) affecting him and his family--and if he is influential his needs are likely to be disproportionately (in terms of population prevalence) expressed in government health policy and provisions. His greatest fear may be of one of the "diseases of affluence" (even the South East Asian Region states that cardiovascular diseases are becoming important,37/ and he may wish to ensure that, should he have a coronary thrombosis, a sophisticated cardiology team will be available to deal with it.

If, on the other hand, he is one of the millions of small farmers in rural areas, or one of the vast numbers of "semi-urbanized" squatters who have migrated to the periphery of tropical cities, he is likely to regard the lethal combination of malnutrition, gastroenteritis, and respiratory diseases which regularly kills or weakens his children (and thus his prospect of future security) as the major problems. In rural areas, the major parasitic diseases, depending on ecology, are additional crushing burdens.

My assessment thus far of what is major has concentrated on mortality, particularly in young children (and its impact on population growth control), and this focuses on the poorest populations. Efforts to assist them must primarily be directed at the provision of the basic health and social services (especially maternal and child health) which

they so greatly lack and at sorely needed basic environmental improvements, especially in water supplies and sanitation. These must be planned so that they involve the maximum of self-help and can be afforded and efficiently maintained by the communities they serve. The recent studies of Feachem et al.,13/ of appropriate water supplies for rural populations in Lesotho point the way, but comparable studies are needed against ecologically and culturally different backgrounds. There is far too little evaluation of the effects of "experiments" in the development of health services or of environmental improvements -- and indeed little effort even to develop an effective methodology.

The British Ministry of Overseas Development has recently created a unit at the London School of Hygiene and Tropical Medicine to begin to tackle this problem. This imaginative move needs to be replicated elsewhere and most particularly in the developing countries themselves which, with better information, better analysis, and better management could undoubtedly get more out of their admittedly sparse health budgets, could avoid spending precious funds on ineffective or infeasible programs, and identify cost-effective changes in their activities. Indeed, the magnitude of the problem of getting the best possible value out of health service budgets has only recently been appreciated in the United States and Britain -- and scarcely at all in some industrialized countries -- but the need is even more pressing in a poor country. The WHO Special Program for Research and Training in Tropical Diseases, although concentrated on six diseases (filariasis, leishmaniasis, leprosy, malaria, schistosomiasis, and trypanosomiasis), is making provision to train and establish epidemiologists, operational research workers, and statisticians to strengthen the ability of the developing countries to measure their own health problems, to plan appropriate control and curative programs and to assess them, and to carry out meaningful trials of new vaccines or drugs in the particular circumstances of their own needs. This will help greatly over the whole field of health -- if it is not left too late nor the effort developed too slowly.

## Major for What?

This question has a number of possible answers other than mortality in young children: major for morbidity, for the quality of life, for working efficiency or for economic growth? Or major in scientific interest or for pharmaceutical companies?

If we consider morbidity and the quality of life, such diseases as leprosy and filariasis in most of the tropics, and in certain areas schistosomiasis, hookworm, Chagas' disease, mucocutaneous leishmaniasis, onchocerciasis, and dengue fever come high on the list.

WHO conservatively estimates that there are 10 million leprosy cases in the world (6.5 million in Asia, 3.5 million in Africa, and 350,000 in the Americas.37/ This is not only a disfiguring and

disabling disease but still causes such social stigma over most of the world that it is associated with a degree of misery out of proportion to the clinical manifestations.

Schistosomiasis, which is a serious and increasing problem (associated particularly with irrigation and hydroelectric dam projects) in many areas of Africa, in Brazil, in the Philippines, and part of Indonesia, can also be regarded mainly as a cause of morbidity. The liver damage it can cause and its severe distorting effects on the urinary and gastrointestinal tracts greatly affect the quality of life. Molluscicides, chemotherapy, and vaccines are all regarded as essential for its ultimate control, but all are deficient. Chemotherapy is being increasingly used--but the greatest impact could come from improvements in sanitation and water supplies.

There are "estimated" to be some seven million cases of Chagas' disease in Latin America and 30 million people are thought to be at risk. It is a disease of poverty and of bad housing which harbors the bugs which transmit it. In its chronic form it is an important cause of cardiomyopathy throughout its distribution, and in some areas the "mega" conditions which it induces in hollow organs (esophagus, bowel, ureters, etc.) cause considerable suffering.

The metastatic muco-cutaneous forms of leishmaniasis cause severe mutilation and suffering in tropical Latin America. The incidence of these complications, which depend on the infecting strain of Leishmania, 22/ following a primary skin lesion varies from 2 percent in Panama to 80 percent in Paraguay.23/ The visceral form of leishmaniasis (Kala azar) appears to be increasing in incidence (and there may be a risk of severe epidemics) in eastern India and in East Africa.

An estimated half million people have been blinded by onchocerciasis in endemic areas of America (mainly in Guatemala and Mexico) and Africa (mainly in the Sudan-savanna and northern Guineasavanna zones in a belt south of the Sahara) -- the severity of the ocular disease depending on the biting habits of the particular vector Simulium fly in each area and on the ocular pathogenicity of the strain of worm.1/ A major program of control by insecticide treatment of the rivers where the fly breeds is in progress in seven West African countries and is proving highly successful. If this success is to be maintained in the longer term, however, much more attention must be given to establishing the ability of the countries themselves to sustain a control program after the international effort ends -- there is already evidence that re-invasion of the controlled area by flies can readily occur, and there may be need to supplement fly control by mass chemotherapy or vaccination, but neither is available.37/

Over the past few years dengue has caused several major epidemics in the north of South America and in the Caribbean area while in certain cities of South East Asia dengue haemorrhagic fever/shock syndrome

has become an important endemic cause of mortality and morbidity in young children. Apart from their seriousness as a cause of lost working days, the American epidemics pose a threat to the receptive southern United States. They probably inhibit tourism (so economically important in many of the islands), and they clearly indicate a wholly unsatisfactory state of control of the vector mosquito, Aedes aegypti, which was so well controlled by Soper many years ago by the disciplined and planned elimination of urban breeding places. As the same mosquito transmits urban yellow fever -- an infection still enzootic in the Amazon basin with a small outbreak in Colombia only last year -- the whole of the countries affected by the dengue outbreaks must be regarded as receptive to this much more lethal disease which in the past has reached as far north as Philadelphia.

If we turn to working efficiency or economic growth as criteria for the importance of diseases, the answers can again be different. The economic effects of diseases in industrialized countries are usually measured by estimates of the absence from work which they cause. Although their impact, particularly on scarce, highly skilled personnel cannot be less in developing countries, it cannot be measured because of the absence of adequate records, the high levels of unemployment and the impossibility of using such criteria to measure effects in the rural and peri-urban populations most at risk. However, Winslow concluded that industrial absenteeism had been substantially reduced by malaria control programs in the Philippines and southern Africa and by yaws control programs in Haiti.34/ A World Bank study of construction and rubber plantation workers in Indonesia showed an 85 percent prevalence of hookworm with iron deficiency anaemia in 45 percent of the victims.35/ Treatment of the anemia at U.S. 13 cents per head was estimated to increase productivity by 19 percent. However, it may be unwise to correct iron deficiency in the face of quiescent infection (e.g., malaria, tuberculosis, brucellosis) in isolated (e.g., nomadic) populations in equilibrium with it.24/ It took very careful work to demonstrate scientifically that schistosomiasis has an adverse effect on working capacity which relates to the intensity of infection.11/ The plantation industries have long known that they needed health services if their labour populations were to be efficient -- and there is increasing realization of this need among construction and mining companies. Incidentally, the World Bank estimates that the cost of feeding intestinal parasites, and the loss of food due to malabsorption following intestinal infections, may amount to U.S. $10 per head per year in populations with high rates of intestinal infections.35/ Hookworms alone have been estimated to cause a loss of blood equivalent to the daily exsanguination of 1.5 million people.3/

Certain diseases, in high prevalence, inhibit the development of valuable agricultural land or other resources: e.g., onchocerciasis has restricted access to land and other resources in western Africa; and fear of leishmaniasis may have had a similar effect in the tropical forests of America. In parts of Nepal, Sri Lanka, and Mexico,

malaria eradiation induced movements of capital and labor into more resource-rich areas with a net increase in output; and a similar effect of trypanosomiasis control was seen in Nigeria.35/ Sleeping sickness is ubiquitous over large areas of tropical Africa and is a highly lethal disease. It requires constant (and expensive) vigilance and control if severe epidemics (the most recent last year in Uganda) are to be prevented. And trypanosomiasis in cattle is probably the main barrier to the development of extensive beef production in Africa.

Many developing countries depend heavily on tourism and many more have potential for this valuable source of foreign currency. But certain diseases act as deterrents. The risk of trypanosomiasis in game parks is one example; and the World Bank recently concluded that the common occurrence of diarrheal diseases among tourists was an important inhibiting factor. Large outbreaks of disease (cholera, dengue, meningococcal meningitis, etc.) can have a major effect, sometimes even affecting trade and commerce because of vaccination requirements and/or restrictions on movement.

On the other hand, land and water developments can expose new disease problems or seriously aggravate existing ones. More and more dams are being built (for hydroelectric power, irrigation or urban water supplies) throughout the developing countries, e.g., in Angola, Argentina, Congo, Cambodia, Ghana, India, Ivory Coast, Mozambique, Nigeria, Pakistan, Paraguay, Rhodesia, Senegal, Surinam. These man-made lakes can be potent sources of mosquito breeding, especially of malaria vectors. Shallow shorelines are particularly dangerous and can occur seasonally, or where a constant water level is maintained, wave action can produce sandbars and pools which favour mosquito breeding. The latter appears to be happening on a large scale in Lake Nasser and if the area were re-invaded by Anopheles gambiae the resulting malaria problem might be very severe.

Man-made lakes are also important sources of schistosomiasis.29/ When the Volta Dam first filled (around 1960) aquatic weeds harbouring snails were widespread, Schistosoma haematobium was probably introduced to the dam by fishermen from the lower Volta, and the disease reached epidemic proportions among both migrants and local people. In Lufira Lake (Zaire) the main sources of snails and of schistosomiasis were the associated swampy areas, the slow-flowing tributaries of the lake, and its canals.25/ Lake Nasser not only poses a danger of schistosomiasis to those who live around the lake but is also greatly aggravating the prevalence and intensity of the disease in the Nile Valley, where snails are now thriving in constantly irrigated areas where seasonal drying used to kill them. Argentina is believed to be free of schistosomiasis but the large number of hydroelectric dams planned for its northern border areas must pose a threat of introduction and establishment of the disease -- well-planned surveillance should be mounted as soon as possible.

Irrigated agriculture is also a prolific source of mosquito breeding. The higher relative humidity it creates may increase the longevity of the mosquitoes and hence their probability of transmitting infections. Throughout its distribution, Japanese encephalitis is particularly associated with irrigated ricefields in which its mosquito hosts, in the Culex vishui complex, breed. Malaria vectors also breed in irrigated ricefields: the dramatic change in a mosquito population biting man when a dry area is irrigated was demonstrated by Surtees et al., in Kenya:31/ a change from 99 percent Mansonia species to 65 percent A gambiae. Food crops also encourage the development of dense small mammal populations and of transmission of infections which they maintain — notable examples are leptospirosis and Argentinian haemorrhagic fever. Kyasanur Forest disease, a previously unknown disease, became epidemic in Mysore, India, when human population pressure on arable land led to the grazing of cattle in forest.4/

Even the highly desirable existence of hospitals and clinics with modern drugs and syringes (but not enough of the latter nor enough training in their use) provided the opportunity for the accelerated development of recent epidemics of an exceptionally lethal disease, Ebola fever, in the Sudan 15/ and Zaire.5/ We can expect further episodes of such "new" diseases, perhaps at an accelerating rate, as the pressures on land and intrusion into new territories increase with world population, and we need to develop much improved surveillance and reporting of outbreaks and create adequate capabilities for a rapid and effective response to investigate and control them -- sooner or later one of them may have pandemic potential.30/

## Conclusions

The great lack of accurate data on the incidence, prevalence, mortality, and morbidity of all diseases in most tropical developing countries makes confident assessment of the relative importance of various diseases very difficult even if the criteria for importance are defined. Most estimates have been of the "broad brush" variety and against undefined criteria.

Whatever the criteria, however, it is clear that malaria and the childhood poverty diseases of malnutrition, diarrhea, and respiratory infections (including measles) are the most important health problems of the largest number of people in the tropics. They are a particularly intractable set of problems because they most affect those populations most deprived of health and social services, adequate water supplies or sanitation. Peri-urban growth, in some areas, is outstripping the ability to contain, far less cure, the problems it creates. Only policies and provisions which reverse rural-urban flow may bring peri-urban problems within range. It may be that for many populations only the cure of poverty and illiteracy will provide lasting solutions to all these problems and this means the better distribution of wealth and

welfare as well as increases in national wealth. But none of this excuses us from efforts to find ways of alleviating this intolerable widespread deprivation. Much more effort could and should be made to devise, apply, and evaluate ways in which affected communities could help themselves: especially economically feasible means of improving nutrition (now recognized to be mainly general undernutrition rather than the lack of specific components such as protein), water supplies, and sanitation. A really major effort is urgently needed to use all possible resources (and particularly exploiting local cultural and social influences) for the health education of impoverished and largely illiterate tropical populations. Such efforts should however be much better designed, analyzed, and evaluated (and largely by developing indigenous expertise) so that progress can be recognized, improved upon, and extrapolated.

There is a pressing need for better operational research methodologies and for more and better trained personnel to oversee and evaluate so-called experiments in the provision of health services and to discover why they represent improvements or deteriorations in outcome. Primarily, this is going to depend on the establishment of viable centers of expertise for research and training. As the health sector is at present weak everywhere in this subject area, no time should be lost.

The presently available weapons for malaria control are faltering and new drugs, insecticides, and vaccines are clearly desirable additions for the armoury. But, along with these efforts, there should be a re-examination and as far as possible a return to the labour-intensive methods of mosquito control which were effective against many anopheline species in the past. An urgent and constructive thought is needed about how optimal packages of integrated control could be devised in various ecological circumstances and about how new (and inevitably expensive) weapons are going to be delivered to their targets in rural areas.

A proportion of the respiratory infections are preventable by immunization programs (diphtheria, pertussis, measles), but the WHO Expanded Immunization Program will succeed only if it reaches deprived populations, if the demographic implications for coverage in a rapidly growing population are recognized,28/ and if coverage can be kept up from year to year from national resources. Large scale once-and-for-all vaccination programs funded from aid sources and not subsequently maintained provide only a short-term benefit and may have serious long-term consequences. The success of smallpox vaccination cannot at present be extrapolated.

There are other important and widespread diseases causing high morbidity in certain geographical areas. Of the endemic diseases, the most important are schistosomiasis, intestinal parasites, filariasis, onchocerciasis, Chagas' disease; of epidemic diseases, African trypanosomiasis, and dengue fever. Of these, schistosomiasis, filariasis, and

dengue have been increasing in recent years and none of them will be adequately controlled (even by new drugs and vaccines) without much more attention to environmental sanitation, water supplies, health education, and the better use of available manpower.

If we consider the quality of life, then leprosy is important in most tropical countries, onchocerciasis, and filariasis in several areas, and the mutilating mucocutaneous forms of leishmaniasis in parts of South America.

Economically, the most important losers of vast amounts of working time may well turn out to be the multitudinously caused febrile illnesses (which may include leptospirosis, virus diseases, and many others as well as malaria). But the debilitating effect of a variety of subclinical (or mainly subclinical) intestinal infections, and of seasonal al infections which may coincide with important phases of agriculture, must be important in reducing rural productivity in many areas.

In all large scale developments in tropical countries -- especially those involving water -- provision must be made for a prior survey of disease risks which may be aggravated, for the health of the construction force, and for active surveillance and appropriate health provisions for the population living in and servicing the development (i.e., usually expected to service the interest on the loans with which it was financed).

Overall, there is a pressing need for better data on health and particularly for improved surveillance and investigation of outbreaks. 30/ The model of the PAHO Caribbean Epidemiology Center at Port of Spain, Trinidad, is strongly commended -- preferably as a resource serving a group of countries and providing training and assistance in surveillance, diagnosis, investigation, and control of outbreaks and disease problems.

The opportunities for research, from the most fundamental to the most applied, on all manner of diseases abound and have intense interest for those who become involved. In terms of its "six diseases" the WHO Special Program and several foundations (McConnell Clark, Rockefeller, Wellcome) are drawing new and high-powered biomedical science into the field. There is probably at least enough money in these diseases to support all the available research workers with good ideas. The Wellcome Trust has just launched a new program to encourage the development of research in more neglected areas -- gastroenterology, respiratory diseases and others -- based on cooperation between strong departments in Britain with counterpart departments in the tropics but with the center of gravity of the work firmly in the tropics. Much less attention has been, and is being, given to trying to ensure that the results of research are applied and evaluated in the field: the greatest need is for more gifted, experienced, and well-trained people to bridge the gap between the laboratory and the field and to help ensure

the applicability as well as the application of new discoveries -- and old but neglected ones. There is a serious shortage, especially in the tropics, of well-trained epidemiologists and statisticians.

The most pressing need in the developing countries is for more trained personnel capable of measuring problems, of devising possible practical solutions, and of evaluating their application. This is not a demand for "folkloric" research (rightly resented by developing country research workers) but for fundamental studies of behaviour, and of the best use of ideas and resources (new and old), in relation to health -- an area only just beginning to receive the attention it deserves in industrialized countries -- and an opportunity for important innovations of world-wide importance. These efforts must be backed by a real effort to devise and test culturally and socially appropriate methods of health education. A major effort is urgently needed to attract, select, train, and develop able personnel for these neglected areas of expertise -- but their countries will retain them only if they provide satisfactory career and research facilities for them.

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# THE PHARMACEUTICAL INDUSTRY'S PERSPECTIVE ON AVAILABLE AGENTS

Paul A. J. Janssen and Denis Thienpont

The major diseases of the developing countries are caused by a multitude of worms, fungi, protozoa, bacteria, viruses, rickettsiae, and by a variety of ill-defined pathogens.

For the prevention, treatment, and eventual eradication of the well-known infectious diseases, three fundamentally different but mutually complementary strategies are to be considered (Figure 1):

1. A first strategy designed to strengthen the ability of the human host to defend himself against the invading pathogens, and based on effective, safe, and inexpensive methods of immunization of the populations at risk, on socio-economic efforts to correct the common nutritional deficiencies in many developing countries and, in some instances, on modern drugs like levamisole, designed to correct certain immunodeficiencies.

2. A second strategy designed to modify the environment so as to lower the probability of contact between the human population at risk and the pathogens living in the environment, and based on a wide variety of methods (hygiene, sterilization, vector and reservoir host control, education, ecology, etc.).

3. A third strategy designed to selectively destroy the pathogens after invasion by chemotherapeutic agents or by specific immunotherapy. Here we need drugs that are not only highly effective, but also safe, easily available, and inexpensive.

As we shall see in the following Tables, both the theoretical and practical importance of these three different strategies depend on the nature of the health problem to be solved:

a. Worm diseases (Table 1). It is unfortunate that the human host cannot yet be immunized against worm infections and that, to the best of our knowledge, scientific progress in this field is so slow that no major practical breakthrough is to be expected until the end of

this century. In theory, the incidence of most worm diseases can be easily lowered by simple hygienic measures, or by more complicated programs designed to control the specific vectors or reservoir hosts. The

FIGURE 1. STRATEGIES FOR ERADICATION OF INFECTIOUS DISEASES

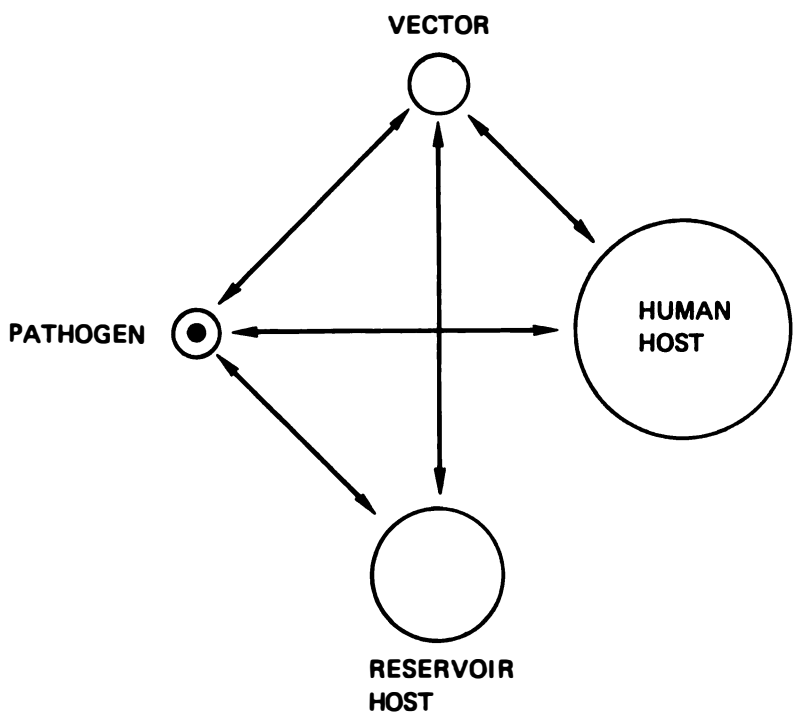


TABLE 1. WORM INFECTIONS

| | IM a/ | VE b/ | RH c/ | HY d/ | CT e/ | $10^n$ f/ |
|---|---|---|---|---|---|---|
| Onchocerca | | + | | | + | ] |
| Wuchereria | | + | | | + | ]...8 |
| Brugia | | + | | | + | ] |
| Schistosoma | | | | | | |
| Mansoni | | + | | | ++ | ] |
| Haematobium | | + | | | + | ]...7 |
| Japonicum | | + | + | | + | ] |
| Fasciolopsis | | + | + | | + | 6 |
| Clonorchis | | + | + | | + | 6 |
| Paragonimus | | + | | | + | 6 |
| Dracunculus | | + | | | ++ | 6 |
| Taenia | | | + | | +++ | 6 |
| Echinococcus | | | + | | ++ | 5 |
| Hymenolepis | | | + | | ++ | 5 |
| Trichinella | | | + | | +++ | 6 |
| Larva Migrans | | | + | | + | 3 |
| Capillaria Phil. | | | + | | +++ | 4 |
| Ascaris | | | | + | +++ | 9 |
| Trichuris | | | | + | +++ | 9 |
| Hookworms | | | | + | +++ | 9 |
| Enterobius | | | | | +++ | 9 |
| Strongyloides | | | | + | +++ | 7 |

a/A cross (+) in this column signifies that an effective vaccine is available and being used.

b/A cross (+) in this column indicates that this is a vector-transmitted disease.

c/A cross (+) in this column indicates that a reservoir host is known to play an important role in transmission.

d/A cross (+) in this column indicates that hygienic measures have been shown to be effective in reducing the incidence of of disease.

e/Three crosses (+++) in this column indicate that effective drugs are available.
Two crosses (++) indicate that available drugs are much better than placebos, but are not good enough.
One cross (+) indicates that available drugs are better than placebos, but are unsatisfactory.

f/Estimated incidence in the world today (log to the base 10).

low feasibility of these methods of prevention is a frustrating fact of life in most developing countries, and explains the deplorable fact that today more than 50 percent of the world's population is infected with worms. Fortunately, however, a few modern broad-spectrum anthelmintics, like mebendazole and levamisole, which are highly effective, safe, and inexpensive, are capable of helping to decrease the incidence of the most prevalent of all worm diseases, the soil-transmitted nematodal infections caused by the classical triad: Ascaris, hookworms, and Trichuris. These same broad-spectrum anthelmintics are the drugs of choice for the treatment of several other nematodal infections which are either less serious (Enterobius), or severe but less common (Trichinella, Capillaria philippinensis).

The most serious endemic parasitological problems of the developing countries are caused by the three major schistosome species, and by the filariae of the Onchocerca, Wuchereria, and Brugia species: vector and intermediate host control strategies are notoriously difficult to implement and frustrating; moreover, fully adequate chemotherapy is not yet available.

The chemotherapy for trematodal infections is generally inadequate.

b. Fungal infections (Table 2). Prevention of fungal diseases is notoriously difficult and often impossible. The human host cannot be immunized against any of the many pathogenic fungi, and environmental manipulations designed to reduce the probability of contact between the population at risk and the fungus cannot be expected to be particularly effective. Antifungal chemotherapy is therefore the only conceivable strategy in most circumstances.

A few modern broad-spectrum antifungal drugs, e.g., miconazole, are highly effective against most superficial fungal infections of the skin, mucous membranes, nails, eyes, and gut. The various dermatophytoses, tinea versicolor, and superficial Candida infections respond very well to these very safe and widely available drugs.

In the tropical and subtropical areas, however, the numerous endemic systemic fungal diseases such as maduromycosis, cryptococcosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis, sporotrichosis, chromomycosis, and histoplasmosis represent major therapeutic problems which cannot be adequately solved with commonly available antifungal agents because only a few parenteral drugs such as miconazole and amphotericin B are known to be effective in these cases.

What is urgently needed here are highly effective, safe, and orally active broad-spectrum antifungals to be used as early as possible in the course of these generally progressive, debilitating, and often fatal diseases. Early diagnosis and easy availability of these drugs will also be a conditio sine qua non for therapeutic success. Our current clinical experience with the orally active broad-spectrum

antifungal agent ketoconazole leads us to believe that rapid progress in the treatment of most systemic mycoses is being made.

TABLE 2. FUNGAL INFECTIONS

| | IM a/ | VE b/ | RH c/ | HY d/ | CT e/ | $10^n$ f/ |
|---|---|---|---|---|---|---|
| Dermatophytoses | | | + | | +++ | 8 |
| Tinea Versicolor | | | | | +++ | 7 |
| Superfic. Candidiasis | | | | | +++ | 9 |
| Systemic Candidiasis | | | | | ++ | 6 |
| Cryptococcosis | | | + | | ++ | 6 |
| Coccidioidomycosis | | | + | | ++ | 5 |
| Para Coccidioido-mycosis | | | | | ++ | 5 |
| Blastomycosis | | | | | ++ | 5 |
| Sporotrichosis | | | | | ++ | 5 |
| Chromomycosis | | | | | ++ | 5 |
| Aspergillosis | | | | | + | 5 |
| Maduromycoses | | | | | + | 4 |
| Histoplasmosis | | | + | | ++ | 3 |

a/-f/See key to Table 1.

c. Protozoa (Table 3). The incidence of malaria is on the increase again, largely because of ineffective vector control and the emergence of drug-resistant strains. Most traditional antimalarials are still highly effective, both prophylactically and therapeutically, in many endemic areas. They are safe and inexpensive, but new drugs, effective vaccines, and adequate vector control programmes are essential ingredients in any workable program designed to significantly decrease the incidence of malaria in the world.

Modern chemotherapy considerably improved the prognosis of invasive amebiasis, but the incidence of the disease remains extremely high in many tropical countries. Its eradication does not yet appear feasible.

There are at least four serious protozoal diseases against which satisfactory chemotherapeutic agents have not yet been found or developed; namely, the various leishmaniases, African and South American trypanosomiasis, and toxoplasmosis. Here again, it is easy in theory but almost impossible in practice in most countries to decrease the incidence of these endemic diseases by manipulations of the environment.

TABLE 3. PROTOZOAL INFECTIONS

| | IM a/ | VE b/ | RH c/ | HY d/ | CT e/ | $10^n$ f/ |
|---|---|---|---|---|---|---|
| Malaria | | + | | | ++ | 8 |
| S. Amer. Trypanosom. | | + | + | | + | 6 |
| African Trypanosom. | | + | (+) | | + | 4 |
| Leishmaniosis | | + | | | + | 5 |
| Toxoplasmosis | | | + | | + | 5 |
| Amebiasis | | | | + | ++ | 8 |
| Trichomoniasis | | | | | +++ | 7 |
| Lambliasis | | | | | +++ | 6 |

a/-f/See key to Table 1.

d. Bacteria (Table 4). Humans can be effectively immunized against pertussis, diphtheria, tetanus, meningoccal infection, and a limited number of other bacterial infections and toxins.

Environmental control is only effective against a few bacterial infections, e.g., plague and cholera. The present emphasis on chemotherapy is therefore appropriate.

Modern chemotherapy for bacterial infections, which started with the discovery of the first sulfonamides less than half a century ago, and made impressive progress since the Second World War with the discovery of many broad-spectrum antibiotics, is still in a period of revolution and adaptation to the continuous emergence of resistant strains.

Better methods of immunization and other chemotherapeutic means to increase the defense mechanisms of the human host are being developed and are likely to play an important role in the prevention of bacterial infections.

TABLE 4. BACTERIAL INFECTIONS

| | IM a/ | VE b/ | RH c/ | HY d/ | CT e/ | $10^n$ f/ |
|---|---|---|---|---|---|---|
| Tetanus | + | | + | | + | 5 |
| Diphtheria | + | | | | + | 4 |
| Pertussis | + | | | | | 5 |
| Meningococcus | + | | | | +++ | 5 |
| Plague | | + | + | | ++ | 2 |
| Tuberculosis | | | + | | ++ | 7 |
| Salmonellosis | | | + | | ++ | 6 |
| Brucellosis | | | + | | + | 5 |
| Clostridia | | | + | | + | 5 |
| Anthrax | | | + | | +++ | 4 |
| Actinomycosis | | | + | | + | 4 |
| Nocardiosis | | | + | | + | 4 |
| Leptospirosis | | | + | | + | 4 |
| Staphylococci | | | | | +++ | 8 |
| Streptococci | | | | | +++ | 8 |
| Gonorrhoea | | | | | ++ | 7 |
| Syphilis | | | | | ++ | 7 |
| Shigella | | | | | ++ | 7 |
| N. Ven. Treponematosis | | | | | ++ | 6 |
| Leprosy | | | | | ++ | 4 |
| Cholera | | | | + | + | 4 |

a/-f/See key to Table 1.

e. Viruses (Table 5). The available chemotherapeutic agents are practically ineffective in the treatment of most if not all systemic viral infections. The widely available antiviral vaccines are designed to prevent yellow fever, poliomyelitis, smallpox, mumps, rubeola, and rubella, and are effective, safe, and inexpensive. Mankind is in need

(1) of safe and effective vaccines capable of preventing the many other viral infections such as the various types of influenza, parainfluenza, hepatitis, herpes, etc.;

(2) of effective and safe chemotherapeutic agents for the treatment of virtualy all types of viral diseases; and

(3) of other methods to strengthen the ability of the host to defend himself against chronic viral infections. Levamisole is a first step in this direction.

TABLE 5. VIRAL INFECTIONS

| | IM a/ | VE b/ | RH c/ | HY d/ | CT e/ | $10^n$ f/ |
|---|---|---|---|---|---|---|
| Yellow Fever | + | + | + | | | 3 |
| Mumps | + | | | | | 7 |
| Rubeola | + | | | | | 7 |
| Rubella | + | | | | | 7 |
| Poliomyelitis | + | | | | | 5 |
| Variola | + | | | | | 1 |
| Dengue | | | + | | | 5 |
| Rabies | | | + | | | 3 |
| Influenza | | | | | | 9 |
| Rhinovir uses | | | | | | 9 |
| Parainfluenza | | | | | | 8 |
| Herpes Simplex | | | | | + | 8 |
| Varicella | | | | | | 7 |
| Inf. Hepatitis A | | | | | | 7 |
| Inf. Hepatitis B | | | | | | 6 |
| Cytomegalovirus | | | | | | 6 |
| Mononucleosis | | | | | | 6 |

a/-f/See key to Table 1.

f. Rickettsias (Table 6). In comparison with the other problems, the treatment of rickettsial infections with available chemotherapeutic agents is minor, several available drugs being quite effective and safe against most known strains.

* * * * * *

In conclusion, our perspective of the available methods of immunization and chemotherapy for the prevention and treatment of the 87 diseases listed in the Tables can be summarized as follows:

(1) excellent methods of mass immunization exist against ten of these diseases;

(2) excellent, highly effective and safe chemotherapy exists against 23 other diseases, for a total of 33 out of 87;

(3) satisfactory chemotherapy exists against 22;

(4) unsatisfactory chemotherapy exists against another 22; and

(5) no chemotherapy at all exists against ten of these 87 diseases.

TABLE 6. RICKETTSIAL INFECTIONS

| | IM a/ | VE b/ | RH c/ | HY d/ | CT e/ | $10^n$ f/ |
|---|---|---|---|---|---|---|
| Fever | | + | + | | +++ | 6 |
| Murine Typhus | | + | + | | +++ | 5 |
| Epidemic Typhus | | + | + | | +++ | 4 |
| Scrub Typhus | | + | + | | +++ | 4 |
| S. Am. Spotted Fever | | + | + | | +++ | 3 |
| Fievre Boutonneuse | | + | + | | +++ | 3 |

a/-f/See key to Table 1.

# ASSESSMENT OF EFFECTIVENESS, SAFETY, AND ACCESSIBILITY OF AVAILABLE AGENTS

## A. DRUGS AGAINST PARASITIC DISEASES

Wallace Peters

### Introduction

From the content of other papers in this Conference it will be evident that diseases afflicting countries of the "Developing World" include those that affect also the countries of what may be termed the "Developed World," modified by genetic, climatic, and socio-economic factors. In addition to these, however, there are other diseases, the geographical distribution of which on the whole is restricted by the same local factors, especially where these control the presence or prevalence of intermediate hosts and vectors. The less specific but universal conditions, i.e., bacterial, viral, immunological, and degenerative diseases account for a considerable level of morbidity and mortality (e.g., mundane intestinal infections in infancy, pneumonia in the older age groups). As drugs used in their treatment, particularly antibiotics, are not specific to developing countries they will not be considered at length in this paper. The main point to be stressed is not lack of effectiveness per se of sulfonamides or antibiotics, for example, but lack of control over their distribution and usage. In certain countries they are grossly misused through being openly advertised in media such as newspapers and the cinema screen, and unrestricted sales are permitted in shops and the open market place. This all too common trend has, not surprisingly, led to rapid development and spread of bacterial resistance to such medicaments. One should also mention here, in passing, the unrestricted use of antibiotic feed additives in agricultural practice in some areas, and abuse and indiscriminate application of potent insecticides, as for protection of cotton crops in many countries, for example, which have resulted in the incidental development of resistance to a wide spectrum of insecticides by important disease vectors, notably malaria-carrying Anopheles mosquitoes.

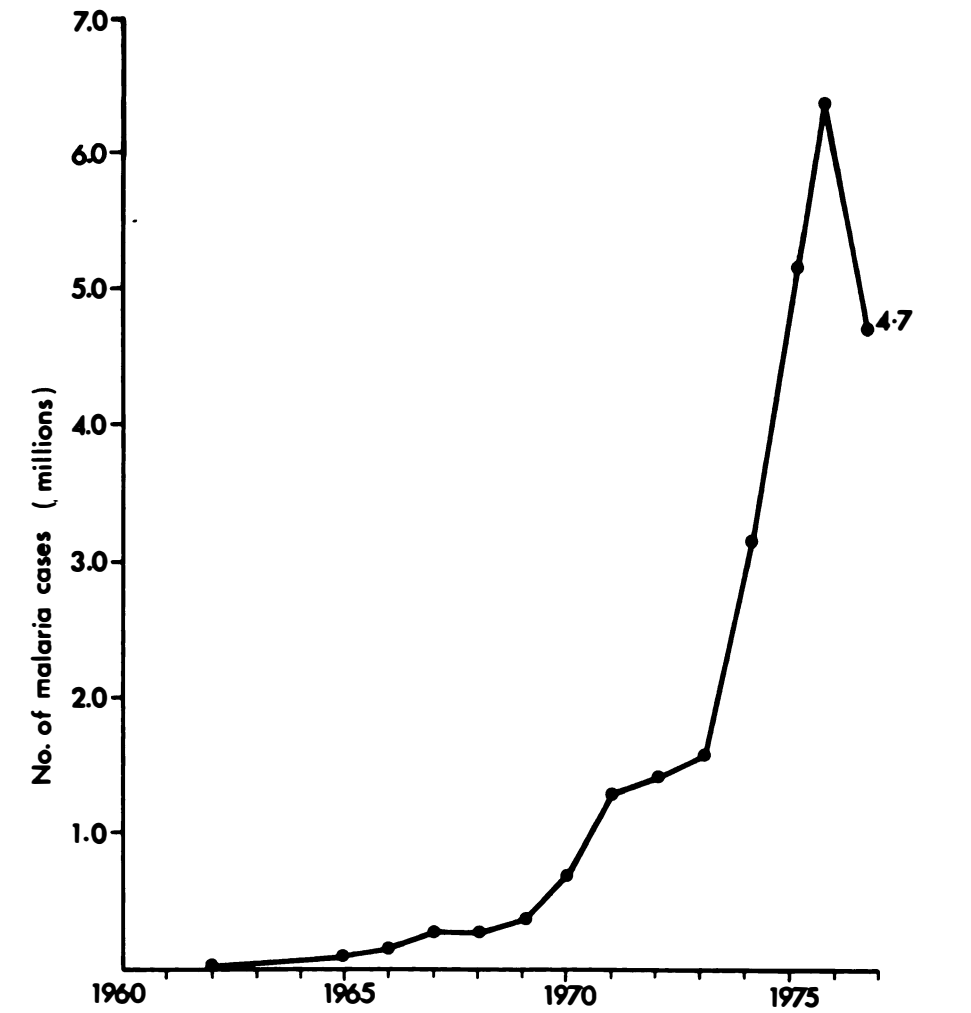
More specific to developing countries are those diseases caused by parasites, and it is drugs used specifically for prevention or treatment of these conditions on which this paper will focus. Parasitic diseases will be considered in two main groups, those caused by protozoa, and those caused by helminths.

## The Parasite Burden

### Protozoal Infections

Without a doubt malaria remains, in spite of two decades of efforts at eradicating it, the most serious protozoal disease afflicting man, and a major cause of mortality. In 1976, it was estimated that 848 million people still lived in areas where transmission continued although active control measures of one sort or another were being undertaken, while 343 million, mainly on the African continent, were receiving virtually no protection at all.17/ In the last few years, the situation has deteriorated with a massive resurgence of transmission on the Indian subcontinent (Figure 1) and elsewhere.

FIGURE 1. NUMBERS OF POSITIVE BLOOD SLIDES REPORTED IN INDIA FROM 1962 - 1977 (in millions)



Epidemic waves of malaria have been recorded in Turkey, for example, a few years ago almost freed of the disease, but in 1977 the site of over 120,000 cases.22/

TABLE 1. NUMBER OF AUTOCHTHONOUS MALARIA CASES (in thousands) FROM 1972 to 1976, BY REGION 22/

| Region | 1972 | 1973 | 1974 | 1975 | 1976 |
|---|---|---|---|---|---|
| Total | 3251 | 4073 | 5181 | 7004 | 7517 |
| The Americas | 284 | 280 | 269 | 356 | 379 |
| South-East Asia | 1920 | 2694 | 4210 | 5992 | 6539 |
| Europe | 21 | 13 | 8 | 12 | 39 |
| Eastern Mediterranean | 855 | 883 | 524 | 447 | 350 |
| Western Pacific | 171 | 203 | 170 | 197 a/ | 210 a/ |
| Ratio of Change (1972=100) | 100 | 125 | 159 | 215 | 231 |

a/Excluding China, Democratic Kampuchea, and Viet Nam.

Next to malaria, trypanosomal infections of Africa and the New World vie with the complex of diseases known as the leishmaniases for second place as serious public health problems, not so much in terms of absolute numbers of cases, as for the morbidity they cause. The numbers of cases reported by World Health Organization are certainly a gross underestimate. While perhaps some 35 million Africans are exposed to sleeping sickness and other forms of African tsetse-borne trypanosomiasis, the actual numbers of cases are unknown. Epidemics arise from time to time, e.g., in Zaire in the 1960s when up to 18 percent prevalence of infection was reported in some foci.18/ An epidemic of unknown but serious proportions is currently raging in the Sudan. African trypanosomiases moreover are a major obstacle to pastoral development and meat production in the tsetse belt of tropical Africa. Several species of this parasite are highly pathogenic for most exotic strains of cattle and other domestic animals that have been introduced to improve the stock, the trypanosome-tolerant local cattle being poor meat-yielding

animals. In South America, Chagas' disease caused by another type of trypanosome carried by large biting bugs affects perhaps another 10 million people. Heart failure in early adulthood and, in some areas, severe functional changes in the intestine result from chronic infection in those who survive the acute stages of this, so far, almost untreatable disease.

The different parasites in the genus Leishmania, a genus widely distributed from China through much of the Old World, and extending through the greater part of Central and South America, produce a variety of diseases of the tegument and of the deep organs of the body such as liver and spleen. Cutaneous leishmaniasis, while frequently self-limiting if untreated, may nevertheless cause disfigurement and disability. The variety that involves mucous membranes of the nose and face can lead to extreme tissue destruction with wholesale loss of facial tissue of a degree rarely encountered today with any other disease. The visceral type of leishmaniasis may occur in epidemic fashion. India is currently in the throes of just such an epidemic. In excess of 100,000 cases of kala azar were estimated to have occurred in Bihar and West Bengal in 1976, leading to more than 4,000 deaths. The roots of this epidemic (as of the malaria epidemic) lie in cessation of DDT spraying against malaria-carrying mosquitoes, a procedure that incidentally killed off house-haunting leishmaniasis-carrying Phlebotomus sandflies.

As will be seen in the following pages, drug treatment is available for prevention and treatment of certain kinds and stages of malaria in individuals, but not in communities. Drugs currently in our hands are grossly inadequate to cope with the other protozoal diseases mentioned here.

## Helminth Infections

To estimate prevalence of helminth infections is an extremely difficult task because of the inadequacy of most of the available statistical data. The writer estimated recently 12/ that in the 1975 world population of just under 4,000 million, there were nearly 4,500 million worm infestations Multiple infections are the rule rather than the exception, especially in developing countries. Thus, in the tropics and subtropics 136 percent of the 3,000 million population, and in the temperate zones of the world only 44 percent of 965 million people may be infested. While some of these data no doubt represent considerable overestimates (e.g., in the USSR and China where large strides have been made in controlling parasitic infections), data for some other areas are probably underestimates.

The two groups of helminthiases on which this paper will focus are the schistosomiases and the filariases. Three forms of schistosomiasis are common in man, leading to disorders of the bowel, the urogenital

tract, and the liver and hepatosplenic circulation. The World Health Organization estimate of 180 to 200 million cases is less than that of the writer, whose estimate is around 270 million. As Weller pointed out, prevalence data, such as there are, frequently are fragmentary, inadequate for technical reasons, outdated, or invalidated by a rapidly changing ecology.16/ Schistosomiasis extends in parallel with the increasing opening up of land for agriculture through development of irrigation systems, as is currently being observed, for example, in the Gezira region of the Sudan and Northern Nigeria.13/ In the absence of adequate control of the molluscan intermediate hosts of these worms and satisfactory application of mass chemotherapy, reliance on health education is worthless except where the level of social discipline is exceptionally high. Thus, Friedheim stated that China and Japan have attained a large measure of schistosomiasis control through social measures based on the proper disposal of excreta.5/ This they have achieved through "a persuading national and semi-religious ideology culminating in a sense of responsibility of the individual towards his personal health and its repercussions on the health of the community." Currently, available schistosomicidal drugs, some of which show great promise, have yet to prove their worth in really large scale control programs.

The important filariases are of several types, the most serious being those that cause damage to the lymphatic system and which are transmitted by mosquitoes, and one that is carried by Simulium (blackflies) which affects primarily the skin and eyes. The former lead to swollen limbs, the condition called "elephantiasis" in many areas of the tropics, while the latter, caused by Onchocerca volvulus, produces "river blindness" in parts of Africa and Central America. Mosquito-borne Wuchereria bancrofti and Brugia malayi may afflict more than 250 million people (although only a small proportion actually develop elephantiasis).19/ Some 20-40 million are exposed to river blindness. Not one safe drug is known that is guaranteed to destroy adult worms in man. Other filarial infections of importance are Loa loa (causing "Calabar swelling") and Dracunculus medinensis or "Guinea worm."

## Malaria and Antimalarial Drugs

In order to explain the outstanding problems relating to antimalarial drugs, it is necessary to recall some features of the parasites that cause this disease. Three common species and one uncommon one infect man.

### 1. Plasmodium falciparum

Man is infected by the bite of an Anopheles mosquito. The parasites that the mosquito injects pass into the liver where they undergo one cycle of development before entering red blood cells. There the asexual parasites grow repeatedly through a 48-hour cycle which leads

to destruction of the host cells. P. falciparum is the most dangerous parasite since it can rapidly kill by destroying red cells in large numbers and by blocking capillaries in the brain. If the patient survives the initial onslaught he builds up an active defence which helps him to overcome later stages of the infection, and gives him a partial immunity against subsequent challenge by this parasite. P. falciparum, known as the "malignant tertian" parasite, is widely distributed in the tropics and is the dominant species in tropical Africa where it may represent 95 percent of all infections. In large parts of its distribution strains have emerged that are resistant to a wide variety of antimalarial drugs.

2. P. malariae

This parasite follows a similar life cycle to P. falciparum but rarely causes a life-endangering infection. It is liable to become very chronic, and hence is the parasite usually responsible for malaria that results from transfusion with blood donated by people who may have been infected many years before. P. malariae is widely distributed throughout the tropics. Unlike the other species its cycle in red blood cells lasts 72 hours.

3. P. vivax

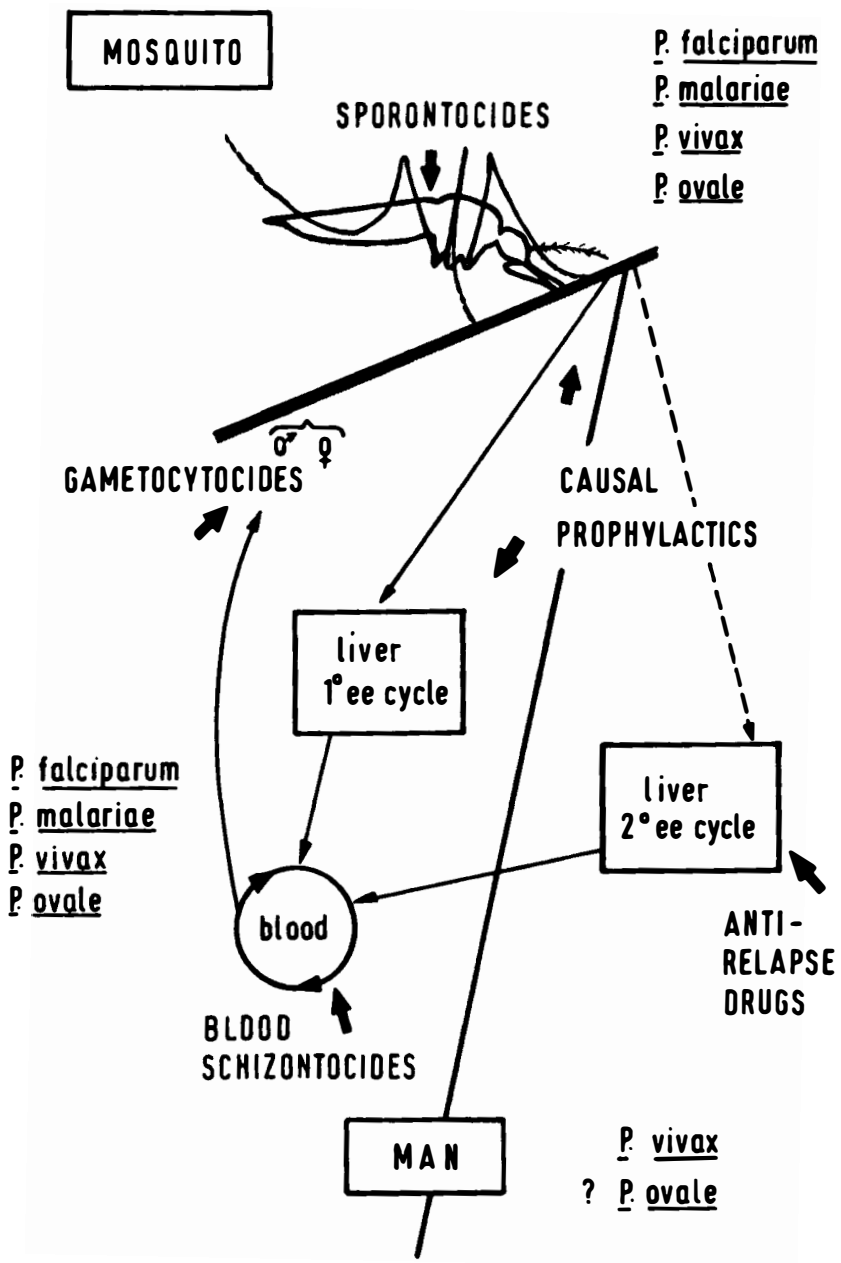
The "benign tertian" parasite has the same general cycle as the others, but secondary forms developing in the liver are responsible for late relapses of parasitaemia and fever. Vivax malaria rarely affects people of Negro stock who are genetically less susceptible than whites. The infection produced by the blood stages (in a 48-hour cycle) is rarely dangerous, but produces anaemia and chronic loss of condition for up to three years if untreated. P. vivax is widely distributed except in Africa, and can survive in a somewhat cooler climate than the other species.

4. P. ovale

This uncommon parasite with a patchy distribution has a 48-hour cycle similar to P. vivax.

Antimalarial drugs in current use have a limited spectrum of activity against the different stages of the life cycle. Some act against the first generation of liver stages (causal prophylactics), others against asexual stages in the red cells (blood schizontocides), some against the sexual blood stages that infect the mosquito (gametocytocides) or the stages in the mosquito (sporontocides), while one drug affects the secondary liver stages of P. vivax (anti-relapse or tissue schizontocidal action). No single drug possesses all these properties. Moreover, the range of action of these drugs differs according to the species of Plasmodium. A summary appears in Figure 2.

FIGURE 2. SIMPLIFIED LIFE CYCLE OF MALARIA PARASITE TO SHOW POINTS OF ACTION OF DIFFERENT TYPES OF ANTIMALARIAL DRUGS



Provided that there is no question of the parasites being actually resistant to a drug, there is a choice of compound that can be used either for prevention or cure of malaria in the individual. However, each drug has its own limitations as regards tolerability even for the individual. Of more significance for the present Conference are the limitations of these compounds when used on a large scale for the control of malaria in human communities. The available compounds are shown in Table 2.

Table 3 shows that the only compounds regarded as completely safe are the "antifols," proguanil, and pyrimethamine. These, however, are too slow in their action to be used for treatment of an acute malaria attack. Moreover, malaria parasites readily become resistant to antifols when used alone, and many resistant strains are encountered over a wide geographical area. This problem is overcome when such compounds are used in association with a sulfonamide or sulfone with which they produce a potentiating action. Several such mixtures are available, and pyrimethamine-sulfadoxine is one example (Fansidar®). Other combinations are pyrimethamine-sulfalene, trimethoprim-sulfalene, and pyrimethamine-dapsone (Maloprim®). The safety of long-term prophylactic use of these compounds, and their safety in pregnancy have not yet been established completely.

Chloroquine and amodiaquine are known to accumulate in retinal tissue and pigmented cells of the skin when given for long periods of time. These compounds are poorly tolerated by some Nigerian people. They may also cause gastrointestinal disturbances in some individuals. Strains of P. falciparum resistant to chloroquine and also resistant to antifols are common in South and Central America, South East Asia, and the Western Pacific. Such strains may also be appearing on the African continent. These problems apart, however, chloroquine and amodiaquine remain the best available compounds for treatment of acute malaria in most cases, and are valuable prophylactics in many areas. Quinine may have to be used for therapy in a few especially severe cases of falciparum malaria. Primaquine is essential to prevent relapses of P. vivax. Courses of treatment range from 5 to 14 days, the shorter courses inviting a 10 percent or greater risk of failure. This drug cannot be given in normal dosage to people with genetically determined blood enzyme deficiencies such as that of glucose 6-phosphate dehydrogenase (G6PD) as it causes severe haemolysis.

For treatment of chloroquine-resistant falciparum malaria only quinine, antifol-sulfa mixtures (e.g., Fansidar®), and mefloquine are effective. Quinine is toxic in the high doses needed and does not always produce radical cure of the infection. Fansidar® is usually curative but is probably best given following a course of quinine therapy which can be administered intravenously in an emergency. Mefloquine is the product of ten years' intensive research and development by the Walter Reed Army Institute of Research (WRAIR) that has cost the United States taxpayer some U.S. $10 million per year. It shows great promise

TABLE 2. SPECTRUM OF ACTIVITY AGAINST DIFFERENT SPECIES OF PARASITES SENSITIVE (S) OR RESISTANT (R) TO CHLOROQUINE a/ OR ANTIFOLS (F)

| | P.falciparum | | P.malariae | | P.vivax | |
|---|---|---|---|---|---|---|
| | S | R | S | F | S | F |
| **Causal prophylactics** | | | | | | |
| proguanil (chlorguanide) | + | ± | + | - | + | - |
| pyrimethamine | + | ± | + | - | + | - |
| **Blood schizontocides b/** | | | | | | |
| chloroquine | + | - | + | + | + | + |
| amodiaquine | + | ± | + | + | + | + |
| quinine c/ | + | ± | + | + | + | + |
| mefloquine d/ | + | + | | ? | + | + |
| pyrimethamine-sulfadoxine (=Fansidar®) | + | + | + | + | + | + |
| pyrimethamine-dapsone (=Maloprim®) | + | + | + | + | + | + |
| **Anti-relapse drug primaquine** | not applicable | | | | + | + |
| **Gametocytocide e/ primaquine** | + | + | + | + | + | + |
| **Sporontocides e/** | | | | | | |
| proguanil | + | - | + | - | + | - |
| pyrimethamine | + | - | + | - | + | - |

a/*P. falciparum* strains resistant to chloroquine are usually also resistant to antifols.

b/Blood schizontocides may be used either for suppression of blood infections (*i.e.*, prophylaxis) or treatment of an acute attack of malaria. They produce a radical cure of *P. falciparum* and probably *P. malariae*, but not of *P. vivax*. For this, the anti-relapse drug primaquine is also needed.

c/Quinine is no longer used for routine prophylaxis or therapy.

d/Mefloquine is still in clinical trial and not yet generally available.

e/Gametocytocidal or sporontocidal drugs are of value for interruption of transmission in a community, but are not necessary for treatment of the individual.

TABLE 3. SAFETY OF STANDARD ANTIMALARIALS

| Compound | Prophylactic dose well tolerated | Safe for indefinite long-term prophylaxis | Treatment dose tolerated | Safe in pregnancy |
|---|---|---|---|---|
| chloroquine | ++ | + a/ | ++ | +++ |
| amodiaquine | ++ | + a/ | ++ | +++ |
| quinine | not used | not used | + | + |
| proguanil | +++ | +++ | not used | +++ |
| pyrimethamine | +++ | +++ | not used | +++ |
| pyrimethamine-sulfadoxine d/ | +++ | ? + | +++ | ? + |
| primaquine | not used | not used | + b/ | ? c/ |
| mefloquine | ++ | ? | +++ | ? |

a/WHO advises giving chloroquine only up to a cumulative dose of 100g.20/ Larger doses may lead to retinal defects.
b/Causes acute haemolysis in certain genetic enzyme-deficient individuals.
c/Usually not administered during first trimester of pregnancy.
d/Contra-indicated in sulfonamide hypersensitive individuals.

for prevention and treatment of all malarias, including chloroquine-resistant P. falciparum, but is still reserved for carefully controlled clinical trials run jointly by the World Health Organization, the United States Army and a Swiss pharmaceutical company. The latter has donated material and resources for this purpose as a contribution to the UNDP/World Bank/World Health Organization Special Program for Research and Training in Tropical Diseases (TDR Program). All these drugs need to be given repeatedly at fairly frequent intervals if they are to be employed for prophylaxis. They therefore do not lend themselves to mass drug administration in large communities. Long and bitter experience has shown that malaria control using repeated drug administration is almost always doomed to failure. To succeed as a mass control measure, a preparation would need to be administrable with complete safety

to entire communities, at infrequent intervals (perhaps from three to six months), and preferably by injection. No such compound or preparation exists at the present time, and its development is a priority objective of the Scientific Working Group (SWG) on the Chemotherapy of Malaria of the TDR Program.17/

The recent malaria epidemic in India, more than 90 percent of which was due to P. vivax infections, well illustrates the logistic limitations imposed by the current world production of antimalarials. The Indian Government estimated that its annual antimalarial requirements in metric tons would be: chloroquine 300, primaquine 4, quinine 8, pyrimethamine 3.5, sulfadoxine 4, and tetracycline 5 (the value of the last as an antimalarial is highly debatable.6/ Annual production of chloroquine in India runs at 30 tons. Sixteen tons of quinine are produced but almost all is exported. In India, the problem is not one of drug resistance but of the need to treat acute vivax malaria with chloroquine, and to prevent relapse with primaquine. Physicians in India, however, regard primaquine with great suspicion in the light of its reputation for causing serious side effects in G6PD-deficient subjects of whom there are many in that country. In Assam and the neighboring states of northeastern India, chloroquine-resistant falciparum malaria does pose a threat, and stocks of quinine and Fansidar R are being sought in case they are needed there. The market price of these two preparations, however, is a serious deterrent in India and elsewhere.

In summary, it is seen that, although excellent antimalarial drugs are available, their deployment and procurement still pose many problems that are far from being resolved while. For mass drug administration, however, suitable drugs are not available.

## Other Antiprotozoal Drugs

The situation is considerably worse with regard to drugs for prevention and treatment of trypanosomiasis in Africa or South America, or for use against the leishmaniases. It may be summarized:

### African Trypanosomiasis

1. Prophylactic drugs --

pentamidine (for human use) This was used extensively, especially in Francophone Africa, to protect communities living in highly endemic areas. While some success was claimed in reducing the infection rate, pentamidine-resistant strains of trypanosomes are by no means uncommon. This drug is also toxic and side effects are fairly frequent.9/ Moreover, early infections may actually be concealed by pentamidine.4,18/

quinpyramine (for animal use) Resistance rapidly developed against this and related drugs when they were used for protection of domestic cattle. The same fate has met drugs belonging to other chemical groupings when used prophylactically in animals, e.g., homidium, isometamidium, and diminazene.

2. Drugs for treatment --

organic arsenicals These are essential for destruction of parasites that have entered the central nervous system. Tryparsamide has been replaced by melarsoprol, which is toxic, although much less so than tryparsamide. Arsenic-resistant strains of trypanosomes affecting man are fairly common, e.g., in Zaire.

suramin A complex organic non-metallic compound, suramin is nephrotoxic. It is also effective only against trypanosomes before they enter the brain where they produce the changes leading to "sleeping sickness".

pentamidine The use of pentamidine is no longer favored in human therapy since it is likely not to produce complete cures and thus may permit insidious development of cerebral infection. It, too, is ineffective against trypanosomes in the brain.

diminazene aceturate This is diamidine has been used with some success in limited clinical trials against arsenic-resistant instances of West and East African trypanosomiasis.14/ Recent studies suggest, however, that it possesses potential neurotoxicity, and the manufacturers do not encourage further human studies with this drug. It is still used fairly widely in cattle.

nitrofuranes Several nitrofuranes have been used in the past. All may cause neurotoxity and changes in carbohydrate metabolism in man, and haemolytic anaemia in G6PD-deficient subjects. Recent clinical studies with levofuraltadone are not very promising.14/

In short, completely safe drugs exist for treatment of established infection either with the West African parasite, Trypanosoma gambiense, or against the East African T. rhodesiense. Chemoprophylaxis in man is no longer considered of significant practical value with the only available compound, pentamidine, and attempts to protect cattle have been marred by drug resistance.

South American Trypanosomiasis (Chagas' Disease)

No drug is suitable for prophylaxis of Chagas' disease caused by T. cruzi. Improvement of housing and residual insecticide spraying of homes and animal shelters are probably the best prophylactic methods

that can be used. Experience in Venezuela and elsewhere has proven the efficacy of these measures.

No safe and well-tolerated drugs are available for treatment of chronic Chagas' disease, although all the following may be effective if the disease is diagnosed in the acute stage.

nifurtimox This compound must be given in very prolonged courses. It is often poorly tolerated and patients therefore frequently fail to complete the treatment. In some areas, cure rates do not excced 80 percent.

benznidazole The evidence so far on this relatively new drug suggests that it may be superior to nifurtimox. It is also toxic, and must be given in rather long courses.

A safe drug that can be administered in a short, intensive course of therapy and produces complete cure of Chagas' disease has not yet been identified. Nitrofurazone has proved too toxic and is no longer used.4/

## The Leishmaniases

Claims have been made for the therapeutic value of many drugs for treatment of cutaneous leishmaniasis, but most are based on uncontrolled studies in cases which would probably have healed spontaneously. Only three groups of specific antileishmanials are available. In addition, the two drugs mentioned above in relation to Chagas' disease are undergoing clinical trials against leishmaniasis. Drugs for prophylaxis are not available.

pentavalent antimonials Sodium stibogluconate and meglumine antimoniate are the only safe and highly specific antileishmanial agents. However, even these must be given in prolonged courses, and there is some tendency for accumulation of antimony in some patients, with subsequent risk of cardiac and other toxicity. Both drugs are very expensive and in short supply.

pentamidine Pentamidine is used as a second-line drug in some cases of leishmaniasis which fail to respond satisfactorily to antimonials. The response in such cases to pentamidine is variable, and problems of drug toxicity must also be faced.

amphotericin B This antibiotic is used as a last resort in a few patients, especially those with mucocutaneous diseases who fail to respond to antimonials. It is highly nephrotoxic and can only be administered under carefully controlled hospital conditions.

The majority of sufferers from these conditions, with the exception of some residents of the economically more favored countries of the Arab world, are poor peasants or labourers who can ill afford the time or money to pay for treatment. Moreover, health services of the countries in which these diseases are endemic are often unable either to mount an effective service for detection and treatment of patients or, in extreme cases, unable even to afford the few drugs that are available. In India, recently faced with an epidemic situation in which possibly 100,000 people developed kala azar, adequate stocks of pentavalent antimonials were impossible to come by even with the assistance of the World Health Organization and bilateral funding agencies. An acute shortage of pentamidine eventuated. This drug is used for treatment of what were believed to be a high proportion of antimony-resistant cases. (Most of these were later found to have been treated inadequately for a variety of reasons, including the high price charged for injections by some unscrupulous private practitioners). The response of the Indian government was to set up a "crash program" for synthesis of sodium stibogluconate within the country. As a result, the drug is now produced by three Indian pharmaceutical manufacturers, and at a very modest price.

As regards the search for and development of new drugs for treatment of African or South American trypanosomiasis, very little effort is being put forth by the private sector, mainly because of the enormous effort involved with absolutely no hope that research and development costs can be recovered, to say nothing of a profit being realized. It has been estimated, for instance, that only 1 in 50,000 compounds screened would have any chance of success.18/ Almost the only work in this field, and with antileishmanials (an even more neglected field),10/ is being carried out either in academic laboratories or by scientists associated with WRAIR. Because of the potential importance of some protozoal diseases to the military, the huge inventory of drugs accumulated during the United States antimalarial program is now being examined for candidate compounds against these other protozoal diseases. Research is now also proceeding at WRAIR, in London, and in Liverpool on new approaches to development of existing antiprotozoal agents through the use of such measures as liposome incorporation. Other laboratories are investigating different ways of making better use of available drugs by making them lysosomotrophic.7/

Much fundamental work in biochemistry is also being undertaken under the auspices of the Ministry of Overseas Development of the United Kingdom, and of the Special Working Groups on the Chemotherapy of Trypanosomiasis and of Leishmaniasis of the World Health Organization TDR Program in the hope of developing a rational approach to discovery of new antiprotozoal agents, as an alternative to empirical screening. It must be noted, however, that the latter approach has in practice proven to be the most fruitful for discovering radically new drugs,15/ whereas the rational approach is necessary to show how new drugs work and to develop superior analogues.

## Anthelmintic Drugs

As mentioned earlier in this paper, the intestinal helminths impose a vast burden on mankind. It is not surprising, therefore, to find that many drugs have been introduced over the years to serve as vermifuges. These range from natural products such as oil of chenopodium and extract of male fern, long used to remove the common roundworm, Ascaris lumbricoides, and the large tapeworms, respectively, to modern synthetic compounds such as dichlorvos (an organophosphate) and mebendazole (a benzimadazole), both of which are active against a broad spectrum of helminths.15/ Davis summarized the activity of then currently employed synthetic anthelmintic agents (Table 4) showing that none of the existing drugs were effective against all species of intestinal nematodes.2/

Advances have been made since that time, especially in the direction of benzimadazoles, some of which exhibit a remarkably broad spectrum but also some inherent toxicity to the host that has yet to be fully evaluated. Another new compound, praziquantel, is also actove against schistosomes, and will be discussed below. Many of these newer agents are relatively expensive, and few of them approach 100 percent effectiveness in a single dose, both very practical considerations for drugs to be employed extensively in poorer communities of the developing world. It is interesting to realise that several newer agents were discovered in the course of screening for anthelmintics to be used in the veterinary field, since the market prospects for veterinary pharmaceutical products of this nature are far more rewarding than anthelmintics to be used to treat poor people. Praziquantel is one such drug. Dichlorvos was not developed as an anthelmintic, but as an insecticide, and it took considerable effort before the company producing it could be persuaded to examine it seriously as an anthelmintic. Metrifonate is another compound of this nature to be discussed below.

### Schistosomiasis

Until the advent of the newer schistosomicidal agents mentioned here, tartar emetic was essentially the only compound used for mass treatment of schistosomiasis. This is a remarkably effective but very toxic organic antimonial which undoubtedly accounted for many deaths due to treatment, and not to the disease. One of the first non-antimonial synthetic agents was lucanthone which proved fairly effective, especially against S. haematobium, but which also proved toxic to the liver, especially in people whose livers were already damaged by the disease. One of the features of schistosomiasis is that any particular drug tends to be more active against one species of parasite than against another. The general trend was for S. haematobium to be more susceptible than S. mansoni, and S. japonicum to be the least responsive of all. This situation has changed with some of the newer drugs. Table 5 shows the compounds currently in use or undergoing clinical trials.

TABLE 4. ANTIPARASITIC EFFICACY OF NEWER ANTHELMINTICS a/ 2/

| | Soil-transmitted helminths | | | | | Faecal-oral-or faecal-fomite-oral transmission | |
|---|---|---|---|---|---|---|---|
| | Transmission by egg ingestion | | Transmission by cutaneous larval penetration | | | | |
| | | | Hookworm | | | | |
| | Ascaris lumbricoides | Trichuris trichiura | Ancylostoma duodenale | Necator americanus | Strongyloides stercoralis | Enterobius vermicularis | Trichostrongylus spp. |
| piperazine salts | 3-4 | 1 | | | | 3 | |
| bephenium hydroxynaphthoate | 2 | 1 | 2-3 | 2 | | | 2-3 |
| tiabendazole | 2 | 1 | 2 | 2 | 3-4 | 3 | 3 |
| levamisole | 4 | | 2 | 2 | | | |
| pyrantel embonate | 4 | 1 | 2-3 | 2-3 | | 3-4 | 3 |
| pyrvinium embonate | | | | | 2 | 3-4 | |
| dichlorvos | | 3 | 2 | 2 | | | |
| mebendazole | 4 | 3 | 2-3 | 2-3 | 1-2 | 4 | |

a/
1 = 0-20% "cure".
2 = 20-60% "cure" -- moderate activity.
3 = 60-90% "cure" -- very good activity.
4 = 90% "cure" -- outstandingly good activity.
The 0-20% "cure" rate is often inseparable from the technical error limits associated with the evaluation of the drug.

TABLE 5. SCHISTOSOMICIDES IN CURRENT USE

| | Susceptibility of | | | Chemical | |
|---|---|---|---|---|---|
| | S.haema-tobium | S.man-soni | S.japoni-cum | Type | Toxicity |
| niridazole | +++ | ++ | + | nitro-thiazole | especially on central nervous system |
| metrifonate | +++ | ± | ± | organo-phosphate | inhibits cholinest-erase |
| lucanthone | ++ | + | ± | thiaxan-thone | digestive tract and liver |
| hycanthone | +++ | ++ | ± | thiaxan-thenone | digestive tract, ?mutagenic |
| oxamniquine | ± | +++ | ± | tetrahydro-quinoline | very few side effects |
| praziquantel | +++ | +++ | +++ | pyrozinoi-soquinol-inone | (in clini-cal trial) |
| C9333-Go/ GGP4540 | (+++) | (+++) | (+++) | isothio-cyanate | (in clini-cal trial) |
| Ro 11-0761 | (++) | (++) | (?) | thiophene | (in clini-cal trial) |

( ) = laboratory data.

All the above compounds are administered orally, except hycanthone (a synthetic metabolite of lucanthone). Hycanthone was the first single-dose, injectable preparation produced, and it gave very promising results in early clinical trials. It proved less effective against S. mansoni than against S. haematobium, but was active enough to arouse considerable interest, particularly in view of the obvious logistic advantage presented by any compound that could be administered in this

way for mass drug therapy programs. It lost favour for two reasons: First, there is a suspicion that it is mutagenic; and second, several patients died from acute liver failure. It is still uncertain whether these are real or exaggerated hazards, but even the suspicion suffices today to damn the most promising compounds, especially if considered for large scale use.

After lucanthone, which rapidly fell out of favour because of its serious side effects, niridazole was the first highly active, non-metallic synthetic schistosomicide. It proved very active against S. haematobium, and was extremely well tolerated in children in whom it is still widely used. It is less well tolerated by some adults, side effects being seen especially in the central nervous system. Niridazole is given by mouth over seven to ten days.

One of the most effective drugs against S. mansoni is oxamniquine, usually given orally for one or two days. It is well tolerated, but is unfortunately only poorly active against other schistosome species. In South America, oxamniquine is considered to be the drug of choice against S. mansoni despite its high price (about U.S. $6.00 per adult treatment course).

The organophosphate metrifonate is one of the cheapest and most active compounds in current use against S. haematobium. It depresses parasite cholinesterase and will, in excessive dosage, also depress this enzyme in the host. This is most likely to occur in individuals with genetic enzyme variants or hepatic damage from any cause in whom side effects can, fortunately, be overcome with various antidotes. On the whole, metrifonate is safe for mass treatment of S. haematobium for which it is currently widely used. It is of little use against the other species.

The newest star on the schistosomicide horizon is praziquantel which appears effective against all three schistosome species when administered in a single oral dose. It is likely to remain expensive because of the complicated synthetic procedure required for its manufacture, even despite its coming into wide use in veterinary practice.

The remaining two compounds are in the early stages of clinical trial, and it is too early to pass judgment. Both show high levels of activity in laboratory models. C9333-Go, at least, exhibits a broad spectrum of action against intestinal helminths and all three schistosome species.

In summary, therefore, several effective compounds are currently available for treatment of one or another form of schistosomiasis. All manifest defects, be it a question of limited spectrum of activity, side effects, or price, and the ideal drug for mass use has yet to be found. If a compound can be developed which, like praziquantel or C9333-Go, is of practical value against human or veterinary helminths

other than schistosomes, then it should be possible in time to reduce the price as larger quantities are manufactured and development costs recovered by the manufacturers.

## The Filariases

One drug, and only one drug is known to reliably and safely kill the blood-dwelling larvae (microfilaria) of the pathogenic mosquito-borne filarias, Wuchereria bancrofti and Brugia malayi, that infect man (Table 6). Diethylcarbamazine (DEC) was discovered some 30 years ago and has never been superceded. It kills the skin-dwelling microfilaria of Onchocerca volvulus that also invade the eye, causing "river blindness", but the reaction to dead larvae is so severe that DEC can rarely be used in patients with this condition. DEC can be used against W. bancrofti to interrupt transmission since the larvae are infective to blood-sucking mosquitoes and these, therefore, are the forms responsible for continuation of the parasite's life cycle. The reaction to dead larvae of B. malayi is also often severe, and thus restricting use of DEC for mass treatment campaigns in areas where B. malayi is common.

TABLE 6. USES OF DIETHYLCARBAMAZINE IN THE TREATMENT AND CHEMOPROPHYLAXIS OF FILARIAL INFECTIONS 1/

| Type of infection | Chemo-prophy-laxis | Micro-filari-cide | Macro-filari-cide | Mass treat-ment | Side reactions: fre-quency | Side reactions: severi-ty |
|---|---|---|---|---|---|---|
| W. bancrofti | (+) | ++ | + | ++ | + | - |
| B. malayi | (+) | ++ | + | + | ++ | + |
| L. loa | + | ++ | ++ | (+) | + | + to ++ |
| O. volvulus | 0 | ++ | 0 | (+) | ++ | + to ++ |
| D. strepto cerca | ? | ++ | + | ? | ? | ? |
| M. ozzardi | 0 | 0 | 0 | 0 | ? | ? |
| D. perstans | 0 | (+) | ? | 0 | ? | ? |

DEC kills some but not all W. bancrofti and B. malayi adults, these being responsible both for continuing production of infective microfilaria, and for mechanical damage to the lymphatic system which may result in elephantiasis. DEC also kills adults of Loa loa, but side effects may be serious. Another drug, suramin, does kill adult O. volvulus. Suramin was originally developed for treatment of sleeping sickness due to African trypanosomes. As stated earlier, it is toxic and cannot be used safely in mass campaigns. In fact, no safe "macrofilaricide" exists that will kill adults of any of these filarial worms. Hence, there is no way to ensure interruption both of disease in affected individuals, and further transmission through vectors.

Of the other filarial worms pathogenic to man, Loa loa is limited to West and Central Africa where it produces ephemeral swellings in the limbs, and may cross the front of the eye causing optic damage. The adult of this worm is very small. This stage migrates through the body and may be removed physically when it appears in a suitable and accessible site such as under the conjunctiva.

Guinea worm is another filarial disease that causes severe damage to subcutaneous tissues and joints where adults may lodge. Several drugs, including niridazole, help to kill adults which may then be carefully withdrawn from tissues. Guinea worm infection (Dracunculus medinensis) is acquired by swallowing infective larvae which live in "water fleas" (Daphnia, Cyclops, etc.) that occur commonly in poorly maintained wells or other open sources of drinking water. These are contaminated by larvae emerging from open wounds in the feet or legs of infected water carriers.

New macro- and microfilaricides are urgently needed, and limited studies are currently being undertaken to identify such agents. Broad spectrum anthelmintic agents such as levamisole and metrifonate are being examined in man, while new compounds are being screened in various animal models. Unfortunately, all existing and widely used animal models are open to criticism concerning the validity of data so derived to the various infections in man. The use of Brugia species for secondary screening has been advocated,8/ and B. pahangi in cats is used extensively.3/ An animal model suitable for laboratory studies on the chemotherapy of O. volvulus is not yet available.

## General Remarks

This paper has focused attention both on existence and lack of specific drugs for prevention or treatment of several important protozoal and helminth infections of man. What cannot be over-emphasised is that chemotherapy is but one means of controlling parasitic infections. Limitation of breeding sites for insect vectors and destruction of larvae, e.g., Anopheles mosquito carriers of malaria, or of the Simulium

vector of "river blindness" breeding in waterfalls in the Volta River, and their control by insecticides, killing of snails that spread schistosomiasis by molluscicides, are all of vital importance, as is destruction of adult insect vectors by such means as residual spraying of houses with DDT or newer compounds. Neither are the latter measures adequate without use of drugs to kill the parasites. The collaboration of the human sufferers, themselves, and of their governments is an essential part of any control program. One of the main reasons why malaria eradication failed was because sufficient weight was not given to the human factors in the epidemiological equations. Reliance on any one single measure is doomed to failure, a point that those concerned with the current campaign to eliminate onchocerciasis in the Volta basin would do well to remember. Destruction of Simulium larvae with insecticides alone will not stop this disease.

Simple improvements in personal hygiene, in water supplies, in disposal of excreta, and in housing do more to reduce or even eliminate many parasitic diseases than the use of specific antiparasitic drugs. Wearing shoes will reduce hookworm infection. A piped water supply will eliminate many hazards due to parasites and to bacterial infection. Putting a plaster finish on mud walls will remove breeding sites for the triatomid bugs that carry Chagas' disease. Constructing a simple ceiling in the bedroom of thatch huts in East Africa has been shown to reduce greatly exposure to W. bancrofti-carrying pest mosquitoes. Nevertheless, and for the foreseeable future, we will continue to need new and better drugs to help prevent and control many parasitic conditions of which a few examples are given here. Full collaboration of the pharmaceutical industry with its impressive physical and intellectual potential for drug development is essential if new antiparasitic agents are to be discovered. In this effort, much help can be given through an agency such as the Council for International Organizations of Medical Science (CIOMS) to smooth the way between industry and national drug regulatory agencies.21/ Support must also be given to academic research laboratories where many fundamental questions can be answered.10/ As Van den Bossche indicated, "Most of the available parasitic agents and, so far as I know, all the lead chemicals had their origin in a rational exploitation of massive empirical screening".15/ This has certainly been the experience of industrial laboratories and of government agencies, such as WRAIR. It is also essential to strengthen the facilities for clinical trials of new drugs as they emerge. This is a feature to which the World Health Organization TDR Program is giving particular attention with the establishment of clinical research centers in endemic areas, and the training of clinical pharmacologists to work in them. These specialists in turn must be provided with career posts that give them security in their professions, a point that is all too often ignored.

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## B. ACCESSIBILITY OF VACCINES

William H. Foege

It has frequently been said that vaccines are among the oldest, most dependable, and most trusted tools of public health. Yet we are reminded, as we begin The International Year of the Child, that more than 2.5 million children will die this year from four diseases which can be prevented by currently available vaccines. Why the great gap in application? Experience of the last decade indicates that technology could greatly improve the situation, but a lack of social will has been a major constraint to successful application.

In the United States, we have recently taken stock of our social will and set new targets to immunize 90 percent of our children against seven childhood diseases by October 1, 1979. We are well on the way to achieving this goal. So well, in fact, that we have set an additional goal -- the elimination of measles as an indigenous disease in the United States by 1982. Our efforts are being coordinated with those of the World Health Organization which we will assist with the "Expanded Program of Immunization."

We still have a distance to go before everyone in this country is freed from fear of crippling or death from vaccine-preventable diseases. But the developing nations have much greater distances to travel -- a fact shown clearly in Table 1. The Table shows that there are 15 infant deaths per 1,000 live births in the United States, and the life expectancy of an infant at birth is 73 years. In Latin America, 84 infants of every 1,000 live births are lost, and an infant born in those nations can expect to live 62 years. In Asia, 117 infants die of every 1,000 born, and life expectancy is 58 years. In Africa, 158 of every 1,000 live births are lost, and life expectancy is but 46 years.

The problem is large, but we are not without solutions. One solution is the use of proven, cost-effective immunization programs in conjunction with other basic health services. Of the many alternatives for health spending, immunization offers some of the greatest benefits in relation to costs. For example, the United States measles vaccine

TABLE 1. INFANT MORTALITY AND LIFE EXPECTANCY BY AREA a/

| Area | Infant Mortality Per 1,000 Live Births | Life Expectancy At Birth, in Years |
|---|---|---|
| United St | 15 | 73 |
| Latin America | 84 | 62 |
| Asia | 117 | 58 |
| Africa | 158 | 46 |

a/ 1978 World Population Data Sheet.

program conducted between 1966 and 1974 cost the Federal Government $108 million. It yielded more than a billion dollars in savings -- savings in medical costs and long-term care expenses that would have been incurred if there had been no measles program. Another study estimated that the nation received a net benefit of $10.34 for every $1.00 of Federal money spent. Even greater returns have been realized from polio immunization programs.

Although it would be inappropriate to extrapolate such benefit-cost ratios to developing countries, we can look at available data and see what an active, nationally supported system for immunization can provide. Thus, at prices currently paid by the United States government, all the necessary vaccine for a child from birth through school entry costs less than $5.00.

A study in The Gambia in 1971 showed that it cost $2.40 to prevent one case, and $48 to prevent one death from measles. That was the total cost for vaccine and for its delivery. Other studies in West Africa have indicated that direct health care dollar returns far exceed investments in measles programs despite the fact that not all children with measles actually have access to a hospital or clinic.

The benefit-cost ratio for smallpox vaccination will soon become the greatest for any health program as benefits continue to accrue while costs fall rapidly.

Quite aside from large scale or even national campaigns, there are examples of successful immunization programs well integrated into other primary health care services. I would like to provide one example. In India, a village-based health program providing basic preventive and curative services to almost a quarter of a million people achieved

remarkable results in three years (Table 2). When the program was started in 1974, infant mortality was 67.6 per 1,000 live births. By 1977, mortality had been reduced to 23.1 per 1,000 live births. At the beginning of the program, only 2 percent of the childhood population had complete DTP immunizations. After three years, that percentage had risen to 85. The completed sequence of polio immunizations was reported for 1.5 percent of the childhood population in 1974, and for 83 percent by 1977. Immunizations were a major component of this successful program.

TABLE 2. HEALTH CARE PROJECT, MIRAJ, INDIA a/

| | 1974 | 1977 |
|---|---|---|
| Infant Mortality/1,000 Births | 67.6 | 23.1 |
| Maternal Mortality/1,000 Births | 3.7 | 0.25 |
| Complete DPt | 2% | 85% |
| Complete Poliomyelitis | 1.5% | 83% |

a/Ram, E. R., Integrated Health Services Project, Miraj, India, in Contact 44, Christian Medical Commission, World Council of Churches.

Immunizations can be the cutting edge of primary health care systems because:

1. Appropriate vaccines prevent morbidity and mortality.

2. Vaccines are cost effective.

3. Vaccines provide long-lasting protection even when only limited patient contact is possible.

4. Immunization programs incorporate the general skills needed for diverse public health or community programs, thus providing a vehicle for other activities.

Although many vaccines are licensed or in use around the world, it would be unfair to confuse the issue or overload systems by promoting vaccine without a clear need. Tables 3 and 4 provide a partial summary of vaccines which might be considered in developing countries. Five

TABLE 3. CURRENT STATUS OF VACCINES

| | Vaccine Available | Vaccine in Developmental Stage | No Vaccine Available |
|---|---|---|---|
| Vaccine Appropriate for Wide-spread Use | 1. Tetanus<br>2. Measles<br>3. Pertussis<br>4. Poliomyelitis<br>5. Diphtheria | 1. Malaria<br>2. Schistosomiasis<br>3. Dengue<br>4. Hepatitis B | 1. African Trypanosomiasis<br>2. American Trypanosomiasis<br>3. Viral Hemorrhagic Fevers |
| Vaccine Appropriate for High Risk Groups Only | Anthrax<br>Meningococcal Serogroups A and C<br>Plague<br>Pneumococcal<br>Q Fever<br>Rabies<br>Rocky Mountain Spotted Fever<br>Rubella<br>Smallpox<br>Tularemia<br>Typhoid Fever<br>Typhus<br>Yellow Fever | Brucellosis<br>Haemophilus Influenza<br>Gonorrhea<br>Herpes simplex<br>Syphilis<br>Parainfluenza<br>Trachoma<br>Varicella/Herpes zoster<br>Leprosy | Cytomegalovirus (CMV)<br>Filariasis<br>Heat Labile *E. coli* Enterotoxin<br>Infectious Mononucleosis<br>Leishmaniasis<br>Lymphogranuloma venereum<br>Onchocerciasis<br>Toxoplasmosis |
| Vaccine of Limited Value | BCG<br>Cholera<br>Shigella | | |

TABLE 4. VACCINE FOR WIDESPREAD USE AND FOR HIGH RISK GROUPS IN DEVELOPING WORLD

| Vaccine | Type | Target | Schedule | Efficacy | Side Effects |
|---|---|---|---|---|---|
| A. Vaccines for widespread use | | | | | |
| 1. Tetanus | Toxoid | a. Pregnant women | Two doses 6 wks. apart, the 2nd at least 6 wks. before delivery & booster every 3 yrs. for additional pregnancies | highly effective (over 90%) | Local reaction, one of safest immunizing agents |
| | | b. All ages | Primary series of 3 doses, reinforcing dose 6-12 mos. later & every 10 yrs. | | |
| 2. Measles | Live attenuated | Susceptible children usually 12-24 mos. | Single injection | Over 90% | Fever, rash, rare convulsions |
| 3. DPT Diphtheria | Toxoid | Infants | 2, 3, 4 mos. & booster | 90% for at least 5 yrs. | Delayed sensitivity reactions & "arthus" type reactions in some older children or adults |
| Pertussis | Inactivated organisms | Infants | 2, 3, 4 mos. & booster | Variable, recent vaccines highly effective | Local reactions in up to 50% of infants, also fever & rarely convulsions |

(Cont'd)

Cont'd

TABLE 4. VACCINE FOR WIDESPREAD USE AND FOR HIGH RISK GROUPS IN DEVELOPING WORLD

| Vaccine | Type | Target | Schedule | Efficacy | Side Effects |
|---|---|---|---|---|---|
| Tetanus | Toxoid | Infants | 2, 3, 4 mos. & booster | Highly effective | Safe, almost no reactions |
| 4. Poliomyelitis | Live attenuated | All ages | Live - Primary series of 3 doses with reinforcing dose(s) | Both highly effective (over 90%) | Live - rarely induced polio in recipients or their contacts |
| | Killed inactivated | | Killed - Primary series of 2 doses with reinforcing doses 3 mos. later | | Killed - almost none |
| B. Vaccines for Identified High Risk Groups | | | | | |
| 1. Anthrax | Inactivated | Workers in wool-working activities | Primary series of 3 injections booster 6 mos. later | Highly effective in limited trials | Minimal but limited experience |
| 2. Meningococcal | Purified Polysaccharide (groups A & C) | All susceptibles over age 1 (group A) or over 2 (group C) | Single dose | No cross protection - over 80 % for homologous type | |

| | | | | | |
|---|---|---|---|---|---|
| 3. Plague | -Live attenuated<br>-Killed inactivated | High risk persons (i.e., lab workers, anthropologists & military personnel | Variable - use manufacturer's recommendations | Apparently effective - no adequate field trials available | Local & febrile reactions |
| 4. Pneumococcal | Purified Polysaccharide Many serogroups | High risk (i.e.,age or underlying medical conditions | Single dose | Type specific protection of 80% in field trials | Frequent mild local reactions & occasional fever |
| 5. Rabies | Inactivated (most used) | Pre-exposure vaccination for high risk (veterinarians & wild life workers) | Variable - use manufacturer's recommendations | Duck embryo & human diploid vaccine appears highly effective | Local reactions common. Rare CNS effects with newer vaccines (common with earlier vaccine) |
| 6. Rubella | Live attenuated | Susceptibles over 1 yr. of age, particularly prepubertal female | Single dose | Highly effective (over 90%) | Occasional arthritis, peripheral neuropathy & perplexed neuritis reported |

(Cont'd)

Cont'd

TABLE 4. VACCINE FOR WIDESPREAD USE AND FOR HIGH RISK GROUPS IN DEVELOPING WORLD

| Vaccine | Type | Target | Schedule | Efficacy | Side Effects |
|---|---|---|---|---|---|
| 7. Smallpox | Living vaccinia | Laboratory workers exposed to virus | Annual vaccination for exposed laboratory workers | Very effective | Rare CNS complications. Also progressive lesions in persons with immunologic defects |
| 8. Tularemia | Live attenuated | -Laboratory workers<br>-Wild life workers | Variable - use manufacturer's recommendations | Limited trials indicate high immunity levels for several yrs. | Local reactions |
| 9. Typhoid fever | Inactivated organism | All ages over 6 mos. if at high risk of infection | Variable - use manufacturer's recommendations | Up to 90% protection from some vaccines | Local reactions & fever common |
| 10. Yellow fever | Live attenuated | All persons over 6 mos. at risk of infection | Single dose repeated at 10 yr. intervals | Highly effective | Mild fever in rare individuals |

are considered useful for universal delivery: Measles, poliomyelitis, diphtheria, tetanus, and pertussis. Others, such as yellow fever and meningococcal vaccine, would have definite regional utility.

When they become available, vaccines against malaria, schistosomiasis, dengue, and hepatitis B will also have widespread applicability. There is a definite urgency to speed development of these vaccines and to begin development of vaccines for trypanosomiasis, hepatitis A, and viral hemorrhagic fevers. We should nevertheless be aware that more than 20 percent of the mortality among children less than five years old in the developing countries can be prevented with currently available vaccines. Table 5 repeats the data used by Senator Kennedy, and shows more than 82 million episodes of illness and more than 2.5 million deaths resulting annually from only four diseases. Therefore, absolute priority must be given to the delivery of available agents. What are the constraints? Dr. Perkins will discuss constraints involving vaccine development, testing, and quality. I will emphasize the need to develop effective systems to deliver potent vaccines to susceptible populations; that is, to make vaccines accessible.

TABLE 5. ESTIMATED ANNUAL MORBIDITY AND MORTALITY OF SELECTED VACCINE PREVENTABLE DISEASES

| | Cases | Deaths |
|---|---|---|
| Measles | 72,000,000 | 1,500,000 |
| Tetanus | 800,000 | 600,000 |
| Pertussis | 8,000,000 | 300,000 |
| Poliomyelitis | 1,800,000 | 200,000 |

Disease surveillance is the foundation on which vaccine delivery systems must be built. Quantifying disease problems and identifying populations at risk are useful for decisions regarding large-scale immunization programs and the necessary investment of personnel and resources. In most developing nations, it will be necessary to train health workers to collect and analyze such data, especially among predominently rural populations. As one example: Neonatal tetanus in Bangladesh has been recognized as a health problem, but it has not been recognized as a major health problem in that country's routine reporting system. Since cases and deaths occur at home, they are seldom brought to medical attention. A recent systematic sample of 120 rural

villages estimated tetanus mortality at 70,000 deaths annually; 2 tetanus deaths per 100 live births, or 20 deaths per 1,000 live births. This single, vaccine-preventable disease is thus responsible for greater mortality in Bangladesh than all the causes of deaths among newborn infants in the United States put together.

Studies in Africa have shown that 5-10 percent of children will die of measles. This tragic and needless loss of life is a powerful argument for placing highest priority on delivery systems for effective agents that are already available.

The development of the necessary social will, a prerequisite to tackling vaccine-preventable problems, requires documentation of the size of the problem. Hence, there is need to develop surveillance systems. Decisions concerning which optional vaccines should be added to the basic core also require data generated from a surveillance system. Documentation of the effects of a vaccine program will require information systems. The lack of good data systems constitutes a major constraint on vaccine programs and on many other primary health care systems.

A second major constraint involves shortages in managerial as opposed to technical skills. Any effort to improve vaccine programs must involve training health workers in planning, implementation, and evaluation of immunization and other primary health care programs. Much is now known about the various systems required to deliver vaccine. This knowledge must be communicated.

In addition to social will and managerial skills, we need simplification of technology. Smallpox eradication was hastened because private industry developed an effective, heat-stable, freeze-dried smallpox vaccine and an inexpensive method of vaccine administration -- the bifurcated needle. Today, immunization programs need vaccines which remain stable in the field, and safe and effective methods for administering vaccines. Recent development of a relatively heat-stable measles vaccine is a step in the right direction. Further advances in heat stability are needed for other vaccines, for benefits do not result even from a well-managed program that delivers impotent vaccine to a child.

Another constraint pertains to ethical and legal aspects of vaccine programs. The most frequent dilemma appears superficially as a conflict between the rights of the individual and the rights of the community. It is a long-held conviction that the rights of the individual must remain sacrosanct. With increasing insistency, however, voices are being heard on the subject of societal medical ethics. How do we protect the individual's freedom of choice and simultaneously consider society's needs? How do we provide compensation for the individual who is injured as a result of participation in community immunization efforts?

Beyond the problems we face in delivering available vaccines, we must turn our attention from the field of the possible to the field of the probable. We must work to develop vaccines for those diseases which cannot now be prevented by immunization. Those diseases for which vaccine is not yet available, but which are important enough to mandate a major effort for vaccine development, include malaria, schistosomiasis, African and American trypanosomiasis. Since these diseases are identified in the Tropical Disease Research Program (TDR) of the World Health Organization, they will receive increased attention in the near future. Other important diseases not included in the TDR are dengue, hepatitis A and B, and the viral hemorrhagic fevers.

The American pharmaceutical industry and academic institutions can play a vital role in development of new vaccines for such important diseases. Their active participation has been responsible for much progress in projects already underway, and in the successful completion of others. Pending development of such greatly needed new vaccines, emphasis on effective use of currently available vaccines is important for two major reasons: (1) Vaccines can significantly and immediately improve the health of the people of the developing world; and (2) vaccine delivery, as it becomes effective, will provide a system for delivery of vaccines now under development.

To reach the goal of efficient, immediate delivery of currently available vaccines, and to develop new vaccines for diseases which presently challenge us in the developing nations, we must mount a cooperative effort unequaled in the history of public health. We must maximize the potential of private industry, of academic institutions, and of governmental institutions in the United States. In view of our successful experiences both in the United States and with the recent international smallpox eradication program, we have a responsibility to help developing nations maximize their potential for delivery and production of vaccine.

In summary, five vaccines, now widely used in many countries, could have a significant impact on the developing world. The challenge is to develop social will, managerial skills, and simplified techniques to facilitate the universal delivery of such vaccines. Sufficient experience already exists to provide assurance that this is possible.

While development of new vaccines should be urgently pursued, establishment of adequate delivery systems for currently available vaccines with their need for surveillance systems, management, and evaluation would provide a solid background both for future vaccine programs, and for other primary health care services. At the same time we must emphasize that disease prevention requires a multifaceted approach of which immunization is only one aspect.

Vaccines are safe, effective, and potentially accessible tools to prevent unnecessary morbidity and mortality. Whereas the challenges to

their successful use in developing countries seem awesome, past experience proves that we can move ahead with confidence. At the turn of the century, who could have predicted the global eradication of smallpox? Who would have envisaged the progress made against poliomyelitis since the late 1940s? Who could have foreseen the decline in measles with the advent of nationally supported immunization campaigns? The synchronized, well-managed use of these vaccines is a test of our will. If we are willing to spend ourselves and our resources to develop well-honed systems for delivery of vaccine, we will be in a position to offer to succeeding generations a more hospitable environment and a childhood free from much unnecessary suffering, crippling, and death.

# C. VACCINE PRODUCTION

Frank T. Perkins

There is no doubt that correct use of potent vaccines has markedly reduced the incidence of some communicable diseases. This fact is no longer disputed but in order to achieve our objective, three factors must be satisfied:

1. Vaccines must be available in adequate quantity;

2. Vaccines must be known to be potent throughout the storage period; and

3. Vaccines must be given to the majority (90 percent or more) of the target population.

The purpose of this communication is to discuss the present situation and future outlook for provision of potent vaccines.

## The Production of Vaccines

Facilities for production of vaccines throughout the world can be scaled up to satisfy global requirements for those vaccines currently available against bacterial and viral diseases. At a recent meeting at WHO, Geneva, major manufacturers confirmed this impression and expressed a willingness to help the developing world to make available the quantities of vaccines to meet demands. The important point that was emphasized, however, was that there must be a global plan giving a "lead in" time of at least one year before substantial increases in demands could be satisfied. In the developing world, 90 countries are developing the infrastructure to deliver vaccine. If they are all ready for vaccine at the same time, the increase in demand will be enormous.

Some developing countries are either producing particular vaccines, but rarely those against childhood diseases, or considering the possibility of going into production. Although WHO is willing to assist in the necessary transfer of technology, and has already written manuals for production of diphtheria, tetanus, and pertussis vaccines, we

question the advisability of starting with vaccine production. It seems much more logical to approach this development in three stages:

1. Establishment of a quality control facility;

2. Establishment of a vaccine blending, filling, and packaging facility;

3. Introduction of vaccine production.

The reason for such a stepwise development is that each stage in development is dependent upon the previous stage having been established. Those developing countries who wish to start or increase their national vacine production face a long-term development program. For the immediate or short-term programs, therefore, we must rely upon existing facilties, most of which are in the developed world.

Far fewer manufacturers are involved in vaccine production in existing facilities in the developed world than there were ten years ago. Biologicals are not profitable to the pharmaceutical industry. A new antibiotic or a breakthrough in prophylaxis in vaccines may bring a temporary return on investment but the vaccines and sera used against childhood diseases barely repay the costs of production. Many large multinational concerns, however, have continued to produce vaccines because of continued demands and because of a policy of providing a full range of biologicals.

The way in which we may see an improvement in this situation is:

1. to have a realistic estimate of future demands;

2. to collaborate with the pharmaceutical industry in fulfillment of the needs;

3. to accept a research and development component in the price; and

4. to stabilize prices by placing advanced orders.

If this were done on a large but realistic scale, the industry has expressed its willingness to cooperate.

In the long-term, many developing countries are contemplating vaccine production for three reasons:

1. Purchase of vaccines from the developed world demands hard currency.

2. There is a need to maintain national employment at a high level.

3. The desire for self-reliance.

The relative importance of each of these factors will be determined by local conditions. As a guide to the economic viability of vaccine production, it might be interesting to consider a population of 20 million with a birth rate of 30 per thousand. Such a population will need vaccine for 600,000 babies per year assuming that they all live. Such a population, therefore, will require:

| Vaccine | No. of doses given | Total No. of doses | Wastage | Needs |
|---|---|---|---|---|
| Polio | 3 | 1.8 million | 50% | 2.7 million |
| BCG | 1 | 0.6 million | 50% | 0.9 million |
| Measles | 1 | 0.6 million | 30% | 0.8 million |
| DPT | 3 | 1.8 million | 30% | 2.4 million |

Thus, total annual requirements for vaccine would be two batches of polio (oral), BCG and measles, and four batches of DPT.

Any country contemplating the expenses incurred in establishing vaccine manufacture should carry out a realistic cost accounting exercise taking into consideration all national benefits and constraints before embarking upon the project. It will be noted that the above calculations assume that all babies live and that all children will be given all doses of vaccine. A conservative estimate is that these requirements for vaccine will be halved which makes the project less economically attractive.

It may be noted that of the 152 countries in the United Nations only 34 have a population of 20 million or more. Of these, 29 are already producing and 9 are exporting vaccines. Clearly, it is necessary to make a very careful analysis of local conditions before encouraging local production of vaccines. On the other hand, one country, with a population of about two million, feels it necessary to continue national production of vaccines because of the precarious position in which they find themselves in the event of international disputes.

A much more attractive proposal for developing countries is to establish a national filling facility. This would requiret vaccines to be imported as bulk concentrates and then to be diluted, blended, filled, labelled, and packaged locally.

This is attractive to the Third World because:

1. Availability of vaccines is in the hands of the national control authority;

2. Labels can be printed in local languages;

3. Instructions on the leaflet can be checked to be in line with national immunization policies; and

4. Costs are reduced.

It is important to appreciate, however, that a national facility, by becoming involved in an essential part of manufacture, will be responsible for quality control of the final product. This is a most important reason for prior establishment of a quality control facility.

The established pharmaceutical industry is sympathetic to this approach because the stages from bulk production to final product are time consuming and expensive in the developed world. Furthermore, existing production facilities would be operating more efficiently.

## Quality Control of Vaccines

The need for establishment of quality control as a primary function cannot be overemphasized. Such a control facility can:

1. Monitor quality of biologicals produced nationally or imported;

2. Monitor keeping properties of preparations (control of the cold chain);

3. Ensure that all subjects are given potent products;

4. Measure antibody responses of the community to vaccines; and

5. Measure herd immunity of a community to an infectious agent.

Establishment of a national control facility, therefore, is one of the most cost effective investments that a health authority can make. This can be done in several stages from simple reading of protocols to full-quality control involving the most expensive tests. All stages of quality control are cost effective. Since production of vaccine must include an efficient filling unit, and since the final product must be subjected to quality control, it is clear why we suggest that establishment of a solid foundation of quality control must precede all other activities.

The pharmaceutical industry is most willing to transfer technology for quality control but understandably has some reservations about transfer of technology on vaccine production. This is not entirely because of guarded secrets or patent rights. With production of any vaccine, unless the process is reproduced in every detail, the products will not be similar. There is little chance that the production procedure will be reproduced with meticulous care in the developing world because of the constraints placed upon resources. This is why provision of vaccine in bulk rather than transfer of technology in production is more attractive to all parties.

## The Modern Concept of Quality Control

Quality control of vaccines, as practised in the developed world today, is a very complex and expensive exercise.

It seems unfortunate that in almost every walk of life a tragedy has to happen before a potentially dangerous situation is fully appreciated. Such was the case with production of killed poliomyelitis vaccine in the Cutter incident. Where drugs are concerned, the thalidomide episode had an enormous impact upon the development of controls. It is equally unfortunate, however, that the outcome of such tragedies is stringent control which is always an over-reaction to the situation.

These two events have been responsible for the present stringent quality control of drugs, including vaccines, and such controls demand a great number of tests involving expertise and time that is a most costly element of production and control. Our control of vaccines, therefore, is a relatively recent event of the last 25 years, whereas legislation requiring the control of biologicals is more than 50 years old. For the first 25 years the means by which such controls were effected involved neither detailed supervision nor submission of protocols or samples.

The anomalies in quality control are somewhat disturbing. These have arisen because such requirements have been built up over a period of rapidly developing research and there has been a tendency to include every test already established for each new product irrespective of its relevance.

A virus vaccine today is examined by every test known to detect an extraneous agent whether that agent is likely to be present either in the seed virus, or in the cell substrate. Poliomyelitis vaccine (oral) is a good example. In the early days of 1959 to 1965, the vaccine was made in monkey kidney cells that may be contaminated with any of 50 simian viruses identified during that period. Consequently, such vaccine was subjected to tests capable of detecting these agents. When the virus is grown on human diploid cells that have been shown to be free from such extraneous agents, however, the virus harvest and the

human diploid cells are not only examined for the presence of the simian viruses, but the human cells are additionally subjected to far more controls than those prepared from monkey kidney. Even today, after years of experience with vaccine production in human diploid cells that have never been shown to be contaminated, the requirements of vaccine control remain unchanged. This illustrates the inflexibility of the quality control of vaccines.

It is ironic that at the same time as such a situation exists, smallpox vaccines known to be contaminated continue to be licensed. The control authorities are able to defend this because of the need for large scale production for the world and because smallpox vaccine is given by the percutaneous route. The same arguments, however, cannot be used for continued production and licensing of yellow fever vaccine, known to contain some or all fowl leukosis viruses. The argument here, however, is that if it became mandatory to produce yellow fever vaccine in chick embryos known to be free from fowl leukosis viruses, then the vaccine could not be made by the developing countries where yellow fever is prevalent. Even though WHO Requirements for Yellow Fever Vaccine were revised only two years ago, it was not possible to demand that the vaccine should be free from these chicken viruses. It was of particular importance, in making such a decision, that millions of subjects have been given vaccine containing fowl leukosis viruses with no record of adverse reactions due to the contaminants.

There are other anomalies concerning quality control. Some tests have not contributed to the safety of the product, but no control authority is in a position to recommend their omission. This is the result of legal considerations rather than scientific argument; for, in the event of a subsequent accident with a vaccine subjected to fewer control tests, a justification for exclusion of some tests based on negative evidence would be severely criticized and possibly punished legally. This is a most serious situation that deserves more attention.

## The Future for Vaccines Against Tropical Diseases

So far, we have been considering vaccines against the ubiquitous childhood diseases and those that have been available for some years, but the diseases that occur only in the tropics present a more serious problem. Such vaccines are, as yet, in the early stages of research. One of the major constraints to development of vaccines or drugs against such diseases is the uncertainty of being able to market the products. Today, however, the challenge before the research potential of the world is to develop biological products against these prevalent diseases. Many obstacles will need to be overcome if we are to succeed. Amongst these are:

1. A greater intensity of research into the immunology and pharmacology of tropical diseases;

2. The "drugs" (including vaccines) will almost certainly be developed in countries in which the diseases do not occur, whereas clinical trials must be carried out in those areas in which the disease is prevalent;

3. An entirely new approach will be needed for quality control of prophylactic or therapeutic agents against these diseases;

4. A coordinated effort between the developed and developing world, on a scale that has not hitherto been envisaged, will be needed for success.

It is important to consider in depth each of these considerations.

## Support by a Number of Countries is Essential

The quality control of vaccines that may be developed against tropical diseases is already demanding attention. WHO is looking at controls that may be necessary for vaccines against leprosy, malaria, and dengue haemorrhagic fever. Such requirements are being formulated but they must be flexible, and subject to change as new findings accumulate. Research organizations require support to give more assistance in this work. It is most important to appreciate that these drugs or vaccines are urgently needed for infections that are causing millions of deaths each year. The price of efficacy, therefore, may be side reactions in a small proportion of those needing the drug or vaccine, and the level of acceptability must be assessed in those communities most in need of the products. The final equation of therapy or prophylaxis against the disease will include mortality of the disease, efficacy of the drug, reactions to the drug, and cost of the disease compared with the cost of the drug. It will be a complex formula but it will be necessary to retain an open and flexible mind on all components before the final answer is reached. Indeed, local conditions may also be the most important determinants and overrule all other factors.

The necessary developments will not be achieved, however, without financial support at a realistic level and sacrifices of research time to these projects.

## Conclusions

In providing vaccines against bacterial and viral diseases of children, there will need to be new thinking for the future. At a meeting in WHO, Geneva, in October 1978, it became clear that the present situation, whereby producers of the world become involved in a vicious auction to quote the lowest price, in order to be awarded large orders from international organizations, must be changed. The pharmaceutical industry cannot continue making vaccines under these conditions,

especially if they are also expected to carry out research and development. An alternative would be to offer each contract to more than one company but the most important consideration should be given to the involvement of governments. If governments would give part of their contribution to the developing world in the form of vaccines bought from their national producers, both producers and the developing world would benefit. Such a plan is worth serious consideration and is being examined for provision of drugs.

As far as future products against tropical diseases are concerned, government support for research is essential. Provision of preparations to countries where tropical diseases are prevalent, and where such countries are least able to afford such drugs or vaccines that may well be much more expensive than present day vaccines, is a problem requiring urgent attention. Stimulation of such developments is an integral component of the research needed, and the necessary support must be discussed at the beginning of any research and development program.

These problems of the developing world are a tremendous challenge. The scientific world is capable of providing answers but such efforts are likely to need government financial support to give impetus to the program. A coordinated effort is essential if we are to be successful in reducing the misery caused not only by diseases for which we have satisfactory vaccines but also by tropical diseases that still remain to be conquered.

No child should occupy a hospital bed with a disease that can be prevented, and our aim is to enlarge the list of preventable disease. This will be achieved only by political will, financial investment, personal sacrifices and, above all, a coordinated effort by government and scientific resources.

# SELECTED PHARMACEUTICAL DEVELOPMENTS REQUIRED FOR PREVENTION OF MASSIVE BLINDNESS IN DEVELOPING COUNTRIES

Barrie R. Jones

## Introduction

The economic and social effects of blindness are such that its avoidance should surely command a priority for action.

I should like to introduce the subject of blinding eye infections by giving some background and proposing an operational approach that specifies the requirements, in principle.

In the developed countries the prevalence of blindness ranges from 0.05 percent to 0.2 percent of the total population. The main causes are illustrated in Table 1. This burden of blindness could be reduced at relatively high cost by preventive application of existing technology and by developments now in progress. (Symposium on Prevention of Blindness in the United Kingdom, Oxford Ophthalmological Congress, 1978 in press - Transactions Ophthalmological Society, United Kingdom)

The developing countries also have these diseases, and tend to spend their resources for health by endeavouring to provide comparably sophisticated therapeutic services for privileged urban communities that constitute only a minute fraction of the total population, and an even smaller fraction of their blindness. They tend to do nothing effective about preventing the appalling additional overburden of avoidable blindness which may be 10 to 40 times higher in their neglected rural populations (Tables 2, 3, & 4).

This is partly the inevitable result of the narrow horizons of politicians and administrators, advised by persons trained through traditional medical schools. It is partly the result of inadequate dignity, respect, and remuneration for research, development, and service in rural community medicine, specifically in prevention of blindness. But it also results from nearly total neglect of these problems by both academia and industry in the technologically advanced countries. For example, we simply do not have the drugs, the systems and the knowledge that we need to deal with onchocerciasis. This Conference may be expected to do something to mobilize resources needed to overcome these deficiencies.

TABLE 1. BLINDNESS IN THE UNITED KINGDOM

| Causes (Soresby) | Percentage of Blind Persons |
|---|---|
| Senile macular degeneration | 27.0 |
| Senile cataract | 22.6 |
| Glaucoma | 12.0 |
| Myopic Choroido-retinal Degeneration | 8.2 |
| Diabetic retinopathy | 7.1 |
| Optic atrophy | 4.2 |
| Vascular retinopathy | 3.2 |
| Uveitis | 3.0 |
| Retinitis pigmentosa | 3.0 |
| Dislocated lens | 1.2 |
| Retinal detachment | 0.9 |
| All other causes (each causing 0.5%) | 8.6 |

PREVALENCE OF BINOCULAR VISUAL ACUITY $<$ 6/60 = 0.2% OF POPULATION

It is now recognized that most of the neglected rural communities with a massive overburden of avoidable blindness have a mixed harvest resulting from trachoma or onchocerciasis, or both, perhaps with malnutrition added -- and in any case there is also, almost invariably, a high prevalence of readily remediable blindness from cataract (Tables 2, 3, & 4). This situation lends itself to a three-phase approach that:

1. Commences with initial intensive intervention that delivers

   a. Surgery to the community to remedy cataract and blinding distortion of the eyelids, and

   b. Intensive chemotherapy, on a community basis, to reduce the reservoir of infection, to block transmission, and eliminate the progression on into blindness.

**TABLE 2. RURAL BLINDNESS IN SOUTHERN IRAN: VILLAGE OF SAR RIG**

| |
|---|
| 6.3% of population blind from trachoma |
| 1.4% of population blind from cataract |
| PREVALENCE OF BLINDNESS BINOCULAR VISUAL ACUITY < CF @ 1M = 8.6% |

**TABLE 3. BLINDNESS IN AN AFRICAN SAVANNA VILLAGE 1/**

| |
|---|
| 2.7% of population blind from onchocerciasis |
| 9.4% of population blind from trachoma |
| 0.3% of population blind from uncomplicated cataract |
| PREVALENCE OF BLINDNESS BINOCULAR VISUAL ACUITY < CF @ 3M = 3.3% |

**TABLE 4. BLINDNESS IN AN AFRICAN RAIN FOREST VILLAGE 1/**

| |
|---|
| 1% of population blind from onchocerciasis |
| 0.6% of population blind from cataract |
| PREVALENCE OF BLINDNESS BINOCULAR VISUAL ACUITY < CF @ 3M = 1.6% |

2. This must be followed by

   - saturation availability in every family of relevant eye ointment, etc.
   - education and assistance for improved personal hygiene, community sanitation, or environmental control, as required.

3. This attack on eliminating avoidable blindness needs to be planned with, and integrated into, development of primary rural health care, and strengthening of district eye services. But it must be appreciated that in these neglected communities it is the perception of benefit from (1) that makes credible and attractive the effort and expenditure for (2) and (3).

## Hyperendemic Blinding Eye Infections

Although there are great differences between Chlamydia trachomatis and Onchocerca volvulus, their transmission and the diseases they produce, the similarities between the factors leading to "blinding trachoma" 8/ and the factors leading to "blinding onchocerciasis" are striking.

In each case man harbours the reservoir of infection, and in each case blindness only results from living in a community with an exceedingly high pressure of transmission of infection. In each case we need safe chemotherapy that can be easily administered by medical assistants, that will reliably produce a large reduction of the reservoir of infection, with much diminished transmission, and will give rapidly perceived benefit to the treated individuals.

If these requirements are met it does not matter if the course of treatment takes some weeks to complete, provided medical assistants can safely and effectively administer it on the required scale.

## Chemotherapy for Hyperendemic Blinding Trachoma

For trachoma control the currently recommended chemotherapy is a tetracycline or macrolide eye ointment applied twice daily for 5 consecutive days once monthly for 6-24 months. This is somewhat irritating, messy, vision-blurring, and of middling efficacy. It takes a long time to yield perceived benefit, and relapse of shedding of C. trachomatis may occur if the treatment course is not protracted; but it can be safely administered by medical assistants or by family members, and so is widely used.

We have investigated oral chemotherapy with doxycycline 5 mg/kg given twice weekly for 3 weeks. Benefit was rapidly perceived and the prevalence of active trachoma in that whole village community, including babies originally too young to be treated and new immigrants, reduced progressively for two years. Not until the third year was there an upswing of transmission with a concomitant increase in prevalence of severe active trachoma. Doxycycline dosage every 3 days for 3 weeks should be even more effective.

We are now investigating the effects of 3 single weekly doses of Kelfizine W (Sulfametopyrazine) in a trachomatous population on the Island of Hormoz.

So far, no serious adverse effects have arisen and the early effects look encouraging, but problems remain of ensuring adequate large-scale supervision of oral dosage, avoidance of overdosage and the possible uncertainties concerning late effects of any high dosage tetracycline therapy on infants, children, and potentially pregnant women who are precisely the persons harboring most of the reservoir of C. trachomatis in these communities. Furthermore, there may be anxieties about the possibilities for emergence of resistant enteric, respiratory and other bacteria.

## Ocular Therapeutic Systems for Trachoma

The principle of continuous controlled delivery of chemotherapy to the eye from a drug-delivery platform that resides in the conjunctival sac, as developed by ALZA Research, would seem to offer the advantages of continuous protracted effective therapy without problems of cost and uncertainties inherent in prolonged systemic chemotherapy.

The original design of "Ocusert®" delivering pilocarpine for glaucoma, can be retained reasonably well by most patients, with appropriate training. But retention was quite unsatisfactory in hyperendemic eye disease without training. Nevertheless, pilot trials of various such devices delivering erythromycin for trachoma, chloramphenicol for acute bacterial conjunctivities, or disodium cromoglycate for allergic vernal conjunctivities yielded slightly higher immediate efficacy than the corresponding ointment or eye drop preparations.

The new principle of supratarsal delivery platforms provides secure and comforable lodgement in a potential space above the upper tarsus. Medial or lateral falling out is prevented by lodgement on the respective canthal ligament. The performance is remarkably good in small numbers of volunteers, even when wearing these inserts for periods up to 2 years. Larger scale trials will shortly confirm or refute these promising pilot studies of continuous, non-irritant chemotherapy for 3-4 weeks at a time from a single insertion in each eye, and which could be carried out by medical assistants.

Time does not permit discussion of the choice of antibiotic, and the attractions of rifampicin, possibly combined with erythromycin. Instead, we must consider the much more difficult problems of onchocerciasis.

## Prevention of Blindness and Control of Onchocerciasis

Elimination of onchocerciasis from Kenya was achieved, and control of the disease in the Volta River Basin is being attempted on a vast scale, by control of the Simulium fly vector. Much progress has been made; but repopulation is a problem since the flies can fly 100-200 miles. Additionally, the longevity of adult Onchocerca volvulus in man means that the extremely costly vector control program will have to be maintained over vast areas for 15-20 years to allow the reservoir of O. volvulus to die out in the control area.

Professor Peters has discussed the paucity and shortcomings of drugs available for onchocerciasis. He has emphasized the difficulties in screening new compounds for activity, in the absence of in vitro systems or animal models of infection with O. volvulus.

I should like to illustrate two ways in which ocular studies can contribute.

## Direct Demonstration of Activity Against Microfilariae in the Cornea

Curled-up, living microfilariae of O. volvulus are near the lower limit of what can be observed clinically in man with a good binocular biomicroscope. This enables drug effects to be observed directly in corneae heavily loaded with microfilariae. Drs. Anderson, Fuglsang, and I have shown that the following pattern consistently occurs with all drugs known to kill onchocercal microfilariae (mf):

1. increased migration of mfs.
2. straightening, immobilization, and opacification of mfs.
3. granular disintegration amidst reaction around many, but not all mfs.

In addition, a highly characteristic sequence of acute inflammatory events rapidly develops in the peripheral cornea and limbus, comprised of:

1. peripheral corneal and limbal globular infiltrates
2. limbitis
3. suppurative perivasculitis (if the reaction is severe)

This sequence has been observed afater oral therapy with diethylcarbamazine (DEC), metrifonate, and suramin, and it has been studied quantitatively in response to topically applied DEC.9/

Within the constraints of prior animal work and volunteer studies to ensure acceptably low toxicity and ocular irritancy, and within constraints of solubilities permitting formulation for ocular absorption, it is possible to use these characteristic phenomena to demonstrate activity, or lack of activity against microfilariae of O. volvulus.10/

Progressively increasing in half-log steps from 0.0001 percent concentrations through 0.0003 percent, 0.001 percent, etc. to reach 1 percent and even 3 percent, we have cautiously applied DEC 3 times in a day, or in half-a-day. This enables us to observe the very earliest signs of action on microfilariae, and of adverse drug effects on the eye.

The purpose of this investigation has not been a search for new anti-microfilarial drugs, but to demonstrate efficacy against O. volvulus in classes of compounds that may have macrofilaricidal activity and which are safer for systemic use in man than is suramin. In this way, we have demonstrated the activity of levamisole 10/ and amoscanate (CGP 450). No activity could be shown with mebendazole (possibly because of its extremely low solubilities), thiabendazole, econazole, miconazole, clotrimazole, dibromopropamidine isethionate, or trifluorothymidine.

The ethical acceptability of such studies, when carried out in an area of blinding hyperendemic onchocerciasis by an expert team under guidance of an investigator who is a national of the country concerned, rests on the following considerations:

1. Patients with severe corneal onchocerciasis need a lowering of their load of corneal microfilareae.

2. Any adverse reactions are detected very early at their onset, and occur in noncritical tissues of the peripheral cornea and conjuctiva.

3. No patient is placed at risk of visual damage by reactions in the critical tissues of the optic nerve or retina, as may be the case with ill-advised systemic therapy with existing drugs.

4. Furthermore, the precision of direct microscopic examinations of these effects from coded treatments, with right/left placebo controls, requires only a few patients to receive very small quantities of drug in one eye for 1-3 days.

Used strictly in this way, we believe that this is a safe and potentially useful method of generating early confirmation or refutation of activity against O. volvulus in its microfilarial form, and which could contribute materially in the search for better drugs.

## Adverse Effects from Chemotherapy of Severe Ocular Onchocerciasis

Systemic therapy of severe onchocerciasis with diethylcarbamazine 1,3,5,7,12/ or suramin 2,4,6,7,11,13/ regularly gives rise to unpleasant cutaneous, ocular or systemic reactions. The dangers are much increased in very heavily parasitized persons. Deaths have occurred, especially following suramin from which the adverse effects are not necessarily entirely related to the parasiticidal effects. Suramin therapy seems especially likely to precipitate or exacerbate onchocercal iritis and possibly optic nerve disease requiring expert additional management to avert blindness.2/

We have studied quantitatively both the direct anti-microfilarial, and the adverse inflammatory effects of topically applied DEC in onchocerca-loaded cornea.9/ When therapy is expressed in terms of average day-time delivery rates, DEC produces:

anti-microfilarial effects at 0.1-0.3 ug/hr.

mild inflammatory effects at 1 ug/hr.

substantial or severe inflammatory effects at 3-30 ug/hr.

There appears to be a therapeutic range of delivery rates within which DEC can kill mfs without causing substantial adverse effects. Furthermore, it appears that after a period of carefully controlled delivery rates, it may be possible for the treated eye to withstand the ordinary highly pulsed doses of DEC without adverse effects. Application of this principle may make it acceptable to use DEC to reduce the microfilarial load, thereby increasing the safety of administration of subsequent suramin therapy.2/

Our work in progress in the Southern Sudan has confirmed that the same adverse inflammatory sequelae occur with ordinary regimens of suramin therapy, including uveitis and severe suppurative perivasculitis in the cornea.

Preliminary studies have shown that these adverse inflammatory sequelae in the eye are not prevented by ordinary intensive day-time administration of various anti-inflammatory drugs or combinations including prednisolone, anti-histamine, anti-serotonin, anti-prostaglandin synthetase, or "anti-allergic" compounds that block release of mediators; namely, disodium cromoglycate, ketotifen, isoproterenol with diethylcarbamazine, or 2-deoxyglucose.

There is therefore an important requirement to study the effects of therapy using various round-the-clock non-pulsed delivery rates of DEC from supratarsal ocular therapeutic systems, to determine whether there really is a therapeutic range of controlled delivery rates within which DEC can kill O. volvulus mfs without exciting substantial adverse

inflammatory reactions. One must also study the effects of combined therapy using anti-filarial and anti-inflammatory drugs of various sorts, and sequences of drug administration under conditions of steady state drug delivery to obviate the overwhelming adverse effects that appear related to peak drug delivery.

The speed and precision of microscopic examination in the eye, under coded conditions, coupled with the right/left internal control opportunity which obviates so many interpersonal variables, offers a very attractive situation in which to study these phenomena which appear to apply to all drugs that kill the microfilariae, including the macrofilaricidal drug, suramin.

It is likely that a modest investment in this application of continous controlled ocular drug delivery could provide data with which to write specifications for drug delivery rates for systemic and topical drug delivery, that may ultimately open the door to safe and beneficial administration, by medical assistants, of effective programmed chemotherapy for onchocerciasis.

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## DISCUSSION: MAJOR DISEASE PROBLEMS OF THE DEVELOPING COUNTRIES: THE CURRENT STATUS OF PREVENTIVE, PROPHYLACTIC, DIAGNOSTIC, AND THERAPEUTIC AGENTS

DR. LEIGHTON CLUFF, referring to Professor Smith's statement concerning the paucity of reliable statistical information available from less developed countries, wondered about the importance of establishing systems for collecting appropriate, reliable data to identify problems and assess impacts of various interventions on improvement of health status.

DR. GORDON SMITH replied that precise data on worldwide prevalences were not what was needed now; it would suffice -- but this is important -- to obtain within particular countries accurate information about the distribution, prevalence, and incidence of diseases against an accurate demographic background. Such information is essential for purchase and distribution of pharmaceuticals or vaccines among large populations, especially when relying on untrained people. Thus, the success of a large-scale vaccination program necessarily depends upon planning based on accurate data including, for example, projections of the size and distribution of the population in the youngest age groups for estimates concerning the amount of vaccine and the distribution effort needed.

DR. TAG MANSOUR asked Dr. Smith if poor communication among the scientific community in developing countries slowed drug research and development efforts.

DR. SMITH noted that he had not been referring to information on drugs, but to information on health and the effects of behavior on health practices. Here, his concern focussed on two problems of communication: (1) how to reach the large majority of the population and inform them about disease, such as hookworm; and (2) communication within the scientific community to disseminate new knowledge. The problem of keeping up with the information explosion is bad enough in developed countries. In countries where resources are scarce, and where only a limited number of scientific journals arrive, the difficulty is compounded by the lack of expertise available to interpret the knowledge to its potential users, and to devise applicable solutions. This problem has been exacerbated by the drain of the best scientists to developed countries.

DR. WALLACE FOX (British Medical Research Council) offered examples from his own experience to show that precise prevalence data may not always be necessary. Thus, the WHO delayed tuberculosis therapy in Africa for several years in the 1950s while sophisticated sampling surveys were performed. The prevalence data thus obtained merely confirmed that there was a tuberculosis problem; little new was added. In

this particular case, statistical information derived through sophisticated methodology was not necessary; a treatment program only required approximate data concerning the numbers of people who might come to the health centers for treatment.

DR. SMITH commented that the problems of therapy differ from problems of prevention. The example of tuberculosis is only useful for specific situations, such as in countries with an adequate number of treatment centers. He agreed that unncessary delay is bad. However, to conduct an effective, long-term preventive program, one needs to know the size and preferred age group for vaccination of the populations likely to be at risk, and therefore their demographic constitution and dynamics.

DR. JOHN BRYANT (Office of International Health, DHEW) referring to comments by Drs. McDermott and Smith, asked how close the linkage is between health improvements and improved living conditions. He noted that an increase in population worldwide means an increase in the absolute numbers of people moving into circumstances of poverty, even though their proportion may be decreasing in relative terms. Are there unused or underutilized resources at the community level that can be used to improve health status? Can we afford to wait for the socio-economic level to improve? Is absolute poverty an obstacle to health improvement?

DR. WALSH McDERMOTT noted that the People's Republic of China has shown that labor-intensive methods can be very effective in situations where the society is mobilized toward common goals. There is a large cultural component to the success or failure of labor--intensive projects. Much of our technical knowledge cannot be applied without simultaneously working to remedy the socio-economic problems.

As to utilizing technology in circumstances where poverty prevails, DR. McDERMOTT believes that it is not realistic to expect people to wash their hands frequently if they have to haul water over long distances. Despite this general limiting principle, some examples can be cited where technology can control diseases linked to poverty without addressing the poverty issue directly -- so-called "technological fixes."

DR. CLUFF requested Dr. McDermott to extend his previous comments about the effects of applying medical technology in conditions where poverty remains unchanged.

DR. McDERMOTT referred to the introduction of chemotherapy for tuberculosis in Wales and in New York City that produced precipitous declines in the tuberculosis rates among the white population, and among Black males in New York City. These changes in the incidence of tuberculosis occurred without noticeable improvements in socio-economic conditions, illustrating two instances where medical technology alone

can make a difference. The same effects of tuberculosis chemotherapy were noted among the aboriginals and among the people of European descent in New Zealand.

DR. McDERMOTT indicated that not enough attention has been paid to investigate the pathogenetic chains of the diseases of poverty, to look for weak points that could be attacked. In this context, he observed that the medical care system had a delivery system long before it had technology (the reverse of the usual situation -- where technology precedes the establishment of the system for its delivery). The tendency of the medical profession is to find an effective agent, plug it into the system, and then move on to something else, instead of perfecting the technology.

DR. SMITH commented that the experience with tuberculosis in New York City cannot be extrapolated to less developed countries. In New York City and other urban areas, access to care was concentrated in a small area. The example of polio vaccine in the developing world should also be considered a very special case, for the large market in the industrialized countries made cheaper production costs and therefore lower export prices possible.

DR. BARRIE JONES commented on Dr. McDermott's experiences with the Navajo in controlling infectious disease. Mass chemotherapy with sulfonamides for trachoma hs been considered a failure because it resulted in little reduction in prevalence of the infection. It is much more meaningful to consider the prevalence of a potentially blinding severity of disease which relates to duration of life in a community with very high pressure of eye-to-eye transmission of infection. Viewed in this light, sulfonamide chemotherapy in the Navajo was followed by very great reduction in severity of disease and, later, abolition of further blindness from trachoma, despite a continuing but diminishing prevalence of very mild trachoma.

DR. JOYCE LASHOFF (Office of Technology Assessment) referred to Dr. McDermott's comments on China, since she had recently spent three weeks in that country. She believes that the political organization of the population, which emphasizes education, sanitation, and assumption of responsibility, is an essential component to the successes of the Chinese health care system, much more so than any cultural factor. She pointed out that education in relation to sanitation has been exceptionally successful, even under adverse conditions. As a rather extreme and somewhat humorous example, she cited the toilet training of water buffaloes in the effort to control the spread of schistosomiasis.

DR. FRANZ ROSA (former Chief of Maternal and Child Health, WHO) wished to introduce, for the record, consideration of the problem of pregnancy and pharmaceuticals. He mentioned the need to find agents to aid in the appropriate spacing of births, and which would not interfere with breast-feeding.

DR. DIETER KOCH-WESER (Department of Preventive Medicine, Harvard University) reiterated Dr. McDermott's comment that health delivery systems antedated technology in the United States. Agreeing that the health care delivery system was very important, he asked whether its lack was not the major problem in less developed countries.

DR. McDERMOTT noted that it is difficult to generalize; the sudden introduction of particular technologies into the industrialized world has had devastating effects on delivery systems. Health delivery systems vary widely among -- and even within — less developed countries, from traditional healers to Western-trained physicians. Most delivery systems in less developed countries can handle non-toxic drugs, while highly toxic drugs require very sophisticated systems. No matter what the system, however, the putative healer must have something to deliver.

DR. CLUFF cautioned that any delivery system introduced into less developed countries be appropriate to the available technology.

DR. McDERMOTT suggested that the "technological substrate" — or the demographic pattern of diseases in a particular country -- be considered when examining the possibilities of introducing a new technology or increasing the availability of the old. For example, if one looks at myocardial infarctions in United States, many of those stricken never reach the doctor because they die first. Such individuals do not figure in the "technological substrate."

DR. EDWARD CROSS (Agency for International Development) asked who has the responsibility for translating research findings into a health care program, if not the researcher.

DR. SMITH replied that it was not necessarily the duty of the researcher to see to implementation of his findings. This responsibility belongs to disease control or health care administrators. However, researchers often fail to communicate effectively with those responsible and use jargon to excess, which limits understanding and application of their findings.

DR. CLUFF asked Dr. Perkins why an effective immunization program must reach 90 percent of the population. Should this figure be a goal for all vaccination programs, and is there any evidence to support the need for such a large effort?

DR. FRANK PERKINS, noting that hard evidence was scarce, cited the recent outbreaks of pertussis in the United Kingdom, which were linked to low vaccination rates. Over the last three years, the percentage of the target group to have been vaccinated had fallen from 85 to 35. He mentioned the psychological importance of setting a target of 90 percent to reach an actual rate of 80 percent.

MS. BARBARA STOCKING (University of Sussex) requested continued discussion about delivery systems for vaccines in developing countries. In the absence of delivery systems, how can vaccination programs reach the majority of the population?

DR. WILLIAM FOEGE replied that it is best to use a primary health care system for a vaccination program if one exists in a particular country. In those vast areas where primary health care centers do not exist, however, mobile teams delivering vaccines to primary health care centers might be a better solution.

DR. CLUFF wondered whether WHO "team" immunization programs have reached immunization rates of 90 percent.

DR. FOEGE replied that the question cannot be answered as precisely as it was posed, and that 90 percent should not be seen as a universal epidemiological target. In the smallpox program, for example, populations were immunized in specific outbreaks. In other programs, each percentage increase of coverage costs more; the additional costs must be balanced against the available resources, and against the marginal rate of return. Worldwide, however, 90 percent coverage has been achieved many times in immunization programs.

DR. OSCAR GISH (University of Michigan) interjected that debate over the effectiveness of immunization programs is meaningless unless the analysis is undertaken within a framework that embraces the economic situation, political environment, and etiology of diseases. He asked whether some of the advances in disease control over the last few decades, for example, smallpox eradication, have made any real impact on living conditions overall. Some studies suggest that the Indian population is less healthy today than ten years ago.

DR. WALLACE PETERS responded by citing a personal anecdote illustrative of the improvements in overall living conditions produced by a specific disease control program. He related the case of a jungle village in Nepal, which had long been rendered uninhabitable by endemic malaria. Thirteen years after the introduction of a malaria control program, the area had been transformed into a thriving agricultural region with noticeable improvement in the residents' quality of life. Other examples among many should include yaws and malaria control in Liberia.

DR. CLUFF observed that the record is replete with evidence that the control or eradication of a single disease has changed the history of mankind.

DR. SMITH asked that Drs. Foege or Perkins provide information on two potentially undesirable effects which may have been caused by the introduction of measles vaccination programs in Africa: (1) the country cannot sustain the effort following withdrawal of foreign

assistance, increasing the likelihood of the virus' return with greater force than ever; (2) the country feels obliged to sustain the immunization program following withdrawal of foreign assistance, and thus skews the spending of the health budget in that direction.

DR. FOEGE replied that much has been learned from the measles programs in West Africa. In The Gambia, measles transmission was interrupted for three years, thus freeing hospital beds for other purposes. The return of measles following cessation of the program has not been more virulent than before the program. Overall, results are mixed, and some countries could not sustain a comprehensive measles vaccination program.

DR. PERKINS commented that immunized individuals enjoy permanent protection against the virus. He did cite another negative side effect from vaccination programs: mothers who perceive the benefits of a program blame the government for not continuing it.

DR. CLUFF asked Drs. Janssen and Jones about the proximate utility of the new pharmaceutical agents and techniques they discussed for developing countries today, especially since successful application depends upon a well-developed personal health care delivery system.

DR. PAUL JANSSEN noted that some agents are easy to administer at low cost. It is possible to eradicate roundworms, for example, without changes in hygiene at the (low) cost of ten cents per person per year.

DR. JONES noted that although fungal diseases of the eye can now be effectively treated in advanced medical centers, management is protracted and difficult to carry out in rural communities of humid tropical developing countries where the problem is probably greatest. Prophylactic ointments now have to be developed, with guidance from local microbiologic studies. Prophylaxis covering the main fungal and bacterial threats, used after all eye injuriess, should be more cost-effective than the individual treatment of a few established cases. He also described the training received by many physicians in developing countries as often irrelevant to the conditions and the health needs in their countries, and noted this as another barrier to successful application of prophylactic and therapeutic agents.

# CURRENT PROGRAMS FOR DEVELOPMENT OF PHARMACEUTICALS

# UNDP/WORLD BANK/WHO SPECIAL PROGRAM FOR RESEARCH AND TRAINING IN TROPICAL DISEASES

Adetokunbo O. Lucas

This paper presents the Special Program for Research and Training in Tropical Diseases as an example of a current activity aimed at providing new and improved pharmaceutical agents that are required specifically in developing countries. This Program was initiated by the World Health Organization and is co-sponsored by the United Nations Development Program and the World Bank. It is receiving support both in cash and in kind from a number of governments and agencies.

It was in May 1974 that the World Health Assembly meeting in Geneva passed a resolution calling on the Director-General to "intensify WHO activities in the field of research on the major tropical parasitic diseases (malaria, onchocerciasis, schistosomiasis, the trypanosomiases, etc.)".

## Objectives

After extensive consultations, a program was designed with two interrelated and interdependent objectives:

1. Development of improved tools needed to control tropical diseases

The first objective is to develop new preventive, diagnostic, therapeutic and vector control methods specifically suited to prevent, treat and control selected tropical diseases in the countries most affected by them. The new methods must be susceptible to implementation:

- at a cost that can be borne by developing countries;
- requiring minimal skills or specialized supervision; and
- in a manner that allows their integration into the health services, especially the primary health care systems of developing countries.

2. Strengthening of biomedical research capability in tropical countries

The second objective is to strengthen research capability in the countries most affected by tropical disease, through training in biomedical sciences and various forms of institutional support. Biomedical research capability in tropical countries must be strengthened -- even if it were only to accomplish the first objective -- because major activities in the specification, development, and testing of new tools must occur in the tropical countries where the diseases are endemic, to ensure that these tools are effective in controlling the target diseases in these countries.

The basic assumptions guiding the design and the operation of the Program can be briefly summarized:

1. The problem

The tropical parasitic and infective diseases remain a major cause of disease and death in many tropical countries, and often constitute a significant barrier to development. Furthermore, in some cases, the process of technological development, as for example the exploitation of water resources in the construction of man-made lakes and irrigation schemes, has aggravated the situation by intensifying transmission in endemic areas and by creating new foci of infection at man-made lakes.

2. Limitations of existing tools

Whereas some of the common diseases in the tropics can be brought under control by the vigorous and rational application of existing knowledge and technology, in the case of some other diseases the available tools seem inadequate for bringing them under control. The evaluation is relative, but one can cite several examples such as the challenge posed by the emergence of drug resistant malaria parasites and leprosy bacilli, insecticide resistant vectors of malaria, and the lack of a suitable drug for killing adult onchocercal worms in man.

3. Promising new lines of research

A third basic assumption is that the application of new advances in fundamental biological sciences such as immunology, cell biology and biochemistry would provide a better understanding of the parasites and the vectors, and thereby yield valuable clues for designing new tools for dealing with them; and that a goal-oriented, multi-disciplinary research program involving researchers from all relevant areas of the biomedical and social sciences would accelerate the development of new or improved measures for the control of these diseases.

## Scope of Operations

On the basis of these criteria, six major diseases have been selected for initial emphasis:

- malaria
- schistosomiasis
- filariasis (including onchocerciasis)
- trypanosomiases (including both African sleeping sickness and the American form, Chagas' disease)
- leishmaniasis
- leprosy

## Research and Development

The activities of the Special Program are directed towards development of any practical tool needed to solve the problems of the selected diseases, and focused on development of new drugs or modification of existing ones, search for vaccines, new methods of vector control, and improved diagnostic tests.

The research activities are carried out by multidisciplinary groups of scientists formed on a world-wide basis. These are called Scientific Working Groups (SWGs) and are formed in the fields of the disease and trans-disease research areas to focus research activities toward the goals of the Program. In addition, there are four other SWGs in trans-disease research areas -- epidemiology, the control of vectors, basic biological sciences, and socio-economic aspects.

One SWG comprises all the scientists who plan and/or carry out research on a specific aspect of the Program. Members of the Group define the research objectives, devise a strategic plan to achieve them, carry out the research according to plan, and review the plan and the research as work progresses.

To develop such a plan and operate a SWG, the scientists must describe or formulate:

- the detailed objectives of the SWG, e.g., the specifications for a malaria vaccine applicable and effective in rural India;
- the current state of the art in relation to the objectives;

- the problems which remain to be solved, i.e., the gaps in knowledge;

- the possible research approaches and disciplines which may solve these problems, as well as the feasibility, sequence, and cost of the activities, or projects, in each line of research;

- a clear strategic plan including each research approach and its line(s) of research, leading towards the final objectives.

One or more SWGs are now operating for each of the diseases selected by the Program. In general, three areas are covered for each disease, either by separate SWGs or by subgroups of one SWG: chemotherapy and drug development; immunoprophylaxis and immunodiagnosis; and where relevant, epidemiology and vector control.

Within this broad framework, the priorities in each component of the Program have been selected on the basis of a careful analysis of needs and opportunities, always in consideration of activities on the subject already undertaken by other agencies.

The overall strategy of the Program is to identify and attempt to fill gaps in the efforts directed towards development of new tools for control of these diseases. For example, investigations showed that several pharmaceutical companies were actively engaged in development of new schistosomicidal drugs, but that one major constraint is the clinical evaluation of promising compounds. The Scientific Working Group on Schistosomiasis therefore accorded high priority to promotion of well-designed, multi-center clinical trials of schistosomicidal drugs. On the other hand, in the case of filariasis, where the SWG had identified the need for a macrofilaricide effective against the onchocercal worm as a top priority, a major constraint is lack of validated biological screens. The SWG on filariasis has therefore supported development and validation of these screens for testing potential filaricides in a network of academic centers stretching from the United States, through the United Kingdom, Germany, and Japan to Australia. Selected compounds supplied by various pharmaceutical companies are now being tested in order to identify useful leads. In addition, clinical trials are being promoted in endemic areas. Each component of the Program is being designed in such a way as to match needs with opportunities in the most rational manner.

## Role of the Pharmaceutical Industry

In planning and implementation of this Program, there has been a conscious and continuous effort to collaborate with all groups and agencies working in this field. The aim of the program is to complement

on-going activities, to stimulate and recruit more interest -- neither to go it alone nor to compete with others active in the field. Advantage is therefore taken of the position of the World Health Organization, as an association of over 150 member states already engaged in collaborative efforts relating to health in many countries. One important issue in this regard is the role of the pharmaceutical industry. The following quotation from an earlier policy document is relevant: (from TDR/PK/76.1 Aims and Attributes of the Special Programme)

> "WHO has always had good relations with the pharmaceutical industry, especially at the technical level, where continuous communication exists between those sections of WHO concerned with the control of parasitic diseases and the representatives of industry concerned with the research and development of pharmaceuticals and pesticides."
>
> "There is no substitute for the facilities and expertise of industry in the search for new chemotherapeutic agents to control those parasitic diseases which concern the Special Programme. On the other hand, WHO can provide facilities for the clinicopharmacological evaluation of new drugs, thereby demonstrating to industry that an outlet exists for their products, and at the same time minimizing delay between pre-clinical experimentation and clinical use."

In pursuance of this policy, collaboration with the industry has been sought in various components of the program, and the program is identifying useful modes of collaborating with industry. Four main mechanisms are in effect:

- participation by industry-affiliated scientists in Scientific Working Groups;
- provision of agents for screening;
- technical services provided under contract; and
- clinical evaluation of new drugs and vaccines.

Currently some 30 scientists associated with 16 pharmaceutical enterprises are members of various Scientific Working Groups, either as participants at meetings or as recipients of research grants.

By the end of the second year of the operation of the Program, 29 research projects were in progress; eight others were under discussion, and three had been completed. This substantial increase in the involvement of the pharmaceutical sector is very encouraging.

The contractual arrangements with industry are being designed in such a way as to protect the public interest and to ensure that any products developed with support from Special Program investments will be made available to affected populations on the best possible terms.

What of the future? The early experience from this Program has confirmed the need for an even greater involvement of the pharmaceutical industry in order to achieve the objectives of the Program. For example, if the screening tests for a macrofilaricide yield useful leads, the further testing and development of such compounds would require the resources of an interested pharmaceutical company. Close collaboration between industry and the Program will facilitate evaluation of promising compounds in laboratory animals and in man.

## Research Capability Strengthening

Intimately related to the search for new tools is the equally important interdependent objective: development of manpower and strengthening of research institutions in the endemic countries of the tropics. The aim is to strengthen the research capability of these countries, and to assist them in achieving self-reliance. In the context of the Special Program, self-reliance for any country includes both the competence to tackle significant national problems and the ability to work to best advantage on their solution with scientists from outside the country.

To this end, the Special Program has established a Research Strengthening Group (RSG) and its Executive Sub-Group (ESG), whose objectives are to:

- strengthen research and training institutions in these countries, so that they can better respond to national and Special Program needs;
- support training of persons from the tropical countries to help meet national manpower needs; and
- contribute to a rapid transfer to the affected countries from the industrialized world of the knowledge, technology, and skills relevant to their health objectives and within the sphere of the Special Program.

The institution strengthening and training activities of the Special Program will in return ensure an increasing involvement of scientists from the tropical countries in the Program's research and development.

Strengthening of the research capability of affected countries is also a particularly relevant component of collaboration with the

pharmaceutical industry. One important constraint in development of new compounds for tropical diseases is the lack of suitable facilities for evaluation of these new products. The training and institution strengthening component of the Program should help in overcoming this obstacle. Already, suitable centers in endemic areas are being equipped, and their scientists are being trained so that they can increasingly participate in clinical pharmacology and field trials of new agents. Involvement of scientists in endemic countries in definition of specifications of the new tools and in their evaluation will promote more effective and more extensive use of any new technology that may emerge. Furthermore, promotion of epidemiological and field research activities in affected countries will increase awareness of the nature and extent of the problems and demonstrate how available technology can be used to best effect.

## Other Relevant WHO Programs

The Special Program for Research and Training in Tropical Diseases must not be viewed in isolation from other WHO acitivities with regard to control of these and other diseases in the tropics. This research program is one among several efforts being made to provide new technology for dealing with problems in developing countries. It should be seen in the context of other major programs such as the Expanded Program of Immunization, which aims at reducing morbidity and mortality from diptheria, pertussis, tetanus, measles, poliomyelitis, and tuberculosis by providing immuni zations against these diseases for every child in the world by 1990. Similar action programs exist or are being developed for control of diseases prevalent in tropical countries.

In addition to the six diseases of concern to the Special Program, WHO is developing, in close collaboration with UNICEF, a program on Diarrheal Diseases Control with an immediate objective to reduce diarrhea-related mortality and malnutrition by implementation of oral rehydration therapy. Research is an essential component of the program to to improve and develop new tools for better treatment, prevention, and control of these diseases. The long-term objective will be prevention and control of these diseases by ensuring adequate sanitation and water supply and improved child care practices.

## Conclusion

The Special Program is now at the period of early growth and development. Further expansion is envisaged during the next few years. But later on the addition of new programs will be balanced by completion of old ones and rejection of unproductive approaches. Even at its highest level of input, the direct contribution of the Special Program to research and training in tropical diseases will be small as compared with the urgent needs. The logical role of the Program is to stimulate

efforts of governments and other agencies, to complement and coordinate those efforts, and to seek out and identify new ideas that deserve attention. Its ultimate goals can be realized only through effective collaboration with national authorities and their institutions and scientists; with the pharmaceutical industry; and with other agencies that are tackling the difficult problems posed by these tropical diseases.

Full documentation on the Program, its content, organization, and operation, is available to interested scientists, as is information on procedures for grant applications, for making a research proposal, and the relevant forms for submitting applications for grants and proposals.

A Newsletter is published periodically to provide interested scientists and institutions with information on the progress and plans for research in the six diseases and trans-disease areas covered by the Special Program. Specific information on the gaps that the Program seeks to fill in the relevant research topics may be obtained on request to the Office of the Director, Special Program for Research and Training in Tropical Diseases, World Health Organization, Geneva, Switzerland.

# THE UNITED STATES PHARMACEUTICAL INDUSTRY

Lewis H. Sarett

The pharmaceutical industry is unique in its research and development capability. The Third World is overwhelmed by the dimensions of its health problems. It probably is inevitable, therefore, that persons concerned with the agonizing plight of the third-world nations have searching questions to put to the industry. Why is your attention so strongly focused on the health needs of the rich nations? What are you doing for the poor? Why do you not do more? Given the insistent nature and the frequency of such questions, I appreciate this opportunity to provide a perspective that, I hope, is devoid of emotion but not of compassion.

I'll shortly get down to specifics. But first let me suggest that because of the way the problem is often described, industry usually finds itself playing against a stacked deck.

WHO can say with very little fear of contradiction that only 3 percent of the funding for biomedical research throughout the world is directed to diseases that afflict the poor nations of the tropics. The implication is that the other 97 percent of such research is oriented to the rich. But a moment's reflection makes it clear that there is a vast overlapping segment from which everyone -- rich and poor -- stands to benefit. When my company developed the first commercial measles vaccine, we certainly were not thinking in terms of "rich world/poor world". Yet we were well aware that measles was, and is, a major killer of undernourished and unprotected populations.

Diseases lend themselves poorly to classification along political or economic lines. To mention another example, demographic studies show, hypertension to be widespread in tropical Africa. Yet hypertension is not a tropical disease because it is not exclusive to the tropics.

What we are talking about today, as we all recognize, is research towards therapeutic agents for diseases that are uniquely tropical in their distribution ... or, at least, endemic in the poor world. To keep the record straight, residents of the tropics stand to benefit

greatly from the general R&D effort now being undertaken by industry. In fairness, the work that is being done in tropical medicine per se should be seen as "in addition to" all the work that has application both to the tropics and to the temperate zones. I am not trying to absolve industry from the role in tropical-medicine research that its unique expertise imposes. What I am saying is that, as things now stand, the score is not 97 to 3.

The organizational framework of current programs in the United States pharmaceutical industry that could have application to the Third World varies widely. Within it, you can find examples of almost every conceivable form of organizational accommodation. Thus, several intramural research projects with the necessary efforts in chemistry and bioloare supported by industrial laboratories in the traditional way. There are industrial research contracts with government agencies such as AID or WHO supplying the funds. There are cooperative projects jointly carried out between industrial groups and academic experts. And there are examples of cooperation between local physicians within an LDC and representatives of industrial medicine, frequently with the assistance of the national ministry of health.

The distinguishing characteristic of research by the pharmaceutical industry is that it is multidisciplinary, involving many subdisciplines of chemistry, biology and medicine. Just as this synergy has been the key to research success by indsutry, it promises to be the key to further progress in developing new therapies for tropical medicine. It may be that cooperative efforts to share expertise can be useful in this area with something less than the "critical mass" of research competence that is the hallmark of the major innovative industrial laboratories today. It may be that a handful of advisors from industry -- sharing the knowledge gained by years of experience -- can help to orient indigenous programs to give them a much better chance of success. I am thinking in particular of programs such as that now being pursued by WHO to exploit to the fullest potential native plants as source materials for medicines. Such research may not be the cutting edge of medical science. But as a practical approach to finding ways to help very poor nations get workable medicines for common conditions, the idea is going to be pursued. If scientists from industry can help with advice and technical know-how, other things permitting, I believe that they should be encouraged to do so.

It may be that the recently announced Foundation for International Technological Cooperation will have a role to play here. Its orientation, if I understand correctly, is not merely to the very poor nations, but also to so-called "middle tier" countries, such as Mexico, Iran, and Brazil. It may well be that the Foundation -- or comparable organizations -- will act as catalysts to facilitate communication and synergize the efforts by those with a role to play in creating new medicines, including industrial scientists, and by the multitude of nations that need them.

Now, however, I would like to examine more specifically research projects targeted at Third-World diseases that are currently being undertaken by the United States pharmaceutical industry. As the source of my data, let me acknowledge the fine cooperation of the research directors of 15 leading members of American industry, who provided information about the activities of their organizations. This sample is considerable when you consider that, while the annual research budget of the 132 members of the Pharmaceutical Manufacturers Association is about $1.3 billion, 20 percent of the member companies conduct about 80 percent of the drug research and development. Additionally, I have made use of a recent survey carried out by the PMA itself, and I should qualify how I have used these data. Twenty-one companies replied that they were currently doing research in one or more areas of tropical medicine, and the same 21 indicated that they have done such work in the past decade.

With regard to specific diseases, the breakdown does not distinguish between current programs and programs that, while active in recent years, may have been discontinued. No doubt a number of companies have reduced their investment in this type of research. Notwithstanding, the survey at least gives an indication of how the work is subdivided within the American component of the pharmaceutical industry. It is in this context that I am using the data. So, while this panoramic view cannot pretend to be completely comprehensive, it should at least reflect major trends.

To facilitate organization, let me discuss first the status of work with regard to the six diseases identified by WHO as prime targets for major efforts in the developing world. These are malaria, schistosomiasis, filariasis, leishmaniasis, trypanosomiasis, and leprosy.

It is important to recognize that, for each of these scourges, medications already exist and which, for many patients, are effective -- if not ideal. In each of these categories, new products have been forthcoming over the past several decades. So, any impression that the pharmaceutical industry has been indifferent to the needs of the victims of these illnesses is demonstrably wrong. A major problem is that -- for comprehensible reasons -- existing medicines are grossly underused in nations where they could be of the most value. This, of itself, is hardly an incentive for industry to pursue the quest of trying to find improved medications. Yet work is going forward in each of these areas.

Parke-Davis, with AID contracts, is studying an immunological approach to malaria and working on cell cultures of malaria parasites. Upjohn is collaborating with investigators in Brazil in the evaluation of an antimalarial agent that came as a spin-off from an antibiotic program. In the PMA survey, some 14 companies report work on malaria. Many companies have provided compounds for screening in the Walter Reed antimalarial program.

Eleven companies report projects in the area of schistosomiasis. Several newer agents exist. Sterling reports that between 5 and 8 percent of its research budget is directed to parasitology, including work in schistosomiasis and amebiasis. Several other companies also have important programs in the parasitology field, which may have analogous applications. It is important to keep in mind that pharmaceutical research is by no means limited to American companies, and we shortly will be hearing about work in the laboratories of European-based companies.

Seven PMA-member companies report work in filariasis. Parke-Davis has a $155,000 contract with WHO for the synthesis of antifilarial drugs.

Parke-Davis also has a $50,000 contract with the Army Medical Command for work on leishmaniasis, a research area where six PMA companies report activity. Squibb is collaborating with WHO to supply a compound that will probably be first tested in Africa. Merck has an active program against trypanosomiasis. The development of nifurtimox by a European company (Bayer) has provided new therapy against Chagas' disease. American companies had also worked in this area.

Leprosy, the only one of the six WHO-priority diseases that is not vector-borne, is listed as the subject of R&D work by six PMA companies. Several new therapeutic approaches are in use or under investigation.

When the vectorand fecally-borne diseases are considered as public health problems, medicines are often at best partial and unsatisfactory answers. The provision of adequate and safe water supplies and a more healthful environment can do much more to erase problems at their source. The broad-based nature of the challenge is clearly recognized, as the WHO/ UNICEF primary health care declaration from Alma Ata attests.

Among the fecally-borne diseases, nine companies report work on typhoid and seven on cholera. Thirteen companies report work on infectious diarrheal diseases, and fifteen on intestinal parasitic diseases. I have already mentioned Sterling's work in amebiasis, and Pfizer has a program on helminthiasis. In passing, I might point out that our company's product for human helminthiasis evolved from earlier and highly successful work to develop anthelimintics for use in animals. I mention this as an additional example of how misleading it can be to try to isolate as a separate entity the work that is being done by industry on tropical diseases. Wyeth also has a program on antiinfective agents.

ALZA has a half-million dollar program against trachoma, and Merck is also working in this field. With onchocerciasis, ALZA is investigating new systems for the delivery of medications.

In the cancer area, Bristol and the National Cancer Institute are

jointly developing neocarzinostatin. The agent is active against hepatoma, which is relatively common in Africa. Viral hepatitis is also known to be a precursor of hepatoma. A vaccine is being developed in our laboratories and at NIH.

In some cases, the special conditions of the tropics require innovations in established therapy and preventive medicine. Measles vaccine, for example, is equally efficacious wherever it is used. But the vaccine developed by SmithKline for transportation and storage under relatively primitive conditions is intended to be particularly useful in remote areas of tropical countries.

Tuberculosis, not a tropical disease *per se* but a scourge in primitive and impoverished societies, is addressed in work at Lederle, Sterling, and Merck. Very preliminary work with one of Merck's new antibiotics, cefoxitin, has shown promising results. Several companies, including Merck, are attacking gonorrhea -- again of great importance in the tropics -- and Merck has a vaccine under development. Sterling has an antigonorrhea agent undergoing clinical evaluation.

Reed and Carnrick has a project in Nicaragua, the Dominican Republic and Venezuela against lice and scabies, conditions that, if not tropical, are particularly prevalent in the tropics.

In the area of fertility control, of critical importance to the Third World, Upjohn is collaborating with WHO in the evaluation of a once every-three-months injectable contraceptive. Pfizer, in collaboration with the German Schering Company, is working to develop a prostaglandin for fertility control. ALZA is collaborating with WHO in fertility-control work, and Wyeth is also active in this field.

In summary, the programs of the American pharmaceutical industry directed to the health problems of the developing world are of long standing. They represent an investment of many millions of dollars and a commensurate deployment of manpower. At the same time, and in their totality, they are only a small component -- almost certainly less than 5 percent -- of the overall R&D effort of the industry.

The low figure, as I have tried to point out, is misleading in terms of the benefits that the Third World can expect to derive from the industry's overall effort. The great amount of work that is being done on infectious diseases alone, while its prime target is bacterial illness, does lead to agents that are useful against such diseases as malaria, leprosy, and tuberculosis. Moreover, basic studies in many laboratories intended to elicit better understanding of disease processes and drug actions have application across the board in all areas of therapy.

As for research specifically targeted to the Third World's particular health problems, it is very clear that the magnitude of the effort

has been decreasing over the past decade. Projects have been dropped or cut back in most, if not all, of the laboratories whose directors provided me with information. The reasons for this are of great interest and concern to this group. They will be reviewed later by Dr. Wescoe.

# THE EUROPEAN PHARMACEUTICAL INDUSTRY

Ernst Vischer and Rudi Oberholzer

The chemical and pharmaceutical industries in European countries have always had a relatively small domestic market. It was therefore essential for them to expand their trade beyond their own national boundaries and become active throughout the world. At an early stage of expansion, their commercial relations also extended to the so-called Third World, and they were confronted with the problems indigenous to these developing countries. This situation provided the impetus for certain specific activities of the European pharmaceutical industries of which the following is a short account, with examples drawn from research, therapy, pest control and eradication, health education and training, and finally technical assistance.

## Research

As to research, the discussion is confined to tropical diseases. One should, however, not forget that very common illnesses such as influenza, the common cold, rheumatism, and especially the bacterial infectious diseases and their sequelae are at least as frequent in the developing countries as in developed countries. Drugs effective against these universal diseases are therefore also important in the less industrialized world, and contribute widely to the pharmacotherapeutic part of the total health-care system.

In respect to tropical diseases, it is generally accepted that medicaments are now available to combat many of them. Some of these drugs have limitations. It has repeatedly been suggested that the pharmaceutical industry makes too little effort to develop new and better therapeutic agents. That is only partially true. A survey 1/ performed among 15 research-oriented European pharmaceutical companies 2/ has shown that seven are actively engaged in this type of research. Their research efforts cover, with varying emphasis, all six tropical diseases emphasized by the WHO 3/ (Table 1). The budget allocated by these seven companies to this field of research came to about U.S. $40 million, and the trend indicates that this amount will increase in the years to come.

TABLE 1. NUMBERS OF EUROPEAN COMPANIES WITH MAJOR ACTIVITIES IN TROPICAL DISEASES AND FAMILY PLANNING

| | |
|---|---|
| Malaria | 4 |
| Schistosomiasis (Bilharziasis) | 4 |
| Filariasis | 4 |
| Trypanosomiasis | 3 |
| Leishmaniasis | 2 |
| Leprosy | 2 |
| Hookworm | 2 |
| Family Planning | 2 |

Several European companies have established research organizations in Third World countries, particularly in India. The most representative one is probably the CIBA/GEIGY Research Center in Goregaon near Bombay with a total staff of 260, of which 35 are scientists.

The yield from these research efforts has been rather meager, and no sensational developments have taken place in the last few years. In view of the particular difficulties besetting this type of research, and taking into account the high expectations and the requirements for such newly developed drugs, this fact is not too surprising.

On the other hand, we know that several existing drugs could be used to greater benefit and more economically in developing countries if the schemes for their application were better adapted to the country's specific requirements and conditions, and if the country's health infrastructure were of a higher standard. It therefore seems logical that, in parallel to our research efforts, the proper use of existing drugs should be further explored. Here is a broad field where the industry, with its know-how, can be of assistance in improving therapy.

## Therapy

As a first example of cooperation towards this end, there is a joint project undertaken by the Government of Indonesia, the Indonesian

Army, and our own company. Indonesia still has a high rate of tuberculosis, and the government was therefore interested in a project to compare diverse schedules for oral treatment with various antituberculosis drugs aiming -- and that was the important point -- at achieving increased patient compliance. At the same time, emphasis was placed on health, education, and on the establishment of centers for diagnosis and therapy. Industry's participation consisted of assisting in the design of the trial plans, providing some diagnostic facilities, analyzing the data, and offering drugs. This project is running satisfactorily and the results obtained so far are promising, both from the medical and from the economic points of view.

A second example is a project in Senegal which WHO undertook in collaboration with the Sandoz Institute. The aim of this project was control of venereal diseases. Five centers for early diagnosis and treatment of gonorrhea, syphilis, and trichomonas infections were established. Further, ways and means for assuring effective and appropriate information to and education of the public were studied to achieve prevention or early care. The contributions of industry were financial and technical, but the latter aspect was probably more important. It consisted in participating in the planning, organization, and evaluation of the project, including the research component. In 1978, operation of the project was taken over by the Senegal Government. The Sandoz Institute still participates in a consultative capacity.

## Pest Control and Eradication

The aim of another joint project, an experiment known as the Lower-Mangoky Project, was to control and possibly eradicate schistosomiasis in a well-defined region in Southwest Madagascar.4/ It was based on an agreement between the Malagasy and the Swiss governments.

By various means, this previously underpopulated area has been turned into arable land particularly suitable for the cultivation of rice and cotton. It attracted many farmers from other parts of the country. Soon it became apparent that the incidence of schistosomiasis was increasing tremendously, due both to the new arrivals and to the newly constructed irrigation system.

In order to check this development, a dual approach was chosen, directed on the one hand against the vector snail and on the other hand against the parasite. Execution of the project was entrusted to the Swiss Tropical Institute, which in turn enlisted the assistance of Shell and CIBA as suppliers and technical consultants for the molluscicide, Frescon, and the chemotherapeutic agent, niridazole, respectively.

The work included making an accurate epidemiological survey in an area of 25,000 acres, and the medical examination of the entire population of about 11,000. Furthermore, the distribution and movements of

the vector snail in the watercourses had to be determined.

On the basis of the data obtained, a small team of doctors and parasitologists went to work. The infected population was treated with niridazole, and Frescon was applied simultaneously to the irrigation system.

After two years, the rate of infection had fallen from 15-50 percent to 2 percent. The annual costs incurred in achieving protection were about 23 Swiss Francs per person. For maintaining this level of protection, the cost was 10-12 Swiss Francs. In 1971, the entire project and the responsibility for its further pursuit were handed over to the Malagasy Government.

Unfortunately, in the continuation of the work, the necessary perseverance and know-how were lacking. Today the disease is no longer under control, and irrigation systems are once again breeding places for the molluscs. Despite this deplorable turn of events, the project showed that it is possible to eradicate schistosomiasis from a particular area by properly applying all the necessary measures, and that the costs of doing so are not unreasonable.

## Health Education and Training

Training has been going on ever since the multinational companies established their own subsidiary companies in developing countries. Training is offered for the benefit of their own staffs, and also for trainees nominated by government authorities. The extent of these training programs is not often realized, and a survey was therefore carried out among 15 European pharmaceutical companies.1,2/ It showed that 1,976 nationals of Third World countries were trained by these 15 companies within the past two years. The average is 132 trainees per company, with a predicted increase of 15-20 percent in the years to come. Two-thirds of these trainees received instruction for up to two weeks, more than one-fourth obtained training for two weeks to three months, and the remaining 7 percent for over three months. The main fields of training were in production (45 percent), quality control (39 percent), and storage and distribution (16 percent). The majority (83 percent) of the trainees were employees of the respective subsidiary companies. The 329 (17 percent) who were not company employees were trainees nominated by the authorities. The total costs incurred in these training programs approximated U.S. $1,000 per man-week.

Industry can also take an active part in other areas of health education and training, such as instruction of medical assistants. A paramedical staff is most important for development of a health-care system in rural areas of developing countries. A training center for such assistants was established in Ifakara, Tanzania, by the Swiss Tropical Institute. It was mainly financed by the Basle Foundation for

Aid to Developing Countries, a foundation created in 1961 by the pharmaceutical companies of Basle. To date, approximately 770 trainees have gone through this school. In 1978, the center was handed over as a gift to the Tanzanian Government, and there is good reason to hope for the successful continuation of its valuable activities.

A further example is a school for laboratory assistants for public health services in Djakarta, Indonesia. This school was established jointly by the Indonesian Government and CIBA-GEIGY to fill a major gap in local education, and to provide various government agencies with qualified technical staff. The school provides an 18-month course and can accommodate 24 students.

The Indonesian government has donated the necessary land, the building, and the general infrastructure. CIBA-GEIGY's contribution included the technical equipment and installations, their servicing, and teaching materials. Furthermore, CIGA-GEIGY placed two qualified teachers at the disposal of the school for an initial period of two years. After two years, the entire project was transferred to the Indonesian Ministry of Health, which is now responsible for the school. The two best qualified students in the first couse were appointed as teachers, and the school is now functioning well. Twelve to fifteen students graduate each year, and they have no difficulty in getting jobs, mostly in government laboratories; none of them work for CIBA-GEIGY.

## Technical Assistance

Before concluding, a few comments should be made about the problems of technical assistance. This is a very tricky problem, indeed, because sometimes technical assistance is taken to mean imparting or receiving technological know-how at no cost. Such assistance agreements can only be successful if they are of mutual interest to both parties; namely, the pharmaceutical industry and the developing country. One such example has recently been published. This concerns collaboration between the government of Algeria and the Behringwerke, a subsidiary of the Hoechst Company of Germany. On the one hand, Behringwerke are enabling Algeria to take up production of vaccines; on the other hand, the Algerian government has undertaken to buy quantities of vaccines from Germany. The assistance rendered by the Behringwerke includes passing on the technical know-how for construction and operation of a production plant for vaccines, anti-sera, and diagnostics. It also entails the training of the necessary Algerian personnel.

This is a fine example of a novel approach towards technical cooperation between a developing country and industry.

Two additional examples of technical assistance in the field of distribution of pharmaceuticals are worth citing. In many developing

countries, this is a very serious problem. The Sandoz Institute has recently entered into collaboration with the government of Mali. The project is concerned with evaluation of the management and logistic aspects of supply and distribution of drugs in a rural area with a population of 20,000. A similar project, also concerned with distribution of drugs, is being undertaken by the Sandoz Institute in a rural area of Upper-Volta.

These few examples of specific activities of European pharmaceutical companies in developing countries show that efforts made by industry towards development of health care in the Third World are probably greater than usually assumed. Yet more could clearly be done. However, not all projects are running as smoothly as those mentioned, and it is sometimes not so easy to establish meaningful cooperation between developing countries and industry. To achieve optimal conditions for the realization of such joint projects, the following points should be taken into account.

First: The real needs of the country in question have to be properly evaluated and defined. It is essential that both partners agree on the goal of the project and stick to it.

Second: There should be a minimum, proper, and functional health-care system and health-care infrastructure in the country; at least, one should be envisaged. Obviously, general health problems cannot be solved merely by applying or supplying medicaments.

Third: A certain level of general education and discipline should exist, together with a willingness to cooperate.

These three points actually call for a competent public administration of at least a minimum intellectual standing, aware of the problems of its country and able to set logical priorities.

Fourth: All joint programs between developing countries and industry depend on two conditions; namely, a sound financial basis and meaningful technical input. Where financing is concerned, it must be realized that the resources of the pharmaceutical companies are limited. They are not and cannot be charitable organizations. Nor, indeed, is charity what developing countries want or expect. Therefore, the necessary financial means must come from other sources. With respect to technical input, however, the pharmaceutical industry, with its intimate knowledge of the products, can contribute much expertise in research and development, in the production and formulation of pharmaceuticals, and in good manufacturing practices and quality control.

Generally, the most important factors for successful cooperation are mutual trust, respect, and mutual understanding. The less administration and red tape, and the fewer politics that are involved, the better.

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# CURRENT PROGRAMS IN UNITED STATES ACADEMIC LABORATORIES FOR DEVELOPMENT OF AGENTS AGAINST SELECTED INFECTIOUS DISEASES

William S. Jordan, Jr.

In the United States, support for biomedical research relating to the major infectious diseases of developing countries is funded by components of three cabinet-level departments:

- Department of Health, Education, and Welfare
  - National Institutes of Health
  - Center for Disease Control
  - Food and Drug Administration/Bureau of Biologics
- Department of Defense
  - Army
  - Navy
- Department of State
  - Agency for International Development

The missions and objectives of these federal agencies are quite different from each other; and the nature and extent of their commitment to studies on diagnosis, treatment, and prevention of infectious and parasitic diseases of tropical and subtropical countries vary accordingly. The National Institutes of Health (NIH), through extramural grants and contracts, support much of the basic research in the nation's academic laboratories. Because most of the extramural funds are allocated in response to investigator-originated proposals, the NIH research grant portfolio is shaped by the interests of university scientists. In contrast, the medical research programs of the armed forces are deliberately designed to deal with those illnesses that threaten the effectiveness of military personnel wherever they may be. The Agency for International Development (AID) and the Center for Disease Control (CDC) also target their research programs and direct support

for the control of specific diseases. The Bureau of Biologics (BoB) serves all groups as it monitors the development of vaccines and other biologics in discharging its licensing and regulatory responsibilities. The Bureau of Drugs, also a part of the Food and Drug Administration, fills the same role for pharmaceuticals, but conducts no research other than regulatory studies in its own laboratories.

Like NIH, all of these agencies fund contracts to support research in academic laboratories. With the exception of AID, they also maintain their own research facilities, both at home and abroad. In the tradition of Walter Reed and William Gorgas, military medicine continues to make valuable contributions to international health. At home, Army investigators recently pioneered the development of meningococcal vaccine; abroad, Navy investigators last year assisted in the study of an epidemic of Rift Valley Fever in Egypt. However, with the rising tide of nationalism and anti-colonialism, military laboratories in foreign countries may find their welcome disappearing, as may other United States research centers. As emphasized by the World Health Organization, the establishment of a true partnership is considered essential to successful collaboration. Such collaboration exists in Kuala Lumpur, Malaysia, where an Army laboratory and an NIH-sponsored International Center for Medical Research, directed by the University of California, share adjacent facilities to their mutual benefit and that of their host, the Institute for Medical Research. The research summarized in this report is conducted at locations such as these, in many university laboratories, and at the other federal research facilites listed under their respective departments.

Estimates of United States Government financial support (and indirectly of the extent of effort) to develop agents and techniques for controlling specific diseases or disease categories were prepared using data provided by the agencies involved. Of particular interest was the amount of research support directed toward the six diseases targeted by the WHO Tropical Disease Research Program, and toward the enteric infections of WHO's new Diarrheal Diseases Program (Table 1). It is frequently emphasized that inhabitants of developing countries do not have only malaria or only intestinal, urinary, or ocular parasites, or leprosy; they often have two or three of these diseases at the same time, and sometimes more. To this list of "tropical diseases" others may be added that occur throughout the world. The control of such diseases -- exemplified by measles and poliomyelitis -- is also vital to the well being of developing countries. Accordingly, data were received indicating support for other selected diseases (Table 3). The data in all tables except Table 2 reflect to the nearest thousand the estimated total expenditures (direct and indirect) for fiscal year 1978 related to the disease categories and to the research areas listed. The omission of a disease category in a later table for a particular agency means that the agency reported no current work in this area. Obviously, other diseases are being studied that were not listed. The data do not include support for United States academic laboratories provided by the

TABLE 1. NATIONAL INSTITUTES OF HEALTH EXTRAMURAL RESEARCH SUPPORT (Estimated) FOR SELECTED TROPICAL DISEASES (FY 1978)

| Infectious Disease | Biological Control | Vaccines and Immunity | Chemoprophylaxis and Treatment | Improved Diagnosis | All Other Research | Total |
|---|---|---|---|---|---|---|
| Total | 806,000 | 2,181,000 | 1,484,000 | 582,000 | 4,082,000 | 9,135,000 |
| Filariasis | 112,000 | 77,000 | 132,000 | 27,000 | 429,000 | 777,000 |
| Leishmaniasis | | 238,000 | 122,000 | 86,000 | 118,000 | 564,000 |
| Leprosy | | 219,000 | 271,000 | 223,000 | 107,000 | 820,000 |
| Malaria | 476,000 | 286,000 | 268,000 | 10,000 | 252,000 | 1,292,000 |
| Schistosomiasis | 218,000 | 292,000 | 285,000 | 109,000 | 957,000 | 1,861,000 |
| Trypanosomiasis | | 194,000 | 32,000 | 103,000 | 438,000 | 767,000 |
| Subtotal | 806,000 | 1,306,000 | 1,110,000 | 558,000 | 2,301,000 | 6,081,000 |
| Enteritis | | 875,000 | 374,000 | 24,000 | 1,781,000 | 3,054,000 |

National Science Foundation, WHO, or private foundations. Further, it is emphasized that the estimates are just that -- estimates. Agency budgets do not lend themselves to this kind of breakdown, and the placement of a research project in one category or another sometimes forces an arbitrary designation.

## Department of Health, Education, and Welfare

### National Institutes of Health

The extramural programs of the National Institutes of Health support research in academic laboratories, with the bulk of the funds for infectious diseases coming from the National Institute of Allergy and Infectious Diseases. Thus, the data in Tables 1-3 reflect the interest and judgments of university investigators, including those at the International Centers for Medical Research.

The International Centers for Medical Research (ICMR) Program was established by NIAID in 1960 to advance the status of the health sciences in the United States through cooperative endeavors with other countries. An ICMR is a discrete research organization sponsored by a medical and/or public health school which provides a stable base for research and training through the development of research centers overseas. Collectively, ICMR units have served as a national resource in creating a pool of investigators knowledgeable in treating tropical diseases and in stimulating young investigators to seek careers in international or geographic biomedical research. In addition to the ICMR in Kuala Lumpur, three others are located in Lahore, Pakistan (University of Maryland), Cali, Colombia (Tulane University), and Panama (Johns Hopkins University).

One other overseas United States supported tropical disease research laboratory that merits special mention is the Gorgas Memorial Laboratory (GML) in Panama, which just celebrated its fiftieth anniversary. Included among its many current programs is the testing of antimalarial compounds in a valuable colony of owl monkeys. Separately chartered and supported by its own Congressional appropriation, the GML is administered through the Fogarty International Center of NIH. Accordingly, for convenience, its expenditures were added to those of the NIH in Tables 1 and 4.

Of the parasitic infections (Table 1), schistosomiasis and malaria attracted the greatest effort of extramural scientists; equal amounts of money were devoted to trypanosomiasis and filariasis. Within the developmental categories for six WHO-targeted tropical diseases, nearly equal amounts were expended for vaccines and related immunological studies and to a search for better chemoprophylactic and therapeutic agents. This latter category, of particular concern to this Conference, consumed little more than a million dollars. Indeed, exclusive of the

TABLE 2. NATIONAL INSTITUTES OF HEALTH EXTRAMURAL SUPPORT FOR RESEARCH AND TRAINING RELATED TO PARASITOLOGY, MEDICAL ENTOMOLOGY, AND LEPROSY (FY 1978)

| | Number | Amount |
|---|---|---|
| Total | 207 | $11,887,583 a/ |
| Individual Grants | 176 | $10,382,023 |
| Program Grants | 2 | 317,102 |
| Contracts | 7 | 484,485 |
| Training Grants | 9 | 552,573 |
| Fellowships | 13 | 151,400 |

a/Exclusive of $2.4 million for ICMRs and $341,000 for GML.

ICMRs and GML, NIH funded only 16 projects for pharmaceutical development, as follows: schistosomiasis, 8; malaria and leprosy, 3 each; and filariasis, 2. Table 2 identifies the nature and number of awards for research and training in parasitology, medical entomology and leprosy.

Although benefits from the expenditures summarized in Table 3 may extend to all countries, the distribution of effort versus the diseases listed reflects the perception of the United States academic community of national needs and research opportunities. Apart from basic research, the major emphasis has been on vaccine development. Of more than 13 million dollars only two million were devoted to chemoprophylaxis and treatment, and more than three quarters of this amount was used for development and testing of antiviral substances.

The intramural laboratories of NIH, located on the Bethesda campus in Maryland and at the Rocky Mountain Laboratory in Hamilton, Montana, are very similar to those in academic medical centers or research institutes, in that the investigators, once recruited in a broad general area, are free to select their own research projects. Studies of those

TABLE 3. NATIONAL INSTITUTES OF HEALTH EXTRAMURAL RESEARCH SUPPORT (Estimated) FOR SELECTED MAJOR DISEASES (FY 1978)

| Infectious Disease | Biological Control | Vaccines and Immunity | Chemoprophylaxis and Treatment | Improved Diagnosis | All Other Research | Total |
|---|---|---|---|---|---|---|
| Total | 545,000 | 3,786,000 | 1,970,000 | 1,515,000 | 5,400,000 | 13,216,000 |
| Bacterial Meningitis | | 736,000 | | | | 736,000 |
| Gonorrhea | | 170,000 | 198,000 | 872,000 | 638,000 | 1,878,000 |
| Pneumococcal Infections | | 722,000 | | | | 722,000 |
| Tuberculosis | | 285,000 | | | 281,000 | 566,000 |
| Mycoses | | 405,000 | 305,000 | 142,000 | 297,000 | 1,149,000 |
| Arboviruses | 120,000 | | | 35,000 | 86,000 | 241,000 |
| Herpes viruses (all) | | | 612,000 | | | 612,000 |
| Rabies | 5,000 | 15,000 | | | 20,000 | 40,000 |
| Rickettsial Diseases | | 32,000 | | 16,000 | 297,000 | 345,000 |
| Respiratory viruses | | | | | | |
| Influenza | 420,000 | 970,000 | 450,000 | 125,000 | 1,768,000 | 3,733,000 |
| Other | | 325,000 | | 325,000 | 297,000 | 947,000 |
| Viral Hepatitis | | 126,000 | 405,000 | | 1,716,000 | 2,247,000 |

diseases highlighted in this report are conducted largely in the Laboratory of Parasitic Diseases and the Laboratory of Infectious Diseases of NIAID. The only mandate these intramural laboratories -- and those supported by extramural funds -- have for research related to developing countries is found in Section 2, Clause 1 of PL 86-610: "To advance the status of the health sciences in the United States and thereby the health of the American people through cooperative endeavors with other countries in health research, and research training." Despite the apparent self-serving nature of this legislative language, intramural investigators are studying all of the five parasitic diseases within the current WHO TDR Program, with a major emphasis on malaria, particularly malaria vaccine (Table 4). Studies of schistosomiasis and trypanosomiasis ranked next, with treatment of each of these diseases receiving only modest attention. Overall, less than five percent of expenditures for parasitic diseases were related to pharmaceutical agents.

While enteritis can be caused by a variety of agents (amebae, Giardia, strongyloides, enterobacteria, etc.), the newly recognized rotaviruses and parvoviruses are currently of greatest interest. Techniques developed or refined by NIAID investigators have permitted rapid confirmation of the importance of these viruses as causes of diarrheal disease. The rotavirus group, especially, has been shown to be an important cause of infant diarrhea in both developed and developing countries.

## Center for Disease Control

The CDC has participated in international health activities since its creation as the Communicable Disease Center. From a laboratory base in Atlanta, microbiologists, parasitologists, entomologists, and epidemiologists are increasingly exploiting research opportunities around the world and providing assistance to others in the implementation of control measures. The contributions of CDC staff to the smallpox eradication program reflected this commitment.

In recent years, CDC has contributed epidemic assistance for such diverse problems as meningitis in Brazil, rabies in Mexico, Lassa fever in Sierra Leone and Nigeria, and African hemorrhagic disease in Sudan and Zaire. In 1978, medical epidemiologists or operations officers were assigned to five African countries in addition to those detailed to Somalia for smallpox eradication. For the past five years, CDC has funded and maintained the Central American Research Station in San Salvador, El Salvador. This laboratory has devoted its research effort to three vector-borne diseases: malaria, Chagas' disease, and onchocerciasis. Malaria research is directed to field surveillance and studies of sterilization of the male mosquito as a method to reduce breeding. Expenditures for these and other tropical disease programs are shown in Table 5. At CDC, only six percent of such funds were related to pharmaceutical agents.

TABLE 4. NATIONAL INSTITUTES OF HEALTH INTRAMURAL RESEARCH SUPPORT (Estimated) FOR SELECTED TROPICAL DISEASES AND OTHER MAJOR DISEASES (FY 1978)

| Infectious Disease | Biological Control | Vaccines and Immunity | Chemoprophylaxis and Treatment | Improved Diagnosis | All Other Research | Total |
|---|---|---|---|---|---|---|
| Grand Total | | 1,771,000 | 78,000 | 448,000 | 2,003,000 | 4,496,000 |
| Filariasis | | 84,000 | | | | 84,000 |
| Leishmaniasis | | 31,000 | 4,000 | | 42,000 | 77,000 |
| Malaria | 157,000 | 372,000 | | | 116,000 | 645,000 |
| Schistosomiasis | 39,000 | 202,000 | 22,000 | 23,000 | 99,000 | 385,000 |
| Trypanosomiasis | | 32,000 | 7,000 | 40,000 | 86,000 | 165,000 |
| Subtotal | 196,000 | 721,000 | 33,000 | 63,000 | 343,000 | 1,356,00 |
| Enteritis | | 150,000 | 45,000 | 160,000 | 335,000 | 690,000 |
| Total Tropical | 196,000 | 871,000 | 78,000 | 223,000 | 678,000 | 2,046,000 |
| Rickettsial Diseases | | | | 75,000 | 525,000 | 600,000 |
| Respiratory viruses | | | | | | |
| Influenza | | 469,000 | | 34,000 | 400,000 | 903,000 |
| Other | | 231,000 | | 16,000 | 200,000 | 447,000 |
| Viral Hepatitis | | 200,000 | | 100,000 | 200,000 | 500,000 |
| Total Other | | 900,000 | | 225,000 | 1,325,000 | 2,450,000 |

TABLE 5. CENTER FOR DISEASE CONTROL RESEARCH SUPPORT (Estimated) FOR SELECTED TROPICAL DISEASES (FY 1978)

| Infectious Disease | Biological Control | Vaccines and Immunity | Chemoprophylaxis and Treatment | Improved Diagnosis | All Other Research | Total |
|---|---|---|---|---|---|---|
| Total | 224,000 | 159,000 | 87,000 | 427,000 | 525,000 | 1,422,000 |
| Filariasis | | 50,000 | | 110,000 | 216,000 | 376,000 |
| Leprosy | | 30,000 | 47,000 | 30,000 | | 107,000 |
| Malaria | 110,000 | 67,000 | 40,000 | 237,000 | 309,000 | 763,000 |
| Schistosomiasis | 36,000 | | | | | 36,000 |
| Trypanosomiasis | | | | 20,000 | | 20,000 |
| Subtotal | 146,000 | 147,000 | 87,000 | 397,000 | 525,000 | 1,302,000 |
| Enteritis | 78,000 | 12,000 | | 30,000 | | 120,000 |

The CDC contributes international laboratory assistance as a WHO reference center for 23 different disease conditions while providing technical support and diagnostic services for United States laboratories. For all the diseases listed in Table 6, it spent nearly equal amounts on studies to improve diagnosis and on studies concerned with chemoprophylaxis and treatment. The allocations for individual diseases appear appropriate to need and/or technical development.

### Bureau of Biologics

As a component of the FDA, a regulatory agency, the BoB does not routinely support programs to develop new vaccines. However, several of its staff members have contributed to basic studies of antigens for use in polysaccharide and viral vaccines in recent years. The BoB is primarily concerned with assuring the safety and effectiveness of biological products by control testing and by the development of new and improved test methods for assessing purity and potency (Table 7). It conducts no studies of parasitic diseases or leprosy. Its arbovirus expenditures are virtually all related to yellow fever vaccine.

## Department of Defense

### United States Army

The United States Medical Research and Development Command conducts studies on the prevention, control, and treatment of infectious diseases through an extramural contract program and through intramural programs of the Walter Reed Army Institute of Research, (Washington, D.C.), the United States Army Medical Research Institute of Infectious Diseases (Frederick, Maryland), the Letterman Army Institute of Research (San Francisco, California), the United States Army Medical Bioengineering Research and Development Laboratory (Fort Detrick, Maryland), and the United States Army Institute of Surgical Research (Houston, Texas). As previously noted, field studies are conducted at a laboratory in Malaysia; there are other overseas units in Brazil, Kenya, and Thailand. Although the Army's program is directed toward reducing or eliminating the deleterious effects of infectious diseases on military populations, the benefits derived also can be utilized by the civilian public health community, especially in developing countries. In addition to the work summarized in Table 8, studies of other diseases of special interest to developing countries were supported, including pseudomonas (burns) $1.2 million; plague, $150,000; melioidosis, $150,000.

The Army clearly considers malaria the most important parasitic infection, and the $6.0 million which it devoted to the development of chemoprophylactic and therapeutic drugs for this disease was the largest expenditure of any agency for research on pharmaceutical agents. The majority of these funds supported work by commercial firms. Of the

TABLE 6. CENTER FOR DISEASE CONTROL RESEARCH SUPPORT FOR OTHER MAJOR DISEASES (FY 1978)

| Infectious Disease | Biological Control | Vaccines and Immunity | Chemoprophylaxis and Treatment | Improved Diagnosis | All Other Research | Total |
|---|---|---|---|---|---|---|
| Total | 112,000 | 391,000 | 856,000 | 877,000 | 699,000 | 2,935,000 |
| Bacterial Meningitis | | | 41,000 | 51,000 | | 92,000 |
| Gonorrhea | | | 472,000 | 66,000 | | 538,000 |
| Tuberculosis | | | 310,000 | 181,000 | 195,000 | 686,000 |
| Arboviruses | 84,000 | | | 535,000 | 303,000 | 922,000 |
| Herpes viruses (all) | | | | | 39,000 | 39,000 |
| Rabies | 28,000 | 19,000 | 33,000 | 9,000 | 96,000 | 185,000 |
| Rickettsial Diseases | | | | | 42,000 | 42,000 |
| Respiratory viruses | | | | | | |
| Influenza | | 172,000 | | 12,000 | 12,000 | 196,000 |
| Other | | | | 23,000 | 12,000 | 35,000 |
| Viral Hepatitis | | 200,000 | | | | 200,000 |

TABLE 7. BUREAU OF BIOLOGICS (FDA) SUPPORT (Estimated) FOR MONITORING BIOLOGICAl PRODUCTS AND DEVELOPING TECHNIQUES FOR SELECTED DISEASES (FY 1978)

| Infectious Disease | Safety and Efficacy of Biological Products | All Other Research (Extramural) | Total |
|---|---|---|---|
| Total | 1,934,000 | 424,000 | 2,358,000 |
| Enteritis | 87,000 | | 87,000 |
| Bacterial Meningitis | 205,000 | 24,000 | 229,000 |
| Gonorrhea | 12,000 | | 12,000 |
| Pneumococcal Infections | 93,000 | 59,000 | 152,000 |
| Tuberculosis | 114,000 | 211,000 | 325,000 |
| Mycoses | 114,000 | | 114,000 |
| Arboviruses | 207,000 | | 207,000 |
| Herpes viruses (all) | 59,000 | | 59,000 |
| Rabies | 84,000 | | 84,000 |
| Rickettsial Diseases | 25,000 | | 25,000 |
| Respiratory viruses | | | |
| Influenza | 354,000 | 24,000 | 378,000 |
| Other | 206,000 | 65,000 | 271,000 |
| Viral Hepatitis | 374,000 | 41,000 | 415,000 |

TABLE 8. U.S. ARMY RESEARCH SUPPORT (Estimated) FOR SELECTED TROPICAL AND OTHER MAJOR DISEASES (FY 1978)

| Infectious Disease | Biological Control | Vaccines and Immunity | Chemoprophylaxis and Treatment | Improved Diagnosis | All Other Research | Total |
|---|---|---|---|---|---|---|
| Grand Total | 75,000 | 9,050,000 | 7,350,000 | 700,000 | 4,125,000 | 21,300,000 |
| Leishmaniasis | | 100,000 | 400,000 | 250,000 | | 750,000 |
| Malaria | 25,000 | 825,000 | 5,975,000 | | 250,000 | 7,075,000 |
| Schistosomiasis | | | 275,000 | | | 275,000 |
| Trypanosomiasis | | 675,000 | 200,000 | | | 875,000 |
| Subtotal | 25,000 | 1,600,000 | 6,850,000 | 250,000 | 250,000 | 8,975,000 |
| Enteritis | | 700,000 | | | 650,000 | 1,350,000 |
| Total Tropical | 25,000 | 2,300,000 | 6,850,000 | 250,000 | 900,000 | 10,325,000 |
| Bacterial Meningitis | | 450,000 | | | 225,000 | 675,000 |
| Gonorrhea | | 100,000 | | | | 100,000 |
| Mycoses | | 275,000 | 75,000 | | 125,000 | 475,000 |
| Arboviruses | 50,000 | 3,975,000 | 375,000 | 375,000 | 2,450,000 | 7,225,000 |
| Rickettsial Diseases | | 1,450,000 | 50,000 | 25,000 | 350,000 | 1,875,000 |
| Respiratory viruses | | | | | | |
| Influenza | | 250,000 | | | | 250,000 |
| Other | | 150,000 | | | 50,000 | 200,000 |
| Viral Hepatitis | | 100,000 | | 50,000 | 25,000 | 175,000 |
| Total Other | 50,000 | 6,750,000 | 500,000 | 450,000 | 3,225,000 | 10,975,000 |

other diseases, the Army spent as much on arbovirus infections as on malaria, but with the emphasis being placed on vaccine development at a cost of $4.0 million.

United States Navy

The Naval Medical Research and Development Command and the Office of Naval Research support extramural contract research at university and commercial laboratories. Intramural laboratories are located at the Naval Medical Research Institute, Bethesda, Maryland, and at overseas Naval Medical Research Units in Egypt and Taiwan, the latter with a detachment in Indonesia. In addition to the data in Table 9, the Navy cited expenditures for pseudomonas ($250,000) and relapsing fever ($44,000) as being relevant to developing countries. Included in the various categories in Table 9 are approximately $1.4 million of special foreign currency program (PL-480) funds.

More than three-fifths of the Navy's R&D expenditures were used to study two parasitic diseases, malaria and schistosomiasis. The program for the latter consists of three major parts: (1) epidemiologic studies to determine prevalence and risk; (2) clinical evaluation of anti-schistosome drugs and studies of infections and immune responses in human schistosomiasis, and (3) development of vaccines. Field studies are being conducted in the Far East, particularly Indonesia and the Philippines, and a five-year longitudinal study of about 1200 persons in villages near Luxor, Egypt, is in progress. Human clinical studies are being carried out in Cairo; vaccine research is conducted at the Naval Medical Research Institute. Vaccines found effective in mice are then tested in monkeys. At present, the most promising approach is immunization with (cobalt-60) radiation-attenuated cercariae or schistosomules; immunized animals showed a 50 to 80 percent reduction in adult worm recovery after challenge with virulent cercariae.

The Navy's malaria program in 1978 was focused almost entirely on solving the many technical and theoretical problems that remain before promising beginnings can be translated into a safe and effective vaccine. Navy scientists, along with others, have made encouraging progress toward development of a malaria vaccine, and this is the subject of later general comment. The Navy's approach is based on the fact that the feasibility of a sporozoite vaccine against falciparum malaria has been demonstrated in human volunteers immunized by the bite of x-irradiated infected mosquitoes. The laboratory model being used to study approaches to the development of methods of treating mosquitoes to obtain the maximum yield of sporozoites involves Anopheles stephensi mosquitoes, Plasmodium berghei, and Swiss mice. In the process of these studies, progress has been made toward development of a highly specific inhibition test employing rabbit anti-sporozoite antiserum and fluorescein-labelled goat anti-rabbit IgG. If this could be converted to an ELISA test, it would present a valuable epidemiological tool and provide

TABLE 9. U.S. NAVY RESEARCH SUPPORT (Estimated) FOR SELECTED TROPICAL AND OTHER MAJOR DISEASES (FY 1978)

| Infectious Disease | Biological Control | Vaccines and Immunity | Chemoprophylaxis and Treatment | Improved Diagnosis | All Other Research | Total |
|---|---|---|---|---|---|---|
| Grand Total | 60,000 | 2,721,000 | 766,000 | 637,000 | 898,000 | 5,082,000 |
| Malaria | 60,000 | 1,410,000 | | | | 1,470,000 |
| Schistosomiasis | | 844,000 | 362,000 | 100,000 | 394,000 | 1,700,000 |
| Enteritis | | 30,000 | | 46,000 | | 76,000 |
| Total Tropical | 60,000 | 2,284,000 | 362,000 | 146,000 | 394,000 | 3,246,000 |
| Bacterial Meningitis | | 185,000 | | | | 185,000 |
| Mycoses | | 38,000 | 322,000 | 157,000 | | 517,000 |
| Arboviruses | | | | 194,000 | 366,000 | 560,000 |
| Herpes viruses (all) | | | | | 20,000 | 20,000 |
| Rickettsial Diseases | | 150,000 | 82,000 | 120,000 | 110,000 | 462,000 |
| Respiratory viruses Influenza | | 40,000 | | 20,000 | | 60,000 |
| Viral Hepatitis | | 24,000 | | | 8,000 | 32,000 |
| Total Other | | 437,000 | 404,000 | 491,000 | 504,000 | 1,836,000 |

a simple means of measuring the persistence of protection following vaccination with sporozoite antigens. Like the Army, the Navy is concerned with three major rickettsial diseases: epidemic typhus, murine typhus, and scrub typhus. Epidemic typhus is still prevalent in many regions of Africa and South America; scrub typhus remains a common disease in the Far East. The ultimate goals of the Navy's program are production of a combined epidemicmurine typhus vaccine and a scrub typhus vaccine. An ELISA test has been developed for both groups of organisms; if purified antigens become generally available, this test can be used for extensive surveys and for the rapid diagnosis of rickettsial infections of man.

Another rickettsial disease, Rocky Mountain Spotted Fever, is a problem in the United States. NIAID has been collaborating with the Army on development of an improved vaccine for this tick-borne typhus.

## Department of State

### Agency for International Development

Under authority of the provisions of Section 104 of the Foreign Assistance Act of 1961, as amended, in relation to disease prevention, AID provides direct support for activities in the principal tropical diseases beyond those which the agency classified as research and development. In 1978, these activities included assistance to nine national malaria control programs at about $4.5 million per year, and support of a multi-donor onchocerciasis control program in West Africa at $4.0 million per year. In addition AID contributed $800,000 to the multi-donor consortium which supports WHO's TDR program (Table 10) for six diseases, and funded additional research on malaria, schistosomiasis, and diarrheal diseases. Research on improved chemotherapeutic drugs was limited to those for schistosomiasis (the expenditures listed for treatment of enteritis largely supported studies of oral rehydration). With reference to other chemical agents, $376,000 were devoted by the malaria program to development of pesticides. As with the other agencies, a significant proportion of malaria research was devoted to vaccine development.

A description of the expenditures of all the federal agencies surveyed for seven tropical diseases makes it clear that investigators have been equally interested in, or attracted to, studies of vaccines ($9.6 million) and to the development and testing of pharmaceutical agents ($10 million) (Table 11). A major expenditure was the Army's six million dollar investment in antimalarials. Excluding this figure from the totals indicates that $3.9 million of $25.0 million, or 15.6 percent of total expenditures for seven major tropical diseases, were allocated to drug development and testing. No attempt was made to assess the reasons for this division of effort, but it is a proper subject for other Conference participants. Perhaps all that is needed are new

TABLE 10. AGENCY FOR INTERNATIONAL DEVELOPMENT RESEARCH SUPPORT (Estimated) FOR SELECTED TROPICAL DISEASES (FY 1978)

| Infectious Disease | Biological Control | Vaccines and Immunity | Chemoprophylaxis and Treatment | Improved Diagnosis | All Other Research | Total |
|---|---|---|---|---|---|---|
| Total | $335,000 | $1,696,000 | $1,094,000 | $150,000 | $1,926,000 | $5,201,000 |
| TDR (WHO) a/ | 100,000 | 200,000 | 200,000 | 100,000 | 200,000 | 800,000 |
| Malaria | 235,000 | 1,246,000 | | | 376,000 | 1,857,000 |
| Schistosomiasis | | | 644,000 | | | 644,000 |
| Subtotal | 335,000 | 1,446,000 | 844,000 | 100,000 | 576,000 | 3,301,000 |
| Enteritis | | 250,000 | 250,000 | 50,000 | 1,350,000 | 1,900,000 |

a/Combined support for six WHO targeted diseases

TABLE 11. U.S. GOVERNMENT SUPPORT (Estimated) FOR DEVELOPMENT OF PHARMACEUTICALS, OTHER AGENTS AND TECHNIQUES FOR SELECTED TROPICAL DISEASES (FY 1978)

| Infectious Disease | DHEW | | DOD | | State (AID) | | GRAND TOTAL ALL RESEARCH c/ |
|---|---|---|---|---|---|---|---|
| | Vaccines | Drugs | Vaccines | Drugs | Vaccines | Drugs | |
| Total | $3,298 b/ | $1,649 | $4,584 | $7,212 | $1,696 | $1,094 | $31,462 |
| TDR (WHO) a/ | - | - | - | - | 200 | 200 | 800 |
| Filariasis | 211 | 132 | - | - | - | - | 1,237 |
| Leishmaniasis | 269 | 126 | 100 | 400 | _ | _ | 1,391 |
| Leprosy | 249 | 318 | - | - | - | - | 927 |
| Malaria | 725 | 308 | 2,235 | 5,975 | 1,246 | - | 13,102 |
| Schistosomiasis | 494 | 307 | 844 | 637 | - | 644 | 4,901 |
| Trypanosomiasis | 226 | 39 | 675 | 200 | - | - | 1,827 |
| Subtotal | 2,174 | 1,230 | 3,854 | 7,212 | 1,446 | 844 | 24,185 |
| Enteritis | 1,124 | 419 | 730 | - | 250 | 250 | 7,277 |

a/Combined support for six WHO targeted diseases.
b/x1000.
c/Includes Biological Control, Improved Diagnosis, and All Other Research as well as expenditures for Vaccines and Immunity and for Chemoprophylaxis and Treatment.

stimuli, such as the discovery that allopurinal selectively damages certain parasites and the obvservation by Dr. Carl R. Alving at Walter Reed that a liposome-encapsulated antimonial agent eliminated leishmaniasis mortality in hamsters.

There is no difficulty in explaining the emphasis on vaccines. The age of immunoparasitology has arrived, and technical developments, particularly in malaria, offer hope that vaccines may be available before all parasites are resistant to antimalarials and all mosquitoes to insecticides. Several approaches are being explored. Drs. Robert Gwadz and David Chen at NIAID have utilized the sexual states (gametes) of P. gallinaceum to immunize chickens. When mosquitoes feed on the chickens, they ingest antibodies against gametes; the antibodies block further development of the parasites in the mosquito, and thus, interrupt further transmission. Dr. Wasim A. Siddiqui and associates at the University of Hawaii effectively immunized owl monkeys against P. falciparum using merozoites in Freund's complete adjuvant as antigen. Dr. Siddiqui and Dr. Shozo Kotani and his collaborators at Osaka University, Japan, have recently reported development of a synthetic compound which they suggest can be safely used with liposomes as an adjuvant for a merozoite vaccine in man. These and other studies were greatly facilitated by the technique developed by Dr. William Trager of Rockefeller University for the in vitro cultivation of the asexual erythrocytic states of P. falciparum.

When the expenditure estimates are totaled for other infections that produce disease and death in the developing countries (Table 12), and this total is added to expenditures for tropical diseases (Table 11), the United States investment in such research and development in FY 1978 is calculated to have been $65 million (Table 13).

Because of the Army's stimulus, expenditures for pharmaceuticals for tropical diseases ranked first for that group, consuming 32 percent of the total, nearly three times that invested in drugs for the other diseases. Expenditures for vaccines and related immunological studies ranked first for the other selected diseases, 36 percent of nearly $34 million. This may simply mean that insufficient funds are being invested in the search for new drugs for all of these infectious diseases. It is noted with some surprise that, collectively, United States agencies spent nearly as much for the seven tropical diseases as for the eleven other selected major disease categories.

Among the questions to be addressed are whether a disproportionate amount of national resources is being devoted to basic epidemiological and immunological studies and to vaccine development rather than to the development of new pharmaceuticals, or whether the total investment in tropical diseases research needs to be increased with a special emphasis on expanded drug research. It is also appropriate to ask whether the infections considered, including those diseases selected for special emphasis by WHO, are the appropriate targets. If it is accepted

TABLES 12. U.S. GOVERNMENT RESEARCH SUPPORT (Estimated) FOR DEVELOPMENT OF PHARMACEUTICALS, OTHER AGENTS AND TECHNIQUES FOR OTHER MAJOR DISEASES (FY 1978)

| Infectious Disease | Grand Total All Research a/ |
|---|---|
| Total | 33,683 |
| Bacterial Meningitis | 1,917 |
| Gonorrhea | 2,528 |
| Pneumococcal Infections | 874 |
| Tuberculosis | 1,577 |
| Mycoses | 2,255 |
| Arboviruses | 9,155 |
| Herpes viruses | 730 |
| Rabies | 309 |
| Rickettsial Diseases | 3,349 |
| Respiratory viruses | |
| Influenza | 5,520 |
| Other | 1,900 |
| Viral Hepatitis | 3,569 |

a/x1000

that they are, it is desirable to consider how United States institutions can better utilize resources to expand existing research and training programs and to create new ones that will encourage United States-supported laboratories (1) to develop closer collaborative arrangements with indigenous institutions and (2) to link operational research activities with appropriate national research and training centers.

The National Institute of Allergy and Infectious Diseases has developed several new program initiatives to meet these objectives. One of these is a modification and extension of the current International Centers for Medical Research. The current and final funding period

TABLE 13. U.S. GOVERNMENT RESEARCH SUPPORT FOR DEVELOPMENT OF PHARMACEUTICALS, OTHER AGENTS AND TECHNIQUES FOR SELECTED TROPICAL AND OTHER DISEASES (FY 1978)

| Research and Development Category | Seven Targeted Tropical Diseases | | Eleven Other Infectious Diseases | | GRAND TOTAL Diseases Surveyed | |
|---|---|---|---|---|---|---|
| | $ x1000 | % | $ x1000 | % | $ x1000 | % |
| Total | $31,462 | 100 | $33,683 | 100 | $65,145 | 100 |
| Biological Control | 1,646 | 5 | 2,554 | 8 | 4,200 | 6 |
| Vaccines and Immunity | 9,578 | 30 | 12,264 | 36 | 21,842 | 34 |
| Chemoprophylaxis and Treatment | 9,955 | 32 | 3,730 | 11 | 13,685 | 21 |
| Improved Diagnosis | 1,778 | 6 | 3,558 | 11 | 5,336 | 8 |
| All Other Research | 8,505 | 27 | 11,577 | 34 | 20,082 | 31 |

of the four ICMR grants ends May 31, 1980, after an existence of 20 years. A new initiative, International Collaboration in Infectious Diseases Research (ICIDR), will supplant the ICMR program and will provide an opportunity to expand selected research activities, to initiate new ones, and to establish additional overseas linkages.

The research emphasis of the new ICIDR program is infectious diseases and the immunology of these diseases. Special attention is given to the six diseases of the WHO Special Program for Research and Training in Tropical Diseases. To provide flexibility and to ensure maximum opportunity for participation, the program is divided into Part A, International Program Project Grants, and Part B, International Exploratory/Development Research Grants.

Part A, International Program Project Grants, embraces broadly based multidisciplinary research programs that have a well-defined central focus or objective, with major portions of the research being conducted overseas by a group of investigators collaborating with one or more foreign affiliates.

Part B, International Exploratory/Developmental Research Grants, encourages an individual investigator to develop a biomedical research program with an overseas affiliate, with most of the work being done in the host country.

As a complementary initiative, NIAID has invited the scientific community to submit program-project grant applications to establish United States-based Tropical Disease Research Units that will bring together relevant biomedical knowledge in a multidisciplinary attack on the world's major tropical and parasitic diseases. In addition to the new knowledge to be gained, it is anticipated that this program will provide badly needed institutional support in the United States and a career ladder for scientists in this area, including those returning home from ICIDR projects.

In a very real sense, the NIAID intramural laboratories already constitute a Tropical Disease Research Unit. NIAID desires to expand the efforts of these excellent laboratories by providing additional positions and funding so that research projects in overseas locations may be undertaken in addition to linkages already established with scientists in Brazil, India, Egypt, Central America, and Africa.

Finally, funds permitting, NIAID proposes to create research fellowships in tropical diseases for young investigators, and international fellowships for senior scientists. Talented new investigators must be attracted to research careers in tropical and infectious diseases if the United States and other nations are to sustain a significant attack on the problems of developing countries.

**Summary**

During fiscal year 1978, the agencies of three United States Departments -- Health, Education, and Welfare (NIH, CDC, BoB), Defense (Army, Navy), and State (AID) -- expended an estimated $31.5 million for research and development related to seven major tropical diseases plus an estimated $33.7 million for eleven other disease categories that are also important health problems in developing countries. For the tropical diseases, intramural and extramural investigators -- the latter principally in university laboratories -- devoted 32 percent of their budgets to studies of pharmaceutical agents; for the other diseases, 11 percent of expenditures were related to drugs for chemoprophylaxis and/or treatment. This difference was attributable to a major emphasis on drugs for malaria by a single agency. For the two groups of diseases combined, investigator interest and/or the nature of financial support favored expenditures for basic research (31 percent) and for vaccines and related immunological studies (34 percent), over work on pharmaceutical agents (21 percent).

## DISCUSSION: CURRENT PROGRAMS FOR DEVELOPMENT OF PHARMACEUTICALS

DR. CLUFF requested that Drs. Sarett and Vischer amplify their comments regarding involvement of the academic community by the pharmaceutical industry in the development of new drugs for tropical countries.

DR. ERNST VISCHER replied that industry customarily enlists the advice of competent members of the academic community. For example, Professor Fox has collaborated very usefully with CIBA/GEIGY, and with local investigators in Indonesia in tuberculosis treatment trials. In other instances, industry has enlisted local faculty members from the medical schools in the countries where pharmaceuticals are to be tested.

DR. CLUFF stated his impression that collaboration between industry and the academic community in Europe differs from the practices utilized in the United States.

DR. LEWIS SARETT noted that American pharmaceutical companies do enlist assistance from people in the academic world, both in industrialized and in developing countries.

DR. ADETOKUNBO LUCAS added that WHO has been stimulating such collaborative efforts as, for example, by support for screening compounds active against filariasis provided by industry at several university centers around the world.

DR. MANSOUR believed that collaboration between the academic and industrial communities in the United States was very limited, in large part due to the patent problem.

DR. SARETT cautioned against overestimating the importance of the patent problem as a constraint to greater involvement of university talent in new drug research for developing countries. Two other constraints are far more significant: Drugs useful for treating tropical diseases must be tested in the countries where the diseases occur, and not in the United States, usually precluding greater involvement of United States academicians. Additionally, centers for clinical investigation of tropical diseases are relatively scarce in the United States, also limiting possibilities for collaboration.

DR. LUCAS suggested the trend for investment spending for research on drugs for tropical diseases appeared upward in Europe and downward in the United States, and requested data from the speakers.

DR. SARETT replied that there are many reasons for a slow overall decline in drug research development in the United States. The proportion of overall research spending for drugs against tropical diseases

amounted to perhaps three to four percent of the $1.3 billion industry annually spends for research.

DR. VISCHER stated that the situation in Europe actually reflects a maintenance of the status quo, and not really an overall upward trend.

# INTERNATIONAL HEALTH: FROM THE PERSPECTIVE OF THE CARTER ADMINISTRATION

Gilbert S. Omenn

## Introductory Comments

I am pleased to have this opportunity to describe the international health perspective of the Carter Administration. I hope that I can contribute to your discussions by providing our view of the broader policy context within which this Conference on Pharmaceuticals for Developing Countries is taking place.

We support Institute of Medicine efforts to elucidate the nature and interactions of the many elements which comprise the complex field of endeavor we call international health. These elements are scientific, medical, public health, commercial, regulatory, social, political, and humanitarian. Based on the experience of the participants, the breadth of the agenda, and the quality of the presentations, I am confident that this Conference will advance our understanding of the current opportunities for use of pharmaceutical agents in the prevention and control of disease in developing countries. As a clinical investigator myself, I am very impressed that this Conference has brought together leading people from academic and industrial sectors, both here and abroad.

Several months ago, I came to the Institute of Medicine on behalf of the White House to seek assistance in addressing the complex issues associated with the conduct of clinical investigations in developing countries. The Institute has agreed to initiate a study of the rationale for undertaking clinical investigations in developing countries, the scientific opportunities and needs for such investigations, social, cultural, and ethical considerations, and various regulatory, legal, and logistical constraints. A distinguished Steering Committee, chaired by Dr. Robert Petersdorf, has been formed, and members of the Steering Committee are attending this Conference as a prelude to their broader review of issues and opportunities in clinical research in developing countries.

## Background

President Carter has a long-standing and deep interest in international health. This interest is a logical and humanitarian component of the President's belief that world peace depends upon a commitment to basic human rights, a commitment which transcends geographical and ideological boundaries.

From the very beginning of his term in office, President Carter has focused attention on human rights, human needs, and health. In a number of major speeches, messages, and statements -- starting with the Inaugural Address -- the President and his top advisors have stressed this Nation's resolve to address the needs of the poorest people in the developing world, those who lack essential food, water, shelter, and health care. In a September 1977 message to the Pan American Health Organization's meeting of Ministers of Health of the Americas, the President emphasized:

> "Our commitment in this regard is total, our resolve firm, our focus on the needs of all people, regardless of politics or ideology. Let me reaffirm here today the United States concern for the social and economic rights of all citizens of the world. A special concern for us is the continued cooperation with the developing nations to assist them in providing for the basic health needs of the poor majority."

Consistent with this focus on basic human needs and with a planned expansion of foreign aid with emphasis on the poorest of the world's people, the Administration conducted an interagency study of international health needs and a review of United States government activities in international health. Chaired by Peter Bourne and including participation by the Office of Science and Technology Policy, the study sought effective ways in which the United States government and private organizations could help reduce the human and economic impact of widespread malnutrition, infectious diseases, and other health hazards, including those associated with frequent childbirth.

That review formed the basis for a Presidential Statement on International Health, issued May 2, 1978. This statement first recognized the tremendous gap between the demonstrated potential for good health and the poor health of people in vast areas of the world today, and then dedicated the Carter Administration to work in partnerhsip with international organizations and with other countries to help people meet their basic human needs, and to improve health, nutrition, and family planning. The President emphasized his intention to strengthen the participation of the United States in worldwide efforts to overcome disease and to improve health.

At the World Health Assembly in Geneva later that same month,

Health, Education, and Welfare Secretary Califano presented four basic principles underlying the program announced by the President:

- A basic level of health, nutrition, and family planning services should be available to the world's poor, whether they live in rural areas or urban slums.

- Developing nations can eventually meet their own health needs if we assist them in strengthening their institutions and building their own health systems.

- Community-based primary health care, including the use of community resources and the local training of appropriate personnel, is the most effective means of achieving the standard of health we desire for all people.

- Prevention of disease and ill health, with special emphasis on providing clean drinking water, basic sanitation, nutrition, and basic immunizations, will be reflected in our own programs and in our support of priorities established by various international organizations.

## International Health Strategy and Programs

With these principles in mind, a general strategy for increasing the effectiveness of United States efforts in international health has been formulated. There are six components to this strategy:

1. Build greater awareness, among the American people, of the legitimacy and importance of our foreign policy goal of improving other people's capacity to meet their basic human needs. A major theme of the Carter Administration's foreign policy is the use of American know-how and financial and human resources to help other nations achieve economic and social development objectives and meet the basic human needs of their peoples.

2. Strengthen institutions in our government which deal with international health problems and improve the use of existing resources through better coordination. A number of initiatives have been taken to strengthen Federal institutions involved with various aspects of international health and to increase substantially the cooperation among these institutions.

Department of Health, Education, and Welfare (HEW) Current HEW authority in international health is limited to those activities that benefit United States citizens at home or abroad. This authority does

permit agencies such as the National Institutes of Health, the Center for Disease Control, and the Food and Drug Administration to undertake certain international activities in scientific exchange, collaborative research, and disease surveillance and investigation. However, many believe that the resources and capabilities of the Department should be available to meet a broader range of international health needs. An International Health Policy Board within HEW has been assessing the need for an expanded mandate in international health, organizational options for strengthening HEW international health efforts, and potential legislative initiatives.

There is also Congressional interest in enhancing the role of HEW in international health. Two of the Congressonal figures most interested in these issues -- Senator Javits and Senator Kennedy -- are addressing this Conference. Senator Javits sponsored a sweeping international health bill last year (S. 3103) and is preparing to reintroduce legislation this session. I understand Senator Kennedy also is contemplating international health legislation this session. However, as Senator Kennedy and especially Walsh McDermott emphasized, health should not be viewed in isolation from other efforts to improve the lives and living conditions of the poor majority.

Department of State The State Department is responsible for development, implementation, and monitoring of United States foreign policy as it relates to both the developed and the developing countries. Its foreign assistance programs aimed at developing countries are administered by the Agency for International Development (AID) (see below). In addition, the State Department has a Bureau for Oceans and International Environmental and Scientific Affairs (OES) with responsibility for policy related to population, the environment, and oceans and fisheries. This Bureau recently has been greatly strengthened by the appointment of Ambassador Thomas Pickering to be the Assistant Secretary responsible for OES. A Congressional mandate contained in Title V of the Foreign Relations Authorization Act for FY 1979 (PL 95-426) directs the Secretary of State to assume primary responsibility for coordination and oversight of all major science and technology activities between the United States and foreign countries or multilateral organizations. To facilitate these responsibilities for interagency coordination under Title V, Ambassador Pickering has activated a Committee on International Science, Engineering, and Technology within the Federal Coordinating Council on Science, Engineering, and Technology (chaired by Frank Press). This Committee will integrate and coordinate Federal agency planning and implementation of international science and technology programs, including those related to international health.

Agency for International Development (AID) The AID program forms the core of United States government efforts to promote better health in the Third World. AID is strengthening its attack on the major health problems of the poor -- common infectious diseases, malnutrition, and high fertility -- by focusing on four key elements: (1) integrated

health delivery systems which provide health, nutrition, and family planning services at the community level; (2) safer water and better sanitation, especially in rural areas; (3) control of malaria and development of better approaches to the control of other tropical diseases requiring special campaigns (e.g., onchocerciasis, schistosomiasis, and trypanosomiasis); and (4) health planning and management to promote coordinaation of these and related developmental efforts for improving health. In Fiscal 1979, AID is obligating $130 million to support health delivery programs, environmental health, disease control, and health planning. An additional $185 million is being devoted to AID's expanded population planning programs, in cooperation with developing countries and other donors.

Peace Corps Through its well-placed volunteers, the Peace Corps is involved in various aspects of international health. Volunteers work as community health personnel, in the training of host-country nationals, in local resource development, and in special disease campaigns, such as immunization programs. The Peace Corps is seeking to strengthen its programming in international health, recognizing that health is a critical component of the development process and of basic human needs.

Interagency Coordination An International Health Subcommittee of the Development Coordination Committee (chaired by AID Administrator John Gilligan) has been established to facilitate coordinated and effective planning and implementation of United States government international health programs. Co-chaired by Jack Bryant of HEW and Steve Joseph of AID, the Subcommittee consists of representatives of HEW, AID, State Department, Department of Defense, ACTION (Peace Corps), Office of Management and Budget, National Security Council, OSTP, and the ISTC Planning Office (see below).

3. Create a new Federal agency to mobilize science and technology for the needs of developing countries, to be called the Institute for Scientific and Technological Cooperation. In his speech in Caracas in March of 1978, President Carter announced he would seek the creation of an Institute for Scientific and Technological Cooperation (ISTC) (earlier called the Foundation for International Technological Cooperation.) The ISTC will work directly with United States and developing country institutions and agencies to improve scientific and technical capabilities for problem-solving in the developing countries and to address cooperatively critical long-term problems of development. The ISTC would be the principal central research and technology development agency within an International Development Cooperation Administration, currently under consideration by the President's Reorganization team. ISTC will provide a key mechanism to implement certain of our objectives in international health as well as appropriate recommendations from the President's Commission on World Hunger, headed by

Ambassador Linowitz. An extremely important part of the ISTC mandate is to work with the middleincome countries in addition to the less developed countries (LDCs). A planning office was formed to prepare a prospectus and budget for the ISTC which was included in the President's Budget Message to Congress last week. The Institute is expected to begin operation in the fall of 1979.

4. More fully involve American universities, technological foundations, and other private organizations in making United States scientific and professional resources more accessible to the developing world. The greatest reservoirs of professional talent in areas related to international health are in the academic community, private foundations, and various private voluntary organizations. The Federal government needs to work in closer partnership with these institutions and organizations to draw more effectively upon those talented people, with their experience and their flexibility, to undertake field-oriented assignments. With the increasing visibility of American commitment to bilateral and multilateral assistance and cooperation, and with the creation of the ISTC, we are confident that the government can build more productive and supportive relationships with private institutions and organizations.

5. Increase cooperation with private industry. The Carter Administration is committed across the board to improving interactions between industry and government and attempting, where feasible, to define complementary governmental and private sector roles. The Administration, on President Carter's instructions, has initiated a major review of industrial innovation. This review is designed to generate recommendations for reducing disincentives to private sector investment in research and innovation and for stimulating industrial innovation through new policies, programs, or incentives. We believe that innovation is important to productivity, trade balance, jobs, and worldwide problem solving.

In international health, the commercial sector accounts for a major portion of all United States international health activity, although the greatest proportion of this commerce, investment, and trade is among developed countries. There is need to enchance commercial sector involvement in international health efforts aimed at the poorer countries, to complement government and private voluntary efforts to improve health in the developing countries. This Conference, supported by HEW, is an important stimulus to such an effort.

6. Work closely with the nations around the world, individually and through organizations such as WHO, UNICEF, the World Bank, and the Regional Development Banks, to improve the health of

people everywhere. The United states is joining with other nations bilaterally and through multilateral organizations such as WHO to develop cooperative approaches to meeting basic human needs and improving health. We have joined with WHO in developing long-term health goals and in developing strategies and plans to meet those goals. We are providing support for such WHO initiatives as the Tropical Disease Research Program, the Expanded Program for Immunization, and the Program for Prevention of Blindness. We were pleased to have Dr. Mahler of WHO visit here in October, and I personally had an opportunity at that time to meet Dr. Mahler, Dr. Lucas, Director of the Tropical Disease Program, and Dr. Bergstrom, Head of the WHO Advisory Committee on Medical Research.

The Carter Administration has strengthened the government's capabilities and financial resources to address health needs of developing countries. We look to the pharmaceutical industry and others in the commercial sector, to universities and foundations, to private voluntary organizations, and to the American people for greater recognition of human needs, and greater efforts to overcome poverty and ill health of a kind that most of us here are fortunate enough not to have known. We believe we and you, here and abroad, have the experience, ingenuity, and commitment to make substantial progress for people throughout the world.

# PROBLEMS AND CONSTRAINTS

# INTRODUCTORY COMMENTS FOR THE PANEL ON PROBLEMS AND CONSTRAINTS, CONFERENCE ON PHARMACEUTICALS FOR DEVELOPING COUNTRIES

William Hubbard

In order to choose those actions with the greatest likelihood of providing needed pharmacotherapy in developing countries, it is necessary to understand the problems and constraints that must be overcome.

Medicinals can be effectively used only within some system for delivery of personal health services. Health practitioners with some training in diagnosis and therapy must be supported with the logistics and communications that allow them to serve the population.

The fundamental determinants of health include pure water, sanitary disposal of human and animal excreta, adequate nutrition and housing, control of disease vectors, health education -- all within a community that has a viable economy and reasonable political stability for a population whose growth in size is balanced by its increases in resources.

Pharmaceutical medicinals -- no matter what their quality or quantity — cannot be more than marginal, albeit essential, technology contributing to the effectiveness of a social and political commitment to providing these fundamental determinants of health and of a suitable personal health service delivery system.

In the United States, the expenditure of corporate funds for research and development has grown steadily in constant dollars at an average rate of 4.5 percent per year since 1960, for a total increase of more than 102 percent in constant dollars by 1976. But federal funding of research and development carried out by industry has decreased by about 30 percent over the same period. Approximately 10,000 companies in the United States are engaged in research and development. However, in 1976, only 40 companies accounted for 53 percent of all corporate funds spent on research and development.

Pharmaceutical companies do not appear among the top 20 companies in annual dollar expenditures for research, a function of their relatively small size within American industry. However, there are three pharmaceutical companies among the top 10 research and development

spenders, when ranked as a percent of sales or in dollars spent per employee. Along with the computer industry, photographic-based companies, and specialized machinery companies, pharmaceutical companies spend more than 50 percent of their net income on research and development.

There is also an extreme concentration of research and development within the pharmaceutical industry itself. Only 14 of the 26 pharmaceutical companies that spend more than one million dollars annually on research and development actually spend at the industry average rate of 50 percent of net income. Only four companies account for 37 percent of research and development, while they produce only 21 percent of the industry sales -- spending at a rate of 10.8 percent of sales on research and development. The next four most research-intensive companies spend only 6.8 percent of sales on research and development -- representing 23 percent of the total industry's research and development and 24 percent of its sales. It is, therefore, grossly misleading to speak as if research and development intensity were similar among all pharmaceutical companies. After the first 8, the next 12 companies represent 47 percent of total sales but only 33 percent of total research and development.

Basic research supported by corporate funds has been declining. From 1953 to 1965, such research was 6 percent to 7 percent of total industry-funded research and development. Between 1965 and 1975, basic research expenditures fell to 3.7 percent of a total research expenditure that was rising. Waste caused by erratic policies and delays in regulatory decisions have made well-intentioned legislation an expensive burden of doubtful cost effectiveness. At the same time, two things have happened: direct costs of research have strikingly increased, and more data of relevance to safety and efficacy have become available through the evolution of science.

In the United States, the past decade has seen a decrease in industrial productivity, an increase in corporate debt, a decrease in corporate earnings margin, a sharp decline in industrial capital formation, and a decline in the measurable returns from expenditures on research by industry. In the pharmaceutical industry itself there is, as a matter of government purpose, an ongoing reduction in the economic advantage to an innovator of a medicinal. All these trends limit the growth of those few companies that already have a heavy research commitment. These trends in the regulatory and general business environments make it unlikely that any new small company can generate the financial resources necessary to develop a long-term research program that consumes 50 percent of its net income or more than 10 percent of its sales.

In the United States, five scientists and engineers work in industry for every two in academia and government combined. It is these scientific professionals in industry who allow our private sector

to translate knowledge into utilizable technology. The relationship of science and technology to the industrial sector is generally weak in less-developed countries and constitutes an impediment to transfer of current technology. The accumulation of industry-based scientists in less-developed countries, and their effective interaction with indigenous academic and government scientists, is a precondition to the development of their self-reliance in using modern technology -- much less their self-sufficiency in creating it.

If regulatory processes in the United States continue to be erratic and slow, and if the general business climate deteriorates further, then prudent officers in senior management positions cannot do other than reduce the risk to the life of the corporation that is inherent in research expenditures that have no reasonable hope of recovery in product sales. If the degrees of uncertainty and unpredictability in government policy and regulatory practices could be reduced, then the ability of management to make assessments of the risks and benefits of research expenditures would thereby be enhanced.

Like all human institutions, the pharmaceutical industry has both structural and operating defects that should be corrected or diminished. At the present time, however, it is the only institution in society capable of translating scientific understanding into new medicinals that are generally available for the public benefit. The problems and constraints that have heretofore operated must be relieved if the pharmaceutical industry is to serve its social purpose with respect to the needs of less-developed countries. Unique capacity carries with it a unique obligation. Even from the most limited commercial view, it is important that the pharmaceutical industry respond to the potential increase in demand for its products by the people in less-developed countries who now have inadequate access to existing pharmaceuticals, let alone access to optimum new pharmaceuticals for diseases peculiar to the southern hemisphere. It is our intention in this panel to describe these problems and constraints so that more effective efforts may be made to solve them.

# CONSTRAINTS ON EXPANDING THE ROLE OF THE U.S. PHARMACEUTICAL INDUSTRY

## A. UNITED STATES INDUSTRY PERSPECTIVES

W. Clarke Wescoe

Yesterday Walsh McDermott, my longtime friend and sometime critic, placed our program in historial perspective in a magnificent way. The problems which we address are biologic and economic (to which I would add — confounded by international boundaries). In respect of the bio-lo-lo gic, the industry has played and will continue to play a leading role; in respect of the economic, the industry has a smaller role to play.

The United States pharmaceutical industry developed in an open market economy that promoted and engendered entrepreneurial activity. It arose de novo from the efforts of industrial pioneers, it was not a spin-off from a pre-existing industry, nor was it a resultant of governmental stimulus designed to encourage economic development. It developed in a time when the infrastructure for health care was already in place; it continued its own development in parallel with the growth of that infrastructure. Its growth mirrored that of the pharmaceutical industry in other "developed" countries -- those countries undergirded by highly developed educational systems, crowned by outstanding universities -- countries concerned for the public health and possessed of mechanisms for providing and improving it.

Concomitant with the growth of medicinal chemistry, it became a research-based enterprise; coincident with the growth of a scientifically based medical profession and sophisticated establishments for the care of the sick, it too became sophisticated.

From its inception the industry was privately financed. The industry represents now a significant investment of capital by millions of shareholders who expect from that investment a reasonable annual return and the possibility of capital appreciation. Indeed, without that appreciation and that return, inflation will erode their investment.

The industry's growth across national political boundaries was funded from its domestic profits; its expansion was funded with American dollars. It served to stimulate, along with other transnational enterprises, the economies of a host of nations. It provided products

and services and, far beyond that, employment, taxable income, and technological advance.

In its own country the industry learned to live with an ever-increasing body of law and regulation as well as a burgeoning number of federal agencies, each of which had impact upon it. There is perhaps no other country in the world where the industry is so tightly controlled, so subject inadvertently to transgress a statue or overlook the letter of one among voluminous regulations.

In its increasing capacity to serve other countries the industry expanded beyond its own hemisphere. Around the world it built facilities -- major manufacturing establishments, packaging facilities, research laboratories. It takes pride in providing medicines for man, in being concerned with health the world around, in finding new products for the diagnosis of and therapy for disease and in being the primary research source for such products. It takes the greatest pride in funding its research almost entirely from its own resources, a logical extension of which fact is that the prices of its products must, in fairness to its shareholders, provide the continuing basis of the long-range research effort.

Because of a record of achievement of which it is justifiably proud, the industry finds itself under constant scrutiny. The scrutiny comes simultaneously from those who believe that medicines (the most cost-beneficial and most easily identified segment of health care expenditures) should cost ever less and from those who critically ask: "What more can you do promptly to elevate the quality of life -- and how cheaply?" Frustrated by the ever-increasing costs of total health care, government understandably turns its eyes constantly to medicines because their costs are so easily identifiable, even though their costs have remained remarkably constant and, in this country, are a declining percentage of total health care expenditures. C. Northcote Parkinson wrote about the inevitability of such scrutiny years ago -- the smaller the figure, the closer the scrutiny -- as he framed those delightful ironies known as Parkinson's Laws. I believe it is understandable too because medicines do not vote whereas all the persons, professional and non-professional, who are involved in health care go to the polls.

Frustration is not a monopoly of government; a sense of frustration is common to the industry as well. For that reason let me address myself to the frustrations rather than the constraints which industry faces as it looks to the prospect of providing pharmaceuticals for the developing countries. The frustrations are many and they are not related entirely or even in largest part to conditions prevailing in the United States or to United States governmental regulations or statutes.

Because I believe the constraints or frustrations relating to domestic regulation may not be as important in the global picture as

some would believe them to be, let me discuss them first. In the first instance, the laws relating to monopoly, the antitrust statutes, the laws regarding restraint of trade, make it difficult, if not impossible, for United States companies to engage conjointly or in a consortium for an attack on any problem. We are an "arms length" nation when it comes to relationships between individual companies. Whereas it appears to us that the governments of many other countries are active partners with industry to stimulate the flow of products to developing countries, there is no indication that the government of the United States desires such an active partnership. In fact, it appears that we have no effective national policy in this regard, that agencies of the government, the legislative, and the executive branches, often are acting at cross-purposes and with widely varying interpretations of what might (or could) be done. Such is part of the price that one is willing to pay for democratic government. Such determines, moreover, that we will never be an OPEC -- an organization of pharmaceutical exporting companies.

In addition, from the standpoint of taxation, our government is interested in assuring that all of the taxes it believes payable are paid in the United States by United States companies. That logical posture has posed, and perhaps will continue to pose, problems for our transnational companies in the areas of research expenditure and the construction of facilities for research, or for the production of special products, or for the underwriting of research conducted abroad for the benefit of other countries. Our own taxing authorities are no different from those in other countries, all of whom are intent upon levying taxes on what they believe to be their fair share of our companies' profits.

Finally, we must consider some of the impediments created by the Food, Drug, and Cosmetic Act, as amended, and by the encyclopedic regulations of the Food and Drug Administration. At present, export provisions of the law permit shipment of a new drug for commercial use only if that drug has had issued an approved NDA. When we talk about products for diseases endemic in developing countries and non-existent in the United States, we speak about products for which an approved NDA is literally not obtainable. For such products (relating to tropical diseases) at the present time, there is little possibility of manufacture in the United States. What is required is either production at a facility outside the United States or construction of a new one elsewhere in the world with all the investment of capital that such costly construction entails. Even from the standpoint of the export of such a compound for initial clinical trials there are extraordinary obstacles. Such export can be accomplished only if the FDA has approved an IND protocol that has met all the requirements and conditions for a study in the United States. The expertise for the evaluation of such protocols exists minimally in the agency at the present time. I do not think the attempt should be made to establish such expertise.

To be sure, the current administration and industry appear to be in agreement that changes in those export provisions must be made. Discussion about changes, however, has always been colored by references to "adulteration" and "misbranding" and "uncertified" -- specific terms (jargon) to United States law. Drugs, legally categorized as "old" are presently allowed to be exported even though technically "adulterated" or "misbranded" under United States law provided, however, that they conform to the laws of the importing country. Similarly, antibiotics are allowed to be exported even though uncertified (certification is an anachronism). The inference is somehow given that to free up export provisions by allowing export of non-approved "new" drugs would lead to the dumping of unfit pharmaceuticals upon the international market. No examples have been given, however, to support a conclusion that such a circumstance will occur or that any such has occurred in the past.

Relative to the export of medicines from the United States, I believe the good judgment of the importing nation and its authorities should be heeded. Not all regulatory agencies of the developed nations agree with requirements imposed by the United States Food and Drug Administration; there are on occasion real matters of scientific difference of opinion and, consequently, differing regulations in different countries. There is an inherent inappropriateness in imposing United States value judgments on the adequacy of the health regulations or the regulatory personnel of other countries. The matter of risk/benefit analysis, the relative matter of safety/efficacy, should be left in the hands of the nation that desires the medicine or of some non-national scientifically based body upon which all nations could rely. There is no reason to believe that standards invoked by United States regulatory officials should be considered as universally supreme.

There is perhaps one final aspect of United States regulations that should be mentioned, the regulatory influence on the availability of participants in the final and critical stage of research -- clinical pharmacology. The area of clinical research is the most difficult of all in the medicine research process; it is the stage where the pharmaceutical industry must turn over to outside scientists (with careful monitoring, of course) the completion of its long, complex, involved and costly research. For such research to be carried out there must be a continuing number of persons available who are willing to participate in trials to test the safety and the efficacy of a product in humans. If we restrict more and more the pool of persons who can participate in such trials (particularly the early ones), we shall make medicinal research ever more difficult.

Because any potential product for use in the treatment of disease endemic to developing countries will have little or no market in the United States, it appears logical that the clinical trials, from Phase I onward, should be conducted in those countries. There is a constraint in that regard; few such countries possess the necessary cadre

of trained individuals capable of carrying on such work. Similarly, extraordinary difficulties can be encountered in the necessary follow-up of the clinical population. It will be difficult to pursue perfect clinical trials but a way must be found. Finally, it will not be possible because of literacy and educational deficiencies to obtain truly informed consent in those trials. I trust, as research progresses in that area in the future, no pharmaceutical company will be criticized for those deficiencies and, contrariwise, governments will accept that burden even though there will be uncommon scrutiny of such trials.

Now let me turn to the broader issues which may be even more dispositive of United States industry's involvement with pharmaceuticals for developing countries. It is important to recognize that the health problems of developing nations have their roots in certain fundamental social, cultural, and economic difficulties, compounded in the instance of some by vector-borne and parasitic diseases. Major components of these health problems are typically poor environmental sanitation, lack of health education, malnutrition, population pressures with explosive urbanization, and an inadequate public health infrastructure that often precludes effective delivery of health care. One or more of these problems is frequently aggravated by pressures of economic development. The pharmaceutical industry is not equipped to deal with these underlying health problems.

A recent study of health issues by the World Bank clearly documents a second important point -- that the most serious disease problems of the developing nations are by no means restricted to parasitic diseases. Even earlier, in 1969, a study published by the Rockefeller Foundation cited statistics showing that nonvector-borne diseases are consistently identified as the major health concerns by these countries themselves. In the case of 28 African countries queried in a survey conducted by WHO, governments listed a total of five nonvector diseases (such as tuberculosis and venereal disease) among their major ten health concerns. Also cited among the ten concerns were deficiencies in organization and administration.

In fact, nonparasitic infectious diseases are commonly the major causes of death and disability throughout the developing world; malaria is the only vector-borne parasitic disease of comparable importance. We have heard the others described as those affecting the quality of life or increased economic productivity. Tuberculosis, pneumonia, typhoid fever, and cholera are massive disease problems on a global basis. The fact that these diseases have been effectively controlled in the more developed countries demonstrates clearly that existing prophylactic and therapeutic measures are adequate to the task. There is thus confirmed that a primary need is often not more or better health technology but its effective delivery.

There can be little doubt that a great deal of human and social benefit could be realized by a more aggressive and systematic

application of the medicines and vaccines that are available now. What appears to be needed is the establishment in each government of priority for health, by which is meant health in its totality, not drugs for specific diseases. That priority is as important as, and indeed crucial to, economic development. Without the development of a viable infrastructure, without a concern for rural as well as urban health affairs, without a program to eradicate causes of infection and reinfection rather than one to treat specific cases, there can be little progress -- only continuing anguish and much recrimination. Some private foundations learned that principle in times past: the creation and growth of sound schools of medicine, nursing and public health had to be supplemented by commitment to active health programs if the goal of better public health was to be achieved. In the long run a better public health program leads to the ultimate economic advantage of better utilization of medicines and thus economy in medical costs and — a springboard to economic development.

I look to an establishment of health as a governmental priority. It should not be a matter of concern that in some less developed countries the cost of medicines runs as high as 35 percent of the health budget. The matter of concern should be that the health budget is so low, not that the countries, in desperation, have turned to the most cost-effective materials -- medicines.

United States-based companies, not surprisingly, have concerned themselves primarily with diseases prominent in the United States. That they have done so is one clear example of their acceptance of domestic social responsibility. Further, their research priorities have had to be directed toward those areas if they were to survive as viable entities in a highly competitive field. In yet another way it could be said that they, in their research priorities, have followed the same direction as has the United States government. The government, unquestionably the largest factor in total health-science research and development expenditures, long ago committed its outlay to research in and the control of the major killers and cripplers in the United States — cancer, heart disease, mental illness, neurological disorders. Thereby, perhaps unwittingly, the public sector permitted the disappearance or deterioration of other programs -- among them tropical health and hygiene. So did foundations. It has not been possible for the private sector, as represented by the pharmaceutical industry, to stem that tide.

Despite public retreat and foundation withdrawal, a significant amount of research directed toward parasitic diseases has been conducted by the industry, and with successful results. There have been developed new and effective agents. As we have heard, there have been several new antibiotics; there have been new antimalarial compounds; there have been developed agents for the therapy of leishmaniasis and filariasis, two of superior promise for the treatment of schistosomiasis, and new amebicides. Still other compounds of great promise have

not yet reached the stage of marketing.

Widespread effective application of medicines for parasitic diseases has been overwhelmingly disappointing. There is little, if any, private market for these medications. If they are to be maximally useful, they must be introduced by means of an integrated public health program. Integrated public health programs pose substantial logistical problems, and demand a great deal of management, organization and planning; in short, they are expensive. Because of lack of public funds to support such programs there has been a general underutilization of available drugs for treatment of tropical diseases. For other reasons, such as derogatory comments about United States drugs, such as "the product of United States company research without an NDA from the United States Food and Drug Administration," proven effective products lie unused in pharmaceutical warehouses. There is more to pharmaceutical research than the thrill of discovery. Underutilization of effective products that represent time, effort, expenditures of funds, and personnel serves as a powerful disincentive to continued research looking to additional new drugs for the same or similar conditions.

In the development of large-scale integrated public health programs required to address diseases unique to developing countries, industry is ill-suited to take the leading role. In every instance the cost of medicine is a small fraction of the total cost of the control program. Unsuited to take the lead role, United States industry is ready to listen to ideas as to how it can help in an effective way.

An overriding constraint (or frustration) for United States-based industry is its perception (and its experience) of how it is regarded by some developing countries. It is difficult to accept the complaints about private enterprise failing to work or to solve extraordinary problems in the face of almost totally planned economic structures. That is particularly so when the planned structure appears to have little or no place for private enterprise or, at the least, private enterprise that is part of a foreign corporation. It is even more particularly so when the climate is little less than hostile to it or detrimental to the interests of its shareholders. Pharmaceutical companies are not organized to act as not-for-profit institutions (even the amount of our tax-deductible contributions are limited). In whatever they do, companies must have the prospect of a reasonable return on investment and on innovation. Companies conduct and must conduct their research in response to market demands which can afford to meet reasonable prices for pharmaceutical products. That all companies have deviated from that norm by producing service drugs reflects a recognition of their social responsibility. To deviate from the norm in entirety would be to act contrary to the needs and expectations of their shareholders.

For a United States-based company today, business conditions, in general, are difficult in a large number of developing countries. Such a company is often faced with a forced dilution of its equity, the loss

of its patents and its trademarks, the denial of the fruits of its labor. The desire on the part of every country to have technology transfer (a poorly defined term) is understood. The desire on the part of every country to export pharmaceuticals is also understood. The desire on the part of every nation to participate in pharmaceutical production from raw materials to manufacture to packaging is understood, even if not practical or economically sound. There are limiting factors to all of these desires -- not every country is ready for all technology transfer, not every country can be an exporter (economics dictates otherwise), not every country can become a total producer. There are needs enough for all to share in the fulfilling in the future. It is our responsibility to plan how to get there -- and how we plan to deal with each other and with the world's health problems equitably -- equitably for industry, for government, and for all people. The single greatest constraint for industry, the largest frustration for the private sector, would be that in struggling for solutions, equitability would be lost.

This Conference is designed to look to the future. It would be tragic if it concluded without proposing a reasonable approach to solving the problems it has discussed. There is, in some medical schools, a regenerated interest in tropical disease. There are some in the political arena who have a similar commitment. Industry is interested in participating in a new and creative thrust -- on an equitable basis. There is need for innovation. I, for one, from the United States industry would like to be a creative partner in that innovative thrust.

## B. FOOD AND DRUG ADMINISTRATION AND PHARMACEUTICALS FOR DEVELOPING COUNTRIES

Donald Kennedy

The subject of this Conference is important and complex, and I appreciate this opportunity to share with you my own views and those of the Food and Drug Administration (FDA), especially because the subject encompasses the evolution of the FDA since its inception some 72 years ago. I will explain.

When FDA was launched, its primary focus was moral rather than scientific. A violative product was defined by its deviation from a fundamental moral construct -- purity. Did the label lie? Was the product adulterated? The moral character of the agency's genesis had a little to do with the political climate at the turn of the century, but much more to do with the state of science at that time. By and large we just did not know what kinds of questions to ask about the chemistry or pharmaceutics of food additives or drugs.

This first period of evolution was succeeded during the 1930s, and with accelerating force during the following decades, by a period of true scientific regulation. We began, with increasing clarity, to discern what the questions were; and our ability to analyze both qualitatively and quantitatively was revolutionized.

Now we are in our third period of evolution, into a new role as a regulator of the transfer of technology from innovator to consumer. We have the ability, and we also have, I believe, the self-confidence and the growing sense of responsibility, to look beyond our expertise to examine how the process itself affects the total society.

That is why I said that our history reflects the subject of this Conference. Both involve precisely those three basic filaments -- of morality, of science, and of technology transfer.

In regard to the first of these, you may not be aware that last month the world's first Encyclopedia of Bioethics was published by the Kennedy Institute for the Study of Human Reproduction and Bioethics at Georgetown. This four-volume publication has 313 articles that address such contemporary problems as advertising by the medical profession,

cryonics, euthanasia, electroconvulsive therapy, eugenics, fetal research, genetic screening, and prisoner experimentation. It dramatizes the inseparability of moral and ethical problems from scientific progress.

These issues share the dynamic nature of science, and cannot be relegated to some dustbin of yesterday's philosophy. There can be no better reflection of that dynamism than the fact that the moral questions surrounding this Conference are not singled out for examination even in this up-to-date encyclopedia.

And yet what we are considering, particularly in relation to the regulation of drugs destined for developing nations, involves morality (or at least can be made to seem to do so) no less than science and — technology transfer. The key question, whether the United States Government should allow the export of useful but potentially hazardous substances not approved for marketing in this country, evokes strong views on both sides.

On the one hand, there is concern that current export policy for some products can result in the "dumping" of inferior or even dangerous substances in countries poorly equipped to evaluate the potential risks involved. On the other, it is claimed that export restrictions deprive citizens of foreign countries of the benefits of important products that, often for rather special reasons, have been deemed unsuitable for use by United States citizens.

Like other Federal agencies that regulate chemicals, the FDA sometimes finds itself at the center of controversy between representatives of these divergent but equally legitimate positions. Over the years, through participation in a number of debates on this issue, we have reexamined the export provisions of our laws to determine if changes were in order. For example, last year, as part of an overall revision of our drug laws, we submitted to Congress significant amendments to the current export provisions governing drugs. Because of the importance of this change, I would like to discuss it here in some detail, including the ways in which it would modify current law and why we believe it is necessary. I would also like to explore the concept of differing risk/benefit rates between nations, and to contrast two relevant examples.

As to current export policy and how we are seeking to change it: under current law, a new drug may not be exported for commercial use unless it is approved for marketing domestically and complies with all the requirements of Title V of the Federal Food, Drug, and Cosmetic Act, and the drug's new drug application. An unapproved new drug may be exported only under an investigational new drug protocol approved by the FDA. The investigational study must comply with all the conditions and requirements that attend a clinical study conducted in this country. Certain categories of drugs that are not classified as "new drugs" -- like antibiotics, insulin, and pre-1938 drugs -may be exported without

any prior notice to the FDA, even when these products may be adulterated or misbranded under domestic standards. These drugs must simply comply with the specifications of the foreign purchaser and the laws of the importing country, and be labelled for export only.

The Administration's new bill, The Drug Regulation Reform Act of 1978, which was given extensive study by committees of both Houses in the last session of the 95th Congress, would revise the current export rules applicable to drugs. Under the Act, two standards for export would apply to all drugs. Approved drugs in compliance with domestic requirements could be freely exported. Unapproved drugs or approved drugs not in compliance with domestic requirements could be exported only after an export permit had been approved by the Secretary. An export permit would be granted only when the exporter of an unapproved or noncomplying drug demonstrated that the importing government had assented to its importation after being informed of its legal status, and the basis for it, in the United States. The scientific and medical data concerning the drug's unapproved status would be made available to the importing government to assure an informed decision. The Secretary would have authority to deny an export permit where such export would be potentially damaging to the public health.

We now provide information on the safety and efficacy of many drugs to the World Health Organization (WHO), and to individual foreign countries. For example, when a drug is withdrawn from the market for reasons of safety, we notify WHO and all those countries that have requested to receive information of this kind. WHO in turn issues special bulletins to all its member governments. Because we have limited authority and resources to provide technical assistance of this kind to foreign countries, we have included a provision in the Reform Act that would authorize the Secretary to provide assistance to foreign governments. FDA would expand its exchange of drug information with foreign health officials and international organizations, such as WHO, and provide training for representatives of foreign governments where it is needed.

We envision that training sessions would be held either in the foreign country or in the United States, as necessary. This technical assistance would not only provide the foreign governent with an informed decision as to the importation of a particular noncomplying or unapproved drug, but would also enhance the overall scientific and technical capabilities of those foreign governments which need such assistance.

In sum, our proposed change in the law would provide greater protection against the export of some drug products such as adulterated and misbranded antibiotics, insulin, and pre-1938 drugs. At the same time, it would make more drug products available to foreign countries that are needed in those countries. This is essentially the same policy Congress adopted in 1976 when it considered the export policy for

medical devices in the Medical Device Amendments.

I want to emphasize that a drug or device deemed unsuitable for distribution and use in the United States may nevertheless make substantial contributions to the health needs of another country. The relative safety and efficacy of a drug or medical device is a composite judgment which must be made by each country based upon many factors, such as the status of the health care system in that country, patient compliance with dosage regimens, alternative therapies that may be available, and other specific characteristics of its population. Some diseases prevalent throughout the world -- especially in the tropics, where most of the developing nations are found -- are rare or nonexistent in this country.

As an illustration of the problems generated by current export provisions, let me discuss Depo-Provera®. The status of this drug is now the subject of an administrative proceeding between the manufacturers and the FDA, and because I am separated by FDA's own administrative procedures from any wide-ranging discussion of the issue of approval of Depo-Provera® that goes beyond the historical, I will confine myself to the question of the impact of such decisions on international use.

In assessing this impact, I should emphasize that decisions to approve or disapprove drugs for use in the United States are based on domestically oriented risk/benefit calculations: that is, given conditions that obtain here, will the benefits exceed the risks or will they not? We are well aware that the ratio between risk and benefit can differ markedly in other nations. For example, at a workshop sponsored by the Program for the Introduction and Adoption of Contraceptive Technology, Dr. Mahmoud F. Fathalla, Professoor of Obstetrics and Gynecology, Assiut University, Egypt, pointed out that the risk/benefit ratio of contraception is different in the developing world because the risk of an unwanted pregnancy to the mother is higher due to high maternal mortality rates.

We realize also that the decision not to approve Depo-Provera® in the United States may cause difficulties for developing countries wishing to use it, and we have made an effort to help resolve this problem. On July 25, 1978, we wrote to health ministries in 68 countries to help explain the reasons for FDA's decision not to approve the new indication for Depo-Provera® and the Department of State advised American Embassies in these countries of the text of our letter by telegram from Secretary Vance.

We met also with a representative of the World Health Organization and offered to provide summaries of our evaluations of the safety and efficacy data of this drug, transcripts of advisory committee meetings during which benefit/risk consideration were weighed, and other data that might assist foreign countries in deciding whether to use it. We will continue to cooperate as much as we can with WHO and other

appropriate organizations by providing data on this or any other drug or device being considered for use in other nations.

A special problem posed by our decision has to do with availability of Depo-Provera R for countries wanting to use it. Many nations rely to some extent on supplies of drugs and/or financial assistance from our Agency for International Development (AID). As you know, AID's policy, based in part on current provisions of the Federal Food, Drug, and Cosmetics Act, has been to refuse to supply drugs or funds for drugs not approved in the United States.

Let me contrast this decision, made necessary by the present statute, with the latitude provided through the Medical Device Amendments of 1976. The latter, perhaps because they are the newest parts of our law, reflect a greater sensitivity to issues such as those we address in this Conference. In South America, there is a need for earlier-generation, manually operated X-ray machines no longer approved for use in the United States. In this country, X-ray devices that automatically limit the beam to the area to be X-rayed are now required because we found that poor operation of the manual machines by United States technicians frequently resulted in unnecessary exposure of patients. The manual machines are still used successfully in some European and Asian countries without causing unnecessary exposure to patients. Such machines are needed in most South American countries because these countries lack the equipment or skilled technicians required to maintain the more complex equipment. Doctors operate these machines; they are trained to limit the beam manually. The Pan American Health Organization recognized this problem and fully supports the use of the manual equipment in South American countries. Obviously, for these countries, the benefits of having X-ray equipment available for use outweighs the potential risk of unnecessary exposure from manual operation.

Because the Encyclopedia of Bioethics fails to address the problem we are dealing with here, it is not surprising that our basic statute fails to foresee that FDA would one day find itself called upon to function as a regulator of the transfer of technology. That understandable lack of foresight clearly handicaps our ability to help meet the therapeutic needs of developing nations.

What we need is statutory authority to make useful drug entities and products available to foreign countries, to do so with due reference to the regulatory decisions of foreign governments, and without subjecting such countries to unreasonable risks from dangerous entities and products.

Much of the developing world is looking to the countries with advanced pharmaceutical industries to provide leadership in research on drugs to meet their unique health problems. We need to find ways that will enable American firms to contribute to this humanitarian effort in a responsible way.

# CONSTRAINTS ON INVOLVEMENT OF THE U.S. GOVERNMENT AND ACADEMIC RESEARCH COMMUNITY, INCLUDING MANPOWER CONSIDERATIONS

Richard M. Krause

I would be dishonest if I did not confess at the start that there is a preference in my heart for speaking out about science rather than policy. But innovative science is for the young, and I recognize the reality of senescence which has sovereignty over our lives. And this inevitability of aging is the reason why I speak on policy and constraints, and not about scientific opportunities. But I am an optimist who takes the long view and believes that the developing countries will develop a science base that will influence their cultural climate 50 to 100 years from now. In this regard, it is of value to recall the circumstances in this country 75 years ago. We were then a nation almost devoid of a scientific establishment. For example, when the Rockefeller Institute for Medical Research was founded at the turn of the century, it was staffed largely by American scientists trained in European laboratories, because there were, at that time, no opportunities for such training in our "developing" country. But Rockefeller became a model for United States biomedical research institutions. Creation of similar research institutions in the developing countries will be required if science in those areas is to flourish in the 21st century.

What are the constraints on involvement of the United States government and research community toward development of pharmaceuticals for primary use in other parts of the world? As I see it, these constraints can be grouped under four headings: legislative constraints; inadequate resources; restrictive attitudes; and a lack of investigators committed to this endeavor in either the afflicted nations or the developed world.

Dr. William Jordan of our Institute has referred to the legislative constraints under which we operate 1/ and I will not go into that matter again in detail here. As he stated, our legislative authority at the NIH is "to advance the status of the health sciences in the United States and thereby the health of the American people". Nothing is said about the health of people in other countries, although "cooperative endeavors with other countries in health research and research training" are permitted.

Each one of us here can mention several cogent reasons why research on tropical diseases is of benefit to the American people. For example, I have no difficulty justifying research on tropical eosinophilia. We know very little about the function of the eosinophil. So, anything that is learned about its role in parasitic immunity may be applicable to research on the eosinophil in asthma and allergic reactions. And yet, such a justification has at least the appearance of a contortion to stay within the boundaries of our authority. Eventually, we must examine what it is we intend to do, and who is to do it, and then develop develop the legislative authority consistent with these goals.

The next constraint concerns resources, or money to purchase and develop those resources. This constraint is linked to legislative matters already discussed and also to attitudes, which I will mention next. But the fact remains that money for research on tropical diseases has been meager compared to funds allocated for research on the health problems in the United States. For example the FY 78 budget for the National Institute of Allergy and Infectious Diseases (NIAID) is a little over $162 million; approximately $20 million dollars, or 12 percent, was budgeted for tropical medicine research. Taking this projection one step further, we find that this $20 million is only 0.67 percent of the total NIH budget for FY 78.

As shown in Table 1, tropical medicine research funded by NIAID with this $20 million is carried out in intramural laboratories, in universities where studies are supported by grants and contracts, and in four International Centers for Medical Research. However, this $20-plus million is spread over more than 20 different focal areas, ranging from amebiasis to yellow fever. Because this is such a wide array of subjects, the amount in any one area is not large. Some notion of the distribution of funds for grants and contracts in several areas is given in Table 2.

The tropical disease research budget represents a societal judgment concerning health priorities. Therefore, in our society, the administrative policy of informing the public is an important element in any adjustment either up or down of this budget for tropical disease research.

Recently, we have reviewed our fiscal commitment to tropical disease research and have come up with what is known in bureaucratic jargon as a "professional judgment" budget, shown in Table 3. This budget reflects our awareness of the need to go from the present $20 million to approximately $40 million to do justice to these important research areas. Thus, we have proposed for the years through FY 84, a strategy that would gradually strengthen our research programs in international health.

I do not know at this time whether funds will become available for

TABLE 1. NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES RESEARCH IN TROPICAL MEDICINE (FY 1978)

| Programs | | Funds | No. of Projects |
|---|---|---|---|
| Total | | $20,310,951 | |
| **Extramural** | | | |
| Grants and Contracts (Parasitology, Medical Entomology, Leprosy, Cholera, Arbovirology) | | $14,633,951 | 212 |
| International Centers for Medical Research | | 2,117,000 | 4 |
| | Subtotal | $16,750,951 | |
| **Intramural** | | | |
| Laboratory of Parasitic Diseases (59 persons) | | 3,158,000 | |
| Rocky Mountain Laboratory (13 persons) | | 402,000 | |
| | Subtotal | $ 3,560,000 | |

TABLE 2. NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES EXTRAMURAL TROPICAL MEDICINE PROGRAM (FY 1978) a/

| Research Area | No. Grants | Grant Funds | No. of Contracts | Contract Funds | Total Funds |
|---|---|---|---|---|---|
| Total | 212 | $13,890,059 | 10 | $743,712 | $14,633,771 |
| Parasitology and Medical Entomology | | | | | |
| Research | 148 | $ 9,578,770 | | | |
| Training | 9 | 562,393 | | | |
| Fellowships | 13 | 167,816 | | | |
| Research Careers | 8 | 272,798 | | | |
| Subtotal | 178 | $10,581,777 | 4 | $254,534 | $10,836,311 |
| Leprosy | 6 | 577,025 | 3 | 230,485 | 807,510 |
| Cholera | 9 | 830,948 | 3 | 258,693 | 1,089,641 |
| Arbovirology | 19 | 1,900,309 | 0 | 0 | 1,900,309 |
| Subtotal | 212 | $13,890,059 | 10 | $743,712 | $14,633,771 |

a/In addition to these grants and contracts, 4 International Centers for Medical Research are funded in the amount of $2,117,000.

TABLE 3. NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES TROPICAL MEDICINE RESEARCH AND TRAINING PROPOSED BUDGET (FY 81-84) a/

| | 1981 | 1982 | 1983 | 1984 |
|---|---|---|---|---|
| Total | $29,500,000 | $32,900,000 | $36,950,000 | $40,500,000 |
| Grants and Contracts b/ | $18,000,000 | $20,000,000 | $23,000,000 | $26,000,000 |
| U.S. Tropical Disease Units c/ | 2,500,000 | 3,000,000 | 3,500,000 | 3,500,000 |
| Overseas Collaborating Laboratories (ICIDR) b/ | 4,500,000 | 4,800,000 | 4,800,000 | 4,800,000 |
| Intramural Research b/ | 4,000,000 | 4,500,000 | 5,000,000 | 5,500,000 |
| Career Development of United States Investigators c/ | 250,000 | 300,000 | 350,000 | 400,000 |
| Training of Scientists from Developing Countries d/ | 250,000 | 300,000 | 300,000 | 300,000 |

a/In 1979 dollars.
b/Ongoing with proposed expansion.
c/Proposed new initiative.
d/New initiative approved and funded.

our institute to carry out these plans. These are issues that in the years ahead will require public debate, and then a choice among the many worthy objectives and demands on the public purse. Realistically or not, I am optimistic about society's generous response when informed of the issues. When it comes to altruism I am inclined to side with Haldane who viewed altruism as one of the powerful instinctive urges for survival of the species.

But I do not propose to dwell here on the origins of altruism. Instead, I shall take up several matters of a different sort concerning the influence of restrictive attitudes on our research enterprise. The first of these is our attitude on the need to know more. There are, on the one hand, those health planners who would be practical and address only those health issues of the developing countries that are most susceptible to immediate solution by using the knowledge which we now have available -- more privies, pure water supplies, decent housing. But, on the other hand, there are those who would be more theoretical and would search for the hintergedanken of tropical diseases, just as biologists have always done in other medical fields.

This "on the one hand" and "on the other hand" calls to mind a story recently heard about Senator Muskie. After one lengthy and indecisive hearing -- with the scientist who was testifying waffling from "on the one hand" to "on the other hand" -- the Senator finally dismissed the witness with the comment that he wished he could find a one-handed scientist

Pasteur would haved made an ideal witness. No "on the one hand" and "on the other hand" for him. He knew what he had to do and how to do it. For, during his lifetime, when he was drawn into the vortex over the argument over basic research and the application of new knowledge, he firmly stated his belief that "there are science and the applications of science linked together as the fruit is to the tree that has borne it."

Let me return for a moment to the Rockefeller Institute for Medical Research when it was being established in what was then a "developing country." Many of those scientists who were recruited to the Institute did, indeed, give their first attention to problems of a practical sort, such as pneumonia. But their philosophy, even then, was to dig deep into problems and from intensive study obtain scientific wisdom as well as practical knowledge. And, as most of you know, from Avery's early studies on pneumonia at Rockefeller there emerged the discovery of DNA as the thread of life and the development of the recently licensed pneumococcal vaccine.

Perhaps the foremost obstacle in regard to developing drugs for tropical diseases is that we do not yet have the necessary scientific knowledge to solve many of the pressing problems. To mention only a few, we are ignorant about the host-parasite relationships in

schistosomiasis; the metabolism of the leprosy bacillus; or mechanisms of replication of viruses causing the most prevalent infections. Dig deeply -- that is the key. And for those of us who trained with W. Barry Wood, we recall this admonition. Start with whatever problem you will, but dig deeply into it. We must nurture and preserve the opportunity to do this. There is no substitute.

And yet today a cautious pragmatism characterizes many funding organizations, including some elements of the Federal government, and this dampens curiosity and innovation. This was recently described by the columnist Art Buchwald in his report of a conversation with a "doctor friend." According to the friend, "Even the government wants results before they'll give you grant money to study something. I know one doctor at the National Institutes of Health who was cut off because, by eliminating one problem, he created three others. He was told that government scientists could no longer create new problems in research. While there was still money for old problems, the word is out that if they lead to new problems, NIH doesn't want to hear about them."2/

I might add that Art Buchwald's column had the same caustic words to say about the foundations and their grant policies.

There is one other aspect of this issue of attitudes that requires our attention — but this matter is of a different sort. What I have discussed so far is our attitude about what we do. This next matter is our attitude about how we do what we do. Put another way, it's the belief that how we do something takes precedent over what we do -- that the form is more important than the substance. And this attitude is having an influence on our government laboratories and I fear on our private institutions as well.

There has been a good deal of comment concerning the effectiveness of our scientific establishment, particularly our national laboratories, because of the constraints imposed upon them by micro-management from the central agency to which they are attached. There has been a progressive trend -- seen to be ominous by some -- of greater and greater agency control over the national laboratories. Greater control over what they do and how they do it. Greater control over the scientific objectives. In general, this control is seen as leading to demands on the national laboratories for short-term solutions. Certainly in part, this micro-management of a national laboratory by a central agency reflects the various pressures brought to bear by more oversight by Congress and the Office of Management and Budget, and indeed, by more public participation in the establishment of research priorities.

There is then debate on the level of involvement of the sponsoring agencies in the management of a national laboratory, whether it is Brookhaven or the NIH, the Center for Disease Control or the Bureau of Standards. This issue has been addressed by Dr. George H. Vineyard, Director, Brookhaven National Laboratory, as follows:

"Among many critical issues, in addition to the perennial question of funds, I would single out these:

At what level should the primary responsibility for directing research programs reside?

Should it be with the individual scientist and his institution, or should it be in Washington?

The first issue arises because of the strong tendency for research to be directed more and more from Washington. As public concern with technological issues has increased, and as this concern has been reflected in Congress and in the Federal agencies, tighter management from above is being imposed. In this laboratory, for example, the degree of detailed involvement of our principal sponsor (ERDA) in setting priorities and determining the nature of each research program is rapidly increasing, and no limit is in sight. Along with this, our budgets become ever more fine-grained and detailed."3/

A similar theme has been evoked by Dr. Donald Hornig in a recent report by an advisory panel to the Office of Technology Assessment.4/

In addition to this issue concerning the level of primary responsibility for research programs, there is emerging another aspect of the problem of science management. I am concerned here with what I call the viscosity in the administrative system. In medical terms, we have become obtunded. And, at least as I observe this matter through the NIH speculum,, we are caught up in the details of administration that accrue from the accumulation of government procedures. By micro-management of administration I am referring to the tedious, repetitive details of the procurement process of goods and services, the personnel process, the management process, the budget process, and the dispersal of research funds and -- let me add -- travel ceilings for investigations abroad. These processes are all taking on a life of their own identity, their own reasons for existence. Whereas, of course, the whole purpose of management should be to nurture scientific imagination rather than suppress it.

In my judgment, from by brief experience at the NIH, at least, these administrative procedures are becoming a greater hindrance to scientific progress than any interference with management of the research itself by the Department. And, as Dr. Harvey Brooks has said, if this viscosity in the system of which I speak retards research progress in government laboratories, you can be certain that similar conditions will prevail in the future in the universities. I suspect that if the biomedical research enterprise founders, it will be on the micro-management of administrative matters rather than micro-management of research objectives, although the influence of the latter is not to be discounted.

In the December 1978 issue of The American Journal of Medicine, the editor, Dr. Alexander Bearn,5/ touched on this matter of excessive paper work in regard to grant applications. In his editorial entitled, "The Washington Paper Chase," Dr. Bearn describes with some humor, the agonies of preparing a proposal. He says, "Work performed by previous investigators is catalogued in excruciating detail. From Pasteur to Popper, nothing is left out.... The methodology is spelled out ad nauseum.... The Budget takes even more time. Secretaries and Research Associates are halved and quartered without mercy.... But at last it is done. Typed, retyped. Up to the business office and back. Signed by Deans, Sub-Deans, Department Chairmen. Routed all over the Medical Center ... to places and people barely known to exist.... Finally it is bundled up, all 70 pages of it, and dispatched to Washington ....

"Slowly, recovery sets in ... but the tranquility is short-lived: the next day the investigator gets 15 research applications to review. Their average length is 48 pages! The investigator thinks: maybe I overdid mine!"

Well, you ask, what to do? I am perhaps too new in government to answer that question but I did have one suggestion a bit perhaps out of Daniel Defoe or Lewis Carroll. I would suggest that we begin by requiring that all administrators in government spend at least 50 percent of their time reading professonal journals -- in that way to acquire new ideas, new perspectives on the substantive research issues of their department. This would leave only 50 percent of their time for writing memos to each other on all sorts of extravagant and extraneous matters. You know of course that when we run out of people to write a memo to, we write a memo "to the record." This regulation would go a long way to vitiate the mischief of administrative micro-management and provide a greater opportunity for managers to return to the regions of professionalism.

The final constraint concerns limitations on the number of specialized medical scientists who are available to work on tropical medicine, and, hand in hand with this limitation, insufficient numbers of research institutions in the developing countries. Without such research institutions, there are too few opportunities to which newly trained scientists can return.

Certainly, the problem has not been a lack of training opportunity in the industrialized world for those from other countries, although there are those who would argue that much of this training has been misguided with inappropriate objectives. For example, NIH's International Research Fellowship program was established just ten years ago and has been supported and administered by the Fogarty Center since its inception. During that time approximately 2,500 qualified young foreign biomedical scientists have obtained advanced research training, and have participated in collaborative research in major educational and research institutions throughout the United States, and at NIH. Of these 2,500,

only 347 have been from the "developing countries" of South and Central America, Africa, and Asia.

Not only have we trained too few of these foreign scientists, we have often failed to link training to any systematic plan for appropriate research opportunities after the trainees return to their own countries. It should not be our intention to limit the peripatetic migration of agile and inquiring minds. This is a traffic as old as humanity -- in which the talented young aspire to challenges in the intellectual and artistic centers of the world — Athens, Rome, Cairo, and Paris. Recall that St. Augustine immigrated to Rome and Maimonides to Cairo. They migrated to make their mark -- or to do their thing, as we would say in this century. Yet, at the same time, if we are to work together with colleagues in other areas of the world, we must find ways for those who are trained here to return to creative environments in their native lands. And this requires building native institutions which provide a stable career opportunity in an atmosphere of creative collegiality.

Perhaps the Foundation for International Technological Cooperation which is now being planned can be a help, but there is, at present, no agency in our government with responsibility to catalyze the intricate chemistry of institution building. Construction of such a fragile structure is a precarious undertaking. Such an institution must employ an exceptional group of scientists in a collegial atmosphere and be assured of long-range support. The Agency for International Development has neither the philosophical nor fiscal responsibility for this sort of institution building. And this surely is beyond the present authority of the Department of Health, Education, and Welfare. It is disturbing that the private foundations, in recent years, have largely abrogated this responsibility for institution building for health research and medicine, although they provided this kind of support in the past. In health, a notable example of such a contribution was the old Peiping Union Medical College, supported originally by the Rockefeller Foundation and later by the China Medical Board. But in the last 20 to 30 years, the Foundation has directed its attention to building institutions concerned with agriculture and animal husbandry. And here there have been impressive achievements. For example: the centers in Mexico, Nigeria, and elsewhere under the auspices of the Consultative Group for International Agricultural Research -- a joint enterprise between Rockefeller and Ford Foundations. But, in a sense, the Rockefeller Foundation left the international health field too soon. We are delighted that, under the vigorous direction of Dr. Knowles and Dr. Warren, it is returning to the fold, applying again its special skills in building and strengthening institutions in other countries of the world.

We can and we should help build institutions in Africa and Asia and South America where the theoretical base of science can find expression. But, in these institutions, native scientists must follow a path that is consistent with cultural, ecological, and economic circumstances

and must take into consideration the medical resources available for solving problems and implementing solutions.

The constraints I have mentioned are not new. We have long been aware that our efforts in tropical medicine were not what we would like them to be. For this reason, over a year ago, I announced, with the approval of Dr. Donald Fredrickson, Director of the NIH, the first steps that our Institute was prepared to take, focusing on four broad objectives. These are:

1. Strengthen tropical medicine in United States universities within the framework of existing biomedical disciplines, e.g., internal medicine, pediatrics, pharmacology, biochemistry, immunology, etc.;

2. Extend current United States research to the developing countries through "linkages" between United States investigators and those in the countries where tropical diseases prevail;

3. Assist in the establishment or strengthening of centers of excellence in developing countries; and

4. Finally, expand opportunities for research training in the United States for young medical scientists and health professionals from developing countries.

Exactly 30 years ago, President Truman asked this country to accept its responsibility in meeting the basic human needs of the people everywhere. On January 20, 1949, in his Inaugural Address, President Truman said:

> "We must embark on a bold new program for making the benefits of our scientific advances and industrial progress available for the improvement and growth of underdeveloped areas. More than half the people of the world are living in conditions approaching misery. Their food is inadequate. They are victims of disease. Their economic life is primitive and stagnant. Their poverty is a handicap and a threat both to them and to more prosperous areas."

Nearly 30 years later, President Carter echoed this theme in his letter to the 1977 World Health Assembly. Endorsing the WHO Tropical Disease Research Program, President Carter said, "these efforts will bring us closer to our goal: a world in which all people can live free from fear of crippling and debilitating diseases." If we are to do that we must break out of the constraints that impede our biomedical research enterprise.

Just recently in his State of the Union message, President Carter called for a "new foundation" and this brought to my mind the report entitled, "Sure Foundations" which I prepared for NIAID on the occasion

of the 200th anniversary of the United States. This phrase, "sure foundations," was taken from a longer statement by Thomas Jefferson. In a remarkable fashion his remarks speak directly to this Conference on Pharmaceuticals for Developing Countries. In 1807, Thomas Jefferson wrote in a letter to his friend, Dr. Caspar Wistar: "The only sure foundations of medicine are an intimate knowledge of the human body and observations on the effects of medicinal substances on that." I can think of no more perceptive analysis of our problem than this one written by Jefferson nearly 200 years ago.

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## DISCUSSION: PROBLEMS AND CONSTRAINTS

DR. KENNETH WARREN, noting Dr. Krause's comments about foundation support for health research applicable to developing countries, stated that the situation has improved considerably in recent years. He reviewed recent trends in foundation support for tropical medicine research. Using the Rockefeller Foundation as a leading example, he mentioned the Foundation's new program of support for collaborative research in tropical medicine between groups in the United States and Great Britain and corresponding centers in less developed countries. The Foundation also supports three immunology groups and two major pharmacology groups (at Case Western Reserve and at Rockefeller Universities) and a research career development fellowship program in tropical medicine. The Foundation has recently awarded two grants to the Institute of Medicine for international health studies.

For several years, the Edna McConnell Clark Foundation has supported a unique program in schistosomiasis research. Within the government, there has been a marked increase in interest in tropical medicine research that is hoped to take the form of greater budgetary commitments to NIAID. Dr. Warren called for increased participation by the pharmaceutical industry in efforts to find new therapeutic agents for diseases endemic to developing countries.

DR. EDGAR MARTIN (US Food and Drug Administration) addressed earlier statements by several speakers that FDA actions are arbitrary and bureaucratic. He stressed that the agency's major concerns are with safety and efficacy of drugs, and that its requirements are exactly the same as those promulgated by WHO in 1975 and 1977. Less strict regulations governing the export of drugs to developing countries might result not only in "dumping" of drugs, but would bring the agency into conflict with WHO. He remarked that existing legislation has loopholes, which permit unsafe practices and exploitation by some members of the industry. From a philosophical viewpoint, he mentioned that new advances in pharmaceuticals do not arise from increased spending alone. Instead, a brilliant scientific breakthrough may be the critical factor in development of new agents.

DR. MANSOUR recalled that he had been sent to Egypt to investigate complications reported to follow use of contraceptive steroids by women infected with schistosomiasis. Apparently, the administration of such drugs had produced severe hepatic problems in these women. He referred to the complex issues surrounding such a case, where drugs perceived as non-toxic in the United States could have unexpected side affects in countries where the prevailing disease pattern was different.

UNIDENTIFIED asked the panel for an example of an innovative product originating in an industrialized country and then applied in developed countries with good return on the investment.

DR. ABDOU SALLAM replied that Egypt offered many successful examples. Three joint venture companies, including Pfizer and Hoechst, have established successful operations in Egypt and are now making better profits there than they do in developed countries. This is due in part to the protected, or centralized market in the Arab Republic of Egypt, which permits very few finished drug imports. Other foreign companies also have licensing agreements with Egypt which permit substantial profits.

DR. HUBBARD interpreted the question to refer to the application of an innovation originating in a developed country. The questioner wanted to define the modus operandi whereby government, pharmaceutical industries, and private sector could cooperate to bring new techniques and products to less developed countries.

DR. SALLAM then cited Egypt's poliomyelitis outbreaks which were controlled by collaboration between WHO, UNICEF, and Egyptian institutions. Subsequently, the Arab Republic of Egypt has continued to shoulder the expenses of the program.

MR. MAX TIEFENBACHER confirmed Dr. Sallam's comments about the profit potential for pharmaceutical companies in Egypt, as experienced by the Hoechst Company since the early 1960s. He also mentioned the company's schistosomiasis research in Egypt, an unusual achievement.

DR. ROBERT HELMS (American Enterprise Institute), an economist, pointed out that numerous American economists would likely disagree with Dr. Lall's statement that the "free markets" could not be relied upon to produce drugs for developing countries at reasonable price. In this regard he asked Dr. Lall how he would reach such a conclusion after having given a catalog of ways governments are interfering with free markets through price controls and import restrictions. He also asked if Dr. Lall thought that India might not have a comparative advantage in drug production — that India would be better off to import pharmaceuticals, and use its scarce resources elsewhere.

DR. SANJAYA LALL referred to the opening statement as a debating point, since "of course" there is no free market, but rather an oligopoly of drug companies. To the question, India's recent performance in export markets suggests that a competitive advantage in production of drugs and fine chemicals obviously exists.

DR. FRANKLIN NEVA (National Institutes of Health) asked for any examples of drug companies' pooling their resources to conduct basic research on diseases endemic to developing countries.

DR. HUBBARD interjected that the United States anti-trust laws would prevent a consortium of United States companies' pooling their resources in such a fashion. Such an agreement would also prevent exploitation of any patent advantage. United States companies are subject to United States law even when they operate abroad.

MR. TIEFENBACHER noted that it has become quite common for European companies to pool resources in selected areas of research, especially on well-defined subjects such as prostaglandin research. He sees definitive advantages in such arrangements, and referred to his company's long involvement in joint research efforts with the Boehringer Mannheim Company in Germany.

DR. SALLAM added that Hoechst is the only one of the three foreign venture companies in the Arab Republic of Egypt which invests in locally conducted research. He invited American firms to consider investing in research activities in Egypt, where favourable conditions exist.

DR. RONALD ST. JOHN (Center for Disease Control) expressed concern about two inter-related problems: (1) the lack of controls at the retail level on over-the-counter sales of antibiotics and other substances in less developed countries; and (2) the promotion and mislabelling by the pharmaceutical industry of particular antibiotics. These two situations have resulted in emergence of many resistant bacterial strains such as gonococci, pneumococci, salmonellae, and shigellae, some of which now respond only to a very few agents. He wondered if international organizations could deal effectively with this problem.

DR. VITTORIO FATTORUSSO commented that these were indeed real problems. However, he was less concerned about misuse when there are no antibiotics in a developing country, than when there is a good supply. He said that the WHO can help to alleviate the situation by disseminating information to health workers.

DR. LALL offered a less optimistic view based on data which show that many drugs promoted and sold over the counter never go through the health system at all. Therefore, the problem really does lie at the national level, where import policies influence decisions about labelling, and warnings on use. The drug companies, themselves, could be at least as helpful as WHO in controlling the spread of resistant strains of bacteria.

DR. SALLAM continued the theme by referring to an experience he had during his term as Minister of Health. His wife's investigations on antibiotic-resistant strains of bacteria in a university hospital indicated that the situation had reached the point where 100 percent of hospital-isolates were resistant to penicillin, and 80 percent to streptomycin. Dr. Sallam admitted that he did nothing, fearing the backlash of public opinion if restrictions on drug sales were imposed.

MR. TIEFENBACHER commented that this problem was not the fault of the pharmaceutical industry alone, but was also related to the lack of infrastructure and effective health delivery systems in developing countries. He stated that WHO plays a useful role through the certification system which assures that high quality products are being imported.

DR. SUNE BERGSTROM (Karolinska Institute) voiced his concern over the problem of how to enlist the enormous research and development potential in the United States to improve health conditions in developing countries. Although WHO has increased its efforts by introducing the tropical disease research program and other training efforts, research and development has actually decreased in comparative terms in the United States. He referred to the extensive networks of clinics being built by WHO in developing countries which represent important resources for clinical testing of new products. Would the pharmaceutical industry be prepared to contract for any testing in underdeveloped countries, perhaps coordinated by WHO? Such arrangements might be similar to the contracts now extant in the cancer field.

DR. HUBBARD responded that serious problems and constraints prevent cooperative efforts among several companies. It is illegal for American companies to form a consortium for common purpose. Tax laws prevent deduction of charitable contributions made abroad. Nevertheless, many opportunities do exist in developing countries for conduct of clinical research and testing of new drugs. Thus, the Upjohn Company has begun discussions with Egyptian scientists along such lines. He then noted that it is not possible to speak on behalf of the United States pharmaceutical industry as if it were a single entity, and that industry's response will necessarily be by one company at a time.

DR. JOHN BILES (University of Southern California) hoped, as a pharmacist, that the Conference Steering Committee would note the importance of allowing individual practitioners to make sound clinical decisions based upon their judgement, and not recommend more government regulations to interfere with their freedom of action.

DR. VISCHER requested that Dr. Fattorusso comment upon the widely varying percentages of national expenditures for health among developing countries. He wondered whether governments of developing countries should not be required to contribute a certain percentage of their annual budgets or of their gross national product (GNP) to expenditures for health, as a precondition to receiving assistance in this sector from international agencies.

DR. FATTORUSSO replied that only the World Health Assembly can recommend expenditures for health to developing country governments. He agreed in principle that most developing countries should contribute a larger share of their resources to the health sector in the future.

MR. TIEFENBACHER wanted to pose the same question to representatives of assistance agencies in the audience: would they be willing to make a greater contribution of their overall assistance budgets to improve public health in developing countries?

DR. HUBBARD replied (on behalf of those addressed) that the question involved high policy decisions. Representatives would be hard put to respond candidly, especially in light of the recently released presidential budget for the coming fiscal year.

DR. SALLAM believes it is unfair to make the populations of developing countries suffer for the low priority accorded to health expenditures by Ministers of Finance and Planning.

UNIDENTIFIED commented at length on increasing bacterial resistance to antibiotics. He stressed the necessity to consider problems of availability of drugs to the public in situations where there were very few physicians, problems of insufficient training, inadequate record systems, and poor patient compliance. He accused many pharmaceutical companies, even so-called "good name" companies, of selling bad products to developing countries. He asked how quality control can be assured for developing countries lacking the minimum facilities to police all imports.

DR. FATTORUSSO replied that this responsibility lies principally with the importing country, which can request a signed certificate by the drug control authorities of an exporting country that the drug is certified for export, and if not, why not. Also, it can request a statement that the manufacturer is inspected at regular intervals and follows good manufacturing practices. One possible solution to this problem is to pool resources at the regional level, thus minimizing the difficulties of dealing with numerous companies.

DR. DAVID FRENCH (Strengthening Health Delivery Systems Project, Abidjan, Ivory Coast) made a point of differentiating between the levels of sophistication among developing countries. For instance, most of the sub-Saharan African countries devote at least 10 percent of their budgets to health. Nevertheless, only 20 to 40 percent of the population has access to pharmaceutical products. He noted a tremendous expectation on the parts of these 20 countries that drug companies will respond to the need for increased availability of drugs. AFRO, the regional office of WHO, has begun training programs to improve the delivery system for essential pharmaceutical products, but availability is still very limited beyond the urban areas.

MR. TIEFENBACHER commented that the WHO program on essential drugs will improve distribution and availability in developing countries. He recommended that Dr. French find out more about the initiative mentioned by Dr. Fattorusso which involves several European companies in attempts to improve pharmaceutical product availability.

# PROBLEMS OF DISTRIBUTION, AVAILABILITY, AND UTILIZATION OF AGENTS IN DEVELOPING COUNTRIES

## A. INDUSTRY PERSPECTIVES

Max P. Tiefenbacher

After concentrated discussion of drugs and diseases in developing nations, it may not be amiss to make the obvious comment that drugs are but one component in the health delivery systems of both industrialized and developing nations. Utilization of drugs, in fact, heavily depends on the existence, structure, and functioning of other elements in the health care system: Qualification and number of health personnel; adequacy and geographical dispersion of hospitals, clinics and health centers; facilities and logistics of drug supply; and the extent of coverage and benefits of national health insurance schemes. These all impact directly upon use of pharmaceuticals and the value of their contribution to public health.

Clearly, then, an overview of the problems and constraints in the availability and utilization of drugs in developing nations must include some reference to the institutions of the health care systems, the major economic and social factors and other contexts of pharmaceutical usage in these countries. Here, we confront a problem of extraordinary complexity. Developing countries are highly diverse and extremely heterogeneous, measured by any of the commonly used criteria. Furthermore, differences exist not only from country to country, but even to a greater degree within individual countries. Thus, common denominators can be derived only in very broad terms. Generalizations are needed to interpret the matters under discussion, to maintain focus on important issues, and -- above all -- to reach meaningful conclusions.

For these reasons, and so as not to lose sight of realities, I have assembled a worldwide statistical survey on health, pharmaceutical, and development indicators. These data were gathered from a large number of published and unpublished sources, and were provided to participants at the Conference. The charts provide a profile of the health scenario in the developing world in facts and figures, in all its staggering gravity, but also its contradictory and irrational elements. Only the most essential data are reproduced in this document. Unfortunately, statistical data are in most instances only available for the macro-cosmos of any one country. Reviewing not only the surface symptoms but also the root causes of the problems under discussion, a more

detailed breakdown by population groups, geographically and by other criteria, is badly needed.

Willy-nilly, most of the developing nations have evolved a mixed system of health delivery, divided into public and private sectors. The private sector follows the familiar western pattern of distribution, with physicians providing services in private offices, clinics, and hospitals, and themselves dispensing or prescribing drugs to be purchased at retail pharmacies. The patient pays for medical services and drugs out of his own pocket or through private or group insurance arrangements.

In contrast, the public sector is administered and financed from tax revenues by government bodies -- normally health ministries -- and frequently also by social security systems. The public sector takes care of health needs of underprivileged parts of the population, mostly through government-run clinics, health centers, and the like. It provides these services at no cost or at minimal cost to the patient. Drugs for the public sector are purchased on a competitive tender basis.

It must be recognized that the private segment of health care functions reasonably well. The overwhelming share of pharmaceuticals is absorbed by this market -- acounting for 75 to 90 percent of the total drug consumption of developing nations. This market caters by no means, as is so often contended, to an elite minority, to a small privileged group of the population. Instead, it benefits a large segment of the Third World population, 20 to 40 percent of the whole, comprising some 300 to 500 million persons. This is the emerging urban middle class social stratum of the population -- the literate, educated, employed, and most productive members of developing societies. Their talents and energies may be as decisive to the future development of impoverished societies, as the emerging middle class was in the economic transformation of Europe and North America. If existence of an educated middle class is a crucial prerequisite to building an industrialized economy, developing countries may indeed be justified in devoting a disproportionate share of resources to their benefit.

WHO, other UN agencies and political groupings are proposing that developing countries allocate resources increasingly to the social periphery of primary health care; for all practical purposes this is to take resources away from the private sector and channel them into the public sector. In a totalitarian regime, this may be enforceable, but in a free society this may be neither feasible nor practicable. An elected government would most likely find itself out of office if it took away medical benefits now enjoyed by the growing middle class -- those who presently provide the funds for these services, and who most likely have limited interest or incentive to share these service with the urban unemployed, or the rural population.

Medicines supplied in the private segment are appropriate to

health needs of the patients. Table 1 points to differences in consumption patterns between some selected developing countries and developed markets. All of Latin America together consumes less anti-diabetic drugs than Holland. India consumes 0.1 percent as many anti-hypertensive drugs as are used in Belgium, although both drug markets are roughly of equal size. Any comparison between the industrialized countries and Africa would show even sharper differences.

TABLE 1. LEADING THERAPEUTIC CLASSES BY SALES THROUGH RETAIL PHARMACIES IN SELECTED DEVELOPED AND DEVELOPING MARKETS

| Country/Class | Market Share % | Country/Class | Market Share % |
|---|---|---|---|
| BRAZIL | | PHILIPPINES | |
| systemic antibiotics | 14 | systemic antibiotics | 19 |
| cough and cold preparations | 6 | cough and cold preparations | 12 |
| vitamins | 6 | vitamins | 8 |
| antispasmodics | 4 | analgesics | 6 |
| sex hormones | 4 | tuberculostatics | 5 |
| analgesics | 3 | nutrients | 5 |
| antirheumatics | 3 | antiasthmatics | 3 |
| psycholeptics | 3 | antidiarrheals | 3 |
| psychoanaleptics | 3 | topical steroids | 2 |
| cholagogues/hepatic protectors | 3 | antacids | 2 |
| PAKISTAN | | VENEZUELA | |
| systemic antibiotics | 25 | systemic antibiotics | 14 |
| vitamins | 13 | vitamins | 8 |
| cough and cold preparations | 5 | cough and cold preparations | 7 |
| analgesics | 5 | analgesics | 4 |
| nutrients | 3 | sex hormones | 4 |
| antianemics | 3 | topical steroids | 3 |
| antidiarrheals | 3 | antianemics | 3 |
| antacids | 3 | psycholeptics | 3 |
| tuberculostatics | 3 | systemic steroids | 3 |
| antispasmodics | 3 | antirheumatics | 3 |

Cont'd.

(Cont'd)

TABLE 1. LEADING THERAPEUTIC CLASSES BY SALES THROUGH RETAIL PHARMACIES IN SELECTED DEVELOPED AND DEVELOPING MARKETS

| Country/Class | Market Share % | Country/Class | Market Share % |
|---|---|---|---|
| JAPAN a/ | | WEST GERMANY | |
| systemic antibiotics | 26 | cardiac therapy | 11 |
| vitamins | 6 | psycholeptics | 6 |
| antirheumatics | 4 | peripheral vasodilators | 5 |
| antacids | 4 | cough and cold preparations | 5 |
| hematologicals | 4 | analgesics | 4 |
| hospital solutions | 4 | vasoprotectives | 4 |
| cardiac therapy | 3 | systemic antibiotics | 4 |
| cytostatics (anti-cancer) | 3 | hypotensives | 4 |
| psycholeptics | 3 | sex hormones | 3 |
| cholagogues and heptic protectors | 3 | antidiabetics | 3 |
| USA | | | |
| psycholeptics (tranquilizers/ sedatives) | 9 | | |
| analgesics | 8 | | |
| systemic antibiotics | 7 | | |
| cough and cold preparations | 6 | | |
| vitamins | 5 | | |
| hypotensives | 4 | | |
| diuretics | 4 | | |
| sex hormones | 4 | | |
| antirheumatics | 3 | | |
| psychoanaleptics | 3 | | |

a/Measured by sales through wholesalers.

In the private sector the population:doctor ratio, the population: hospital ratio, and per capita drug consumption reach levels that can be considered adequate, albeit minimal. Health standards have been steadily improving. Average life expectancy increased by about eight years in 34 poorer countries between 1960 and 1975. It would be safe to assume that the lion's share of this is attributable to the population in the private sector.

It is the public sector that is woefully in disorder from any vantage point. This applies to the medical infrastruture, medical care

provided by governments, drug supply, and to the other essential health services that are so often referred to for the underserved parts of the population: the poorest, the unemployed, the geographically unaccessible.

The state has the responsibility to secure their health and provide opportunities for physical well-being. It is often said that this responsibility cannot be met because of severe lack of funds. But as Tables 2 and 3 demonstrate, it is by no means a matter of poverty alone. Matters of health mostly have very low priority in developing countries. Health must compete for available funds with national defense, and in almost all countries it lags woefully behind. The same holds true in terms of spending for health matters as a percent of GNP.

TABLE 2. NATIONAL EXPENDITURE ON HEALTH AS % OF GNP

| Country Category | Total as % GNP |
|---|---|
| **Low Income** | |
| India | 1.0 |
| Ethiopia | 0.8 |
| Kenya | 1.7 |
| **Middle Income** | |
| Philippines | 0.5 |
| Iran | 0.6 |
| Brazil | 0.5 |
| **Centrally Planned Economies** | |
| Hungary | 3.0 |
| USSR | 3.5 |
| **Industrialized** | |
| Italy | 8.0 |
| W. Germany | 8.0 |
| U.S.A. | 7.9 |

In general developed countries spend 5-8 percent of GNP on health care, of which 10-20 percent represents expenditure on pharmaceuticals. Figures vary more in low income countries but pharmaceutical expenditure rarely rises to US $2 and often accounts for up to 50 percent of total health care. Figures relate to 1975 or latest available year.

TABLE 3. DISTRIBUTION OF PUBLIC FINANCE IN SELECTED DEVELOPING COUNTRIES (1975)

| Country Category | Total Nat'l Finance Local Currency millions | % Distribution Education | Health | Defence |
|---|---|---|---|---|
| **Low Income** | | | | |
| Bangladesh a/ | 6307 | 10.3 | 2.5 f/ | 6.7 |
| Ethiopia | 1049 | 15.5 | 4.4 | 17.6 |
| India | 174100 d/ | 8.0 e/ | 3.3 e/ | 12.1 |
| Kenya a/ | 219 | 21.1 | 6.6 | 6.5 |
| Sri Lanka c/ | 8150 | 10.5 | 6.1 | 2.2 |
| Tanzania c/ | 6640 | 12.5 | 6.2 | 11.0 g/ |
| **Middle Income** | | | | |
| Bolivia | 6293 | 27.5 | 9.0 h/ | 16.5 |
| Brazil a/ | 58556 | 5.0 | 1.0 | 14.0 |
| Colombia a/ | 46528 | 18.4 | 7.4 | 8.6 |
| Dominican Rep. | 495 | 9.0 | 5.0 i/ | 9.6 |
| Ghana | 1162 | 20.3 | 8.2 | 7.7 |
| Nigeria b/ | 18006 | 14.1 | 5.5 | 20.7 |
| Sudan | 245 | 3.5 | 2.1 | 16.3 |
| Thailand | 67 | 22.0 | 5.0 | 19.4 |
| Venezuela a/ | 39497 | 10.8 | 6.1 i/ | 5.0 |

a/1974
b/1973
c/1976
d/National Finance plus States' Finance (not balanced).
e/Data given only for States' Finances. The figure including National Finance is not available.
f/Other health expenditures in the non-itemized entry for "Development Expenditure" are excluded.
g/Including law administration and police.
h/Including "social welfare."
i/Including other "social services."

TABLE 4. HEALTH CARE AND DEVELOPMENT AID PROVIDED BY MAJOR DONOR NATIONS (1976)

| Principal Donors | Gross Bilateral Development Aid US$ millions | Aid to Health | | | | |
|---|---|---|---|---|---|---|
| | | Wide Definition | | | Narrow Definition | |
| | | US$ millions | % of Total | Amount of Capital Aid US$ millions | US$ millions | % of Total |
| Total | 13605 | 867.9 | 6.4 | 687.3 | 623.7 | 4.6 |
| Australia | 342 | 4.3 | 1.3 | 2.5 | 3.3 | 1.0 |
| Belgium | 231 | 3.4 | 1.5 | 3.4 | 3.4 | 1.5 |
| Canada | 688 | 34.5 | 5.0 | 34.5 | 8.6 | 1.3 |
| France | 2268 | 261.6 | 11.5 | 261.6 | 261.6 | 11.5 |
| Germany, West | 1544 | 82.3 | 5.3 | 70.8 | 13.8 | 0.9 |
| Great Britain | 724 | 12.7 | 1.8 | 12.7 | 1.8 | 0.2 |
| Japan | 981 | 11.9 | 1.2 | 4.7 | 7.7 | 0.8 |
| Netherlands | 925 | 145.9 | 15.7 | 119.6 | 129.6 | 14.0 |
| Sweden | 376 | 55.3 | 14.7 | 53.1 | 26.8 | 7.1 |
| USA | 5527 | 256.5 | 4.6 | 124.4 | 167.1 | 3.0 |

STRUCTURE OF AID TO HEALTH IN THE WIDE DEFINITION (CAPITAL AID ONLY)

| Country | Capital Aid US$ millions | Allocation of Capital Aid (%) a/ | | | | |
|---|---|---|---|---|---|---|
| | | Hospitals, clinics, dispensaries | Family plan-ning | Basic health services | Social welfare services | Water supply |
| Germany, West | 70.8 | 3 | - | - | - | 93 |
| Netherlands | 119.6 | 7 | - | - | 46 | 23 |
| Sweden | 53.1 | 25 | 25 | - | - | 40 |
| USA | 124.4 | - | 6 | 30 | - | 60 |

a/Percentage figures are approximations

Furthermore, development aid provided by major donor nations largely disregards health care (Table 4). Only 3 to 5 percent is spent in this area, and much of this goes into sanitary services, family planning, medical education, and other health related areas.

But it is not only a matter of finances. The health delivery systems in the low-income areas of developing countries are grossly inadequate, poorly organized, and often conspicuous by their absence. This is certainly one of the very central problems and constraints to better utilization of drugs, and — I wish to stress again -- this is a problem centered in the public sector. In a recent report to the World Health Organization, the Pan American Health Organization acknowledges that

> ... despite the considerable efforts made in most of the Latin American countries to extend the network of institutions providing health services, including basic sanitation, on a national basis, the services are badly distributed, fail to reach important groups of the rural population and are inadequate to meet the demands of a rural population which is settling in the cities in increasing numbers and under wretched conditions.

State-run health insurance systems -- the core of the public sector -- are rudimentary at best in most developing countries. In many, not much has changed since colonial times. Social security systems, where they exist at all, exclude large segments of the population from medical benefits. Dependents of employed workers may receive only partial care -- maternity benefits alone, for example, and these only for employed women. Agricultural workers are often excluded, especially in least developed countries, where they constitute 80 to 90 percent of the labor force. Vast geographical areas may be ineligible for medical benefits. In advanced parts of the developing world the typical pattern of development of social security proceeds from coverage of employees of relatively large firms in the capital city or other large urban centers, expanding vertically and geographically as hospitals and other medical facilities can be built and staffed in cities and rural areas. Needless to say, expansion has been slow, largely because of underfinancing.

Some Latin American countries, notably Brazil and Uruguay, are about to attack the problem in a comprehensive and vigorous way. They are developing strong initiatives in creating national welfare services in the health field that extend health care to the needy and underserved.

If further proof were needed of the gross deficiencies of the public sector, it can be found in the use of drugs against tropical diseases. They are the big killers in the tropics. But as Table 5 shows, in six of the more advanced developing nations, antiparasitic

TABLE 5. COMPARATIVE RANKINGS OF THE LEADING TEN THERAPEUTIC CLASSES IN SELECTED DEVELOPED AND DEVELOPING COUNTRIES

| Therapeutic Class | Brazil | Pakistan | Philippines | Venezuela | Japan | USA | West Germany |
|---|---|---|---|---|---|---|---|
| systemic antibiotics | 1 | 1 | 1 | 1 | 1 | 3 | 7 |
| cough and cold preparations | 2 | 3 | 2 | 3 | - | 4 | 4 |
| vitamins | 3 | 2 | 3 | 2 | 2 | 5 | - |
| analgesics | 6 | 4 | 4 | 4 | - | 2 | 5 |
| psycholeptics | 8 | - | - | 8 | 9 | 1 | 2 |
| sex hormones | 5 | - | - | 5 | - | 8 | 9 |
| antirheumatics | 7 | - | - | 10 | 3 | 9 | - |
| antacids | - | 8 | 10 | - | 4 | - | - |
| hypotensives | - | - | - | - | - | 6 | 8 |
| cardiac therapy | - | - | - | - | 7 | - | 1 |
| psychoanaleptics | 9 | - | - | - | - | 10 | - |
| cholagogues | 10 | - | - | - | 10 | - | - |
| antispasmodics | 4 | 10 | - | - | - | - | - |
| nutrients | - | 5 | 6 | - | - | - | - |
| antianemics | - | 6 | - | 7 | - | - | - |
| antidiarrheals | - | 7 | 8 | - | - | - | - |
| tuberculostatics | - | 9 | 5 | - | - | - | - |
| topical steroids | - | - | 9 | 6 | - | - | - |
| diuretics | - | - | - | - | - | 7 | - |
| hematologicals | - | - | - | - | 5 | - | - |
| hospital solutions | - | - | - | - | 6 | - | - |
| cytostatics | - | - | - | - | 8 | - | - |
| peripheral vasodilators | - | - | - | - | - | - | 3 |
| vasoprotectives | - | - | - | - | - | - | 6 |
| antidiabetics | - | - | - | - | - | - | 10 |
| antiasthmatics | - | - | 7 | - | - | - | - |
| systemic steroids | - | - | - | 9 | - | - | - |

drugs account for only 1 to 2 percent of total drugs consumed.

As this is central to the main issue under discussion, I would like to emphasize that, if it were just for the private sector, this Conference would most likely not have taken place at all. It is the public sector that gives cause for alarm.

New strategies and new visions must undoubtedly be found to correct the deplorable state of the public sector. Curative medicine, modeled after health care practices of rich industrialized nations, offers little help. The primary health care program as recommended by the Alma Ata Conference in September last year may well offer a solution. The basic philosophy is sound, but only workable if national governments are willing to provide the financial support, and if the program obtains the bilateral aid and multilateral technical cooperation it deserves.

The research-based pharmaceutical companies have much to contribute to development of the public sector. They have frequently been called upon to play a more significant role in addressing disease problems of developing countries. Therefore, it is only proper to analyze problems and constraints that inhibit industry from such greater involvement.

It has now become commonplace to observe that the pharmaceutical industry is over-regulated. This is a worldwide phenomenon. In the developing world the traditional regulatory thrust is less toward assurance of safety, efficacy, and quality, as it is economic and political in nature. This impetus has escalated in recent years to the point at which international drug companies are now operating in large areas of the developing world under conditions that are quickly becoming intolerable. They are being pressured on half a dozen fronts -- most importantly patents, trademarks, and prices, but also dilution of equity, import restrictions, restrictions in transfer of royalties, and dividends.

Let me touch briefly on the nature and consequences of certain policies to restrict the activities of the multinational pharmaceutical industry in developing countries.

## Patents

It has become fashionable in Third World countries to attack patent practices of the multinational drug producers. The proclaimed reason for this assault on patent rights is that industry is employing the international patent system to prevent local production and secure import monopolies. The patent system, it is charged, makes possible an alleged overpricing of drugs by preventing emergence of local competitors who would drive prices down through market rivalry.

Although these charges have been refuted time and again, developing nations have systematically undermined patent protection for pharmaceuticals. Table 6 illustrates that patents in the Third World countries have for all practical purposes become an illusion. Patents on pharmaceutical products are simply not allowed in nearly a quarter of the nations. In other cases, patents are not legally enforceable in local courts. Or patents may be issued only for manufacturing processes, requiring a reversal of the burden of proof to those challenging the patent. In still others the patent life of five or ten years is consumed in testing the product for efficacy and safety, and securing government regulatory approval for marketing. Thus, a patent may well have expired before the manufacturer has marketed his product. Finally, an increasing number or countries routinely demand compulsory licensing, at fees so low as to be meaningless.

TABLE 6. PATENT PROTECTION FOR PHARMACEUTICALS IN SELECTED DEVELOPING COUNTRIES

| Country | Patent situation satisfactory | Patents legally possible, but worthless a/ | Patents not allowed |
|---|---|---|---|
| CENTRAL & SOUTH AMERICA | | | |
| Brazil | | | + |
| Argentina | | + | |
| Chile | | + | |
| Venezuela | | + | |
| Peru | | + | |
| Ecuador | | | + |
| Colombia | | + | |
| Paraguay | | + | |
| Uruguay | | + | |
| Mexico | | | + |
| Costa Rica | | + | |

a/Patents may be obtained which cover only the manufacturing process, they are not enforceable, their life is too short or other legal obstacles deprive the patentee of any real protection.

(Table 6 - Cont'd)

(Cont'd.)

TABLE 6. PATENT PROTECTION FOR PHARMACEUTICALS IN SELECTED DEVELOPING COUNTRIES

| Country | Patent situation satisfactory | Patents legally possible, but worthless | Patents not allowed |
|---|---|---|---|
| **ASIA** | | | |
| India | | + | |
| China | | | + |
| Taiwan | | + | |
| Philippines | | + | |
| Iran | | + | |
| Syria | | + | |
| Lebanon | | + | |
| Turkey | | | + |
| Indonesia | | | + |
| Thailand | | | + |
| Afghanistan | | | + |
| Saudi Arabia | | | + |
| Pakistan | | + | |
| **AFRICA** | | | |
| Egypt | | + | |
| Algeria | + | | |
| Libya | | + | |
| Tunisia | | + | |
| Cameroon | | + | |
| Chad | | + | |
| Zaire | | + | |
| Dahomey | | + | |
| Gabon | | + | |
| Ivory Coast | | + | |
| Madagascar | | + | |
| Mauritania | | + | |
| Morocco | | + | |
| Nigeria | + | | |
| Togo | | + | |
| Senegal | | + | |

a/See previous page.

Until the early 1970s, assaults on the patent system were on a national basis by individual countries. Since then the pharmaceutical industry has become subject to an even stronger centralized pressure from some UN agencies, in particular UNCTAD (United Nations Conference on Trade and Development) and WIPO (World Intellectual Property Organization), aiming at a drastic curtailment of the rights of the patentee, imposing heavy burdens on licensors of pharmaceuticals and related technologies.

In stark contrast to the weakening of patent rights in the developing world, industrial nations are tending toward strengthening patent protection for pharmaceuticals although, for socio-economic reasons, they too exert utmost pressure to reduce the cost of drugs. Even socialist countries have realized -- after a period of trial and error -- that the classical patent system is a solid foundation for transfer of technology and other valuable forms of international cooperation. The traditional patent system is often faulted for retarding progress in developing countries, but no evidence has been presented to show a notably improved level of technology or available drugs in countries which have weakened or abolished patent protection for pharmaceuticals. Indeed, virtual abolition of patent protection in Brazil and India, by way of examples, has neither reduced prices of pharmaceuticals, nor brought benefits to the country in economic terms, nor has local industry derived any real advantages.

Mr. Arcot Ramachandran, Secretary to the Department of Science and Technology of the Government of India, stated at the WIPO Columbo Symposium 1977, "that the provision on compulsory licences and that on licences of right have not yielded the results expected of the patent system in India. It appears that the provision of the license of right has resulted in a situation where patents relating to these areas; namely, chemical processes, drugs, and food articles, are not longer being presented for registration". In other words, transfer of technology from industrialized nations to India has already started to dry up. This process will continue as research oriented pharmaceutical companies find it inadvisable to file patent applications in India.

## Trade Name Restriction

A growing number of developing countries are abolishing or restricting trade names, and are requiring or encouraging prescription by generic name. Where trade names have been abrogated, such as in Pakistan, the result has been chaos. The market was flooded by generic drugs inadequately tested or made with slipshod or nonexistent quality control standards. Physicians found they could no longer accurately predict the effects of drug therapy, complicating management of disease and endangering patients. Consumers came to insist upon trade named drugs, and a black market in branded products soon appeared. The scheme was abandoned.

## Price Controls

Almost all developing countries control local selling prices of pharmaceuticals and the transfer prices of intra-company imports. It is an extremely difficult undertaking for any government to arrive at a satisfactory formula for control of drug prices. As a convenient expedient, governments resort to freezing drug prices, allowing adjustments for the massive inflationary rate or devaluation of their currencies only at long intervals. Such arbitrary measures short-change local subsidiaries -- plunging them into one financial crisis after another.

There is rampant misunderstanding of the basic principles of intra-company pricing policies of multinational research-oriented drug companies. This is particularly so in regard to transfer prices for active principles from which local subsidiaries produce finished products.

It has become customary to assess the reasonableness of such trans fer prices by comparing them with prices offered by imitators, who usually quote on the basis of straightforward manufacturing costs of the substance. Research-oriented pharmaceutical companies, however, are not merely offering commodities, but a complex package of goods and services. In addition to the active principle they also provide regulatory data (manufacturing and quality procedures, stability data, animal pharmacological and toxicological studies, all available clinical data, updating of these data during the product's life), medical and other technical services support, product information services which give the local company full access to worldwide experience with the product, and above all financing of research and developing aimed at discovery of future products.

Once discovered, developed, and marketed, most new drugs are capa ble of being copied at minimal expense by any firm with experience in the relevant field of manufacture. It is quite evident that such companies can offer active ingredients at prices well below those of research-oriented companies.

Arbitrary and inequitable price controls have led to price levels in developing countries that are substantially lower than in most industrialized nations.

When comparing the weighted averages for 1977 in my company, Hoechst, we find that developing countries have price levels 35 to 50 percent lower than Germany.

There can be little doubt that because of the low-price levels, problems in transfer prices and in the remittance of dividends and royalties, developing countries do not carry their share of research and development costs of the multinational drug companies. These

escalating expenses are increasingly borne by consumers in developed nations, and by drug companies which see a steady decline in their rate of return.

As can be seen, government interventionist policies, bureaucratic regulations, and manifold restrictions on activities of research-oriented pharmaceutical companies in developing nations have increased to a critical point. For our industry developing countries have become high-risk low-profit environments, posing every possible disincentive to any attempt to respond creatively to their needs, urgent as these may be.

This is a road on which I do not see that there will be a turning back as long as a deep seated suspicion of the free market system in pharmaceuticals dominates the thinking of UN agencies -- as long as these UN agencies actively support the program of the so-called non-aligned countries in urging governments of developing countries to adopt drug policies controlling foreign investments, transfer of technologies, industrial property and patents, prices, drug information, eliminating brand names and adopting generic names and, last but not least, slashing the number of products on the market. The little room for individual initiative left to drug companies is to be further reduced, virtually putting them in a strait-jacket.

Until recently, Sri Lanka had practiced drug policies of this nature for a number of years. Many faults have come to light. These include distribution of substandard drugs, acute shortages of life-saving medicines, proliferation of bureaucratic restrictions, and a crippling of the effectiveness of physicians. Since November 1977, the new government of Sri Lanka has largely abandoned the system. Many controls have been modified or dismantled. But surprisingly, some international agencies are still encouraging developing nations to adopt the very programs that Sri Lanka has discarded. It appears that the Chinese sage Confucius was right when he said that, "experience is a book that everyone writes, but nobody reads".

Though we are concerned with pharmaceuticals in developing countries, it is only proper to point out that developments in the industrialized world now also pose major challenges to research-oriented pharmaceutical companies. Increasing regulatory stringency in every country and at every stage of development has fostered a slowdown in the introduction of improved pharmaceuticals. In addition to regulatory inhibitions, the productivitiy of research has declined for other reasons. Cost containment by health insurance systems results in extreme pressures on economic issues of vital importance to the industry. Especially for smaller companies, the drug market has become dramatically less accessible. Profit margins of the industry have declined in recent years, particularly when adjustments for inflation are made. Thus, industry's resources to engage in high risk ventures with small market return are shrinking.

Continuing deterioration of the business climate in developing countries will increase disenchantment and frustration of pharmaceutical company managers in these nations. Increasingly, they will look homeward. Ultimately, the hostile environment must lead one day to withdrawal of multinational companies from the least developed countries. I do not foresee a sudden and dramatic exodus, but a gradual retreat. The companies will fade from the scene by virtue of thousands of daily decisions taken on their operational levels.

In fact, I wonder whether multinational corporations have not already begun this process of withdrawal from the developing world. I recall my own experiences in the 1950s, when so many companies entered with courage and enthusiasm into Third World countries, taking pride in their operations and the value of their contributions to the economy and society, willing to venture high risks and long-term investments. Since those days of promise and achievement, the corporate spirit has undergone a profound change. It has given way to a sense of caution and restraint. The future is no longer perceived to lie in the vast, underserved portions of the world, but in the highly industrialized countries of North America, Europe, and the Far East. Research, investment -- the thrust of priorities in general -- has clearly shifted to the markets of the industrialized world.

Proponents of destruction of the free pharmaceutical market in developing countries may pride themselves at having made so many drug companies accept their terms for operating in their countries. They may not be displeased by this eventuality. However, if they were governed less by ideology and more by a hard analysis of the gains and losses involved, they would realize that it cannot be in the best interests of their countries to destroy the operational base of those who now supply from 60 to 70 percent of the pharmaceuticals; who constitute the core of drug production in their countries; who have contributed so greatly to their industrial and social development; who are the best hope for new drugs, not only for tropical disorders, but for progress in medicaments for all the unconquered diseases they experience now and in the future.

In conclusion, let me say that health and well being of the peoples of the developing world is far more dependent on political and economic decisions than on scientific and technological developments. Governmental policies alone cannot ensure the welfare of a nation, but they can provoke its decline.

Therefore, the message of this Conference must be addressed to a wider audience than the distinguished scientists and statesmen who are within this hall. They must reach the ears not only of the United States Congress and the President, not only governmental health agencies and the academic community. They must wing beyond the seas, to legislators and policymakers of the developed nations and international organizations concerned with health, economic development, and

multilateral aid. But most importantly, they must be heard and understood by governments of developing nations. It is within their power to create economic and social environments that will enlist the aid of the developed world. It is equally within their power to erect barriers to meaningful assistance.

## B. PERSPECTIVES ON THE DISTRIBUTION AND AVAILABILITY OF PHARMACEUTICALS IN AFRICA AND THE MIDDLE EAST

Abdou M. Sallam

I am pleased and honoured to be here today at the National Academy of Sciences, sharing in this Conference on "Pharmaceuticals for Developing Countries". It is a subject to which I have given the last 25 years of my life, first as Chairman of CID, "Chemical Industries Development Company", the largest pharmaceutical company in my developing country, Egypt, then, as Chairman of the Pharmaceutical Organization, entrusted with responsibilities concerning pharmaceuticals, planning, local manufacture, import, distribution, and price fixation. Now, I am Chairman of ACDIMA, "The Arab Company for Drug Industries and Medical Appliances", created to shoulder the responsibility for developing not only a pharmaceutical industry for the Arab World, but also the manufacture of all that is needed by the health service; namely, pharmaceutical raw materials, package materials, and medical appliances.

Africa and the Middle East comprise 68 developing countries with a population of about 600 million: 400 million in Africa, and 200 million in the Asian Middle East countries. This population represents 14 to 15 percent of the world's population (4,300 million). Africa, home to 10 percent of the world's population, accounts for only 2 to 4 percent of the word's drug consumption of $49 billion, with an average annual per capita consumption of only $3. In the Middle East Asian countries, the situation is a bit better: 5 percent of the world's population here accounts for 2 percent of the world's drug consumption, with an average annual per capita consumption of $5.

For the whole world the average per capita consumption was $11 in 1977. Developing countries, which comprise 75 percent of the world's population (3,200 million), consumed less than 20 percent (a per capita consumption of $3), while the developed world, comprising 25 percent, accounted for more than 80 percent of the $49 billion world's consumption of drugs, with an average per capita consumption of $34.

In developing countries the per capita consumption in 1977 varied from 90 cents in North Yemen, and $2.0 in Nigeria, to $20.0 in Kuwait. In the developed countries, consumption varied from $46 in the United States, to $55 in Japan, $57 in France, and $65 in West Germany, for an

average of $34. Six of the most advanced countries, (U.S.A., Japan, West Germany, France, Italy, and England), home to only 12.5 percent of the world's population, accounted for 55 percent of the world's consumption.

The consumption and availability of drugs in Africa and the Middle East are influenced by several factors:

First: the intrinsic characteristics of drugs Drugs differ significantly from other consumables. As there is always a risk in taking any drug, potential risks limit consumption. Because of prevailing endemic diseases in developing countries, these possible risks are greater than in developing countries mainly because of prevailing liver afflictions mentioned for steroid hormones this morning; thus, drugs have to be registered before their use can be permitted.

Proper legislation is vital to permit drugs to be circulated on the market. A significant trend in all Middle Eastern and African countries is beginning to emerge in new legislations.

Another unique intrinsic characteristic of drugs is that they usually have to be prescribed by a doctor. Thus, physicians act as "purchasing agents" for the consumer. The consumer, all over the world, is thus "captive" to a degree not present in any other industry.

The question of branded versus generic drugs is very important to the majority of developing countries wishing to benefit from the availability of reasonably priced generic drugs of adequate quality.

Second: the characteristics of the population Physical size, age distribution, mortality rate, urban concentration, culture, and traditions are important determinants of drug use. Having been previously colonized, and with high illiteracy rates, the majority of the population in the Arab and African countries still prefer imported drugs.

Third: type and pattern of illness Diseases of the elderly populations of industrialized countries differ basically from those of the younger populations of developing countries.

Fourth: the social security system The systems differ widely from country to country. However, the trend is toward an integrated and comprehensive public system, with increased governmental controls.

Fifth: price controls In countries such as Egypt and Iraq, with efficient and sufficient control of the drug market, there are also price controls. The public price is fixed over longer periods (at least for one year), and is not changed unless major unforeseen events occur.

Further, and applicable both to imported and to locally manufactured drugs, the public price is fixed in relation to the need, and not according to the cost of purchase or manufacture. Cost is only one of many factors taken into consideration. The more essential a drug (as for life-saving drugs), the more it is used for long periods of time (as with antidiabetic and anticancer drugs), and the poorer the patient is likely to be (as in the case of antituberculosis drugs), the lower the public price will be. This is offset by fixing the public price of drugs of lesser import, such as vitamins and tonics, at prices much higher than cost, thus allowing the importer or local manufacturer a net overall profit of 10 to 15 percent on his business activity. With this form of internal subsidy, drugs are made more easily available to meet the real needs of the masses without any financial burden having to be shouldered by the government.

Sixth: the environment Climatic conditions determine the nature of many infectious and endemic diseases which prevail in Africa and the Arab countries.

Seventh: medical practice and the existing infrastructure In developing countries, "shock treatment" tactics often tend to be used to combat infections peculiar to the local settings. The relative scarcity of doctors and institutions, and the high cost of drugs relative to per capita income, also influence drug consumption.

Eighth: political and economic instability Many African states gained their independence relatively recently. They have not yet attained political stability. The crisis of development in Africa is characterized by:

- Excessive dependence on external forces, resulting in local repercussions from economic fluctuations among the industrialized countries.
- Inflation has led many governments to resort to deficit financing which has inevitably aggravated inflationary pressures.
- Many African states are burdened by rapidly growing, crippling debts.
- Except for the countries of the Arabian Gulf, Libya, and perhaps Algeria and South Africa, African and Arab countries suffer — to varying degrees -- from shortages of hard currency.

Overall, drug consumption is growing relatively rapidly, with annual growth rates of 16 percent in Africa and 19 percent in the Middle East being recorded. Consumption by the smaller urban populations is much greater than among the much larger rural populations.

Measures aimed at controlling prices, quality, and quantity of

drugs are now being exercised by many African and Middle East countries. In Kuwait, for example, a new ruling has been introduced, requiring registration of all pharmaceutical products registered prior to 1978. This measure is an attempt to prevent import of pharmaceuticals which do not comply with the regulations, and to reduce the number of preparations available on the market.

In most countries of the area, a large number of products is registered of which only a fraction is actually used. In the Sudan, for instance, 15,000 products are registered, while only 3,500 are being used.

Local production (if it exists at all) is carried out by several (usually) small manufacturers and under inadequate conditions. On the whole, the Arab world manufactures 44 percent of its consumption, whereas Africa manufactures less than 10 percent of its current requirements. Egypt, however, satisfied 85 percent of its requirements through local manufacture; Morocco produces 70 percent, Iraq 40 percent, and Syria 15 percent. In most other Arab and African countries local manufacture accounts for smaller fractions of indigenous consumption despite the fact that experience (in Egypt) has shown that local manufacture of a previously imported drug saves about two-thirds of the hard currency paid to import it as a finished product. In other countries, various fractions of local manufacture are accounted for by drugs produced under licence (with varying conditions) from foreign producers. The output of local manufacture is limited by difficulties in importing raw-materials, the cost of which is often greater than the price offered by overseas suppliers for finished products. The incentive to local production (costing about 15 to 20 percent more than the lowest tender price) is often not sufficient to ensure utilization of plant capacities for local manufacture.

Usually, local manufacture also entails small sacrifices in the appearance of the package for the sake of making the public price as low as possible.

Relatively little is spent on research and development. Many available medicinal plants and raw materials are not studied or exploited. Only weak linkages exist between industry and the research centers among faculties of pharmacy, medicine, veterinary medicine, and the sciences. Unfortunately, drugs and vaccines for veterinary use do not receive due attention; the rights of animals are sacrificed to the demands of mankind.

## Recommendations for Future Implementation

1. The many small national markets must coalesce into larger regional markets to collaborate on and coordinate import policies, thus making possible purchases at better prices and under more favorable

conditions. More funds would then become available to improve availability of pharmaceutical products and facilitate their distribution at lower public prices. Real savings for patient and community would result. The countries of the Arabian Gulf have already adopted a pool arrangement for drug imports.

2. Encourage, finance, and provide generous incentives for research on innovative drugs directed against major scourges, and especially the diseases endemic in tropical areas. Strengthen the links between the pharmaceutical industry and research centers. Investigate medicinal plants and other potentially useful natural resources.

3. Intensify and upgrade control measures and facilities; devise appropriate rules and regulations for production units, machinery, and buildings; adopt proper manufacturing procedures; ensure proper storage and transport conditions; schedule appropriate sampling intervals, including for on-the-shelf products.

4. In Arab and African countries, it would be better to avoid permanency of registration in favor of 5-to-10 year intervals. This would permit revision and elimination of obsolete drugs, and increase the alertness of registration authorities toward nationally or internationally discovered side-effects. It would also prevent unnecessary accumulation of drug lists. Any changes should be communicated readily and frequently to physicians and pharmacists.

5. When considering availability and distribution of drugs, strive for equity between:

   a. urban and rural populations;

   b. rich and poor; and

   c. needs of human beings and those of animals.

6. Seek inter-regional cooperation, as advocated by international authorities (APEC, UNIDO, UNCTAD, WHO), toward creation of regional cooperative production of pharmaceuticals and establishment of Technology Centers (COPPECS) to realise the following:

   a. Establishment of priority lists for the pharmaceutical needs of each developing country.

   b. Adoption of a generic nomenclature.

   c. Establishment of national procurement agencies for purchase and supply of pharmaceuticals.

   d. Revision of patent and trademark laws.

e. Establishment, where possible, of a domestic pharmaceutical industry, beginning with formulation and packaging, and developing towards more complex production activities, if economically feasible.

A realistic example of regional collaboration is now undergoing trials in Arab countries. These countries established a Pan Arab Pharmaceutical Company (ACDIMA) in accord with the previously stated aims and on a diversified basis also embodying medical instruments, appliances, and devices, together with meeting the needs of veterinary medicine. All these activities are to be supported through a research and development capability which is to guarantee the appropriate adoption, adaptation, and improvement of the pharmaceutical technology which has been transferred.

The company was established in March 1976, and has been collaborating with other countries and with UNIDO to begin implementation of essential projects for production of:

- Pharmaceutical raw materials, including some antibiotics; and some synthetic bulk pharmaceutical chemicals.

- Pharmaceutical packaging materials, such as glass containers and hard gelatin capsules.

- Other pharmaceuticals, such as medicinal plant extracts, extracts of animal by-products, veterinary pharmaceuticals, and large volume parenteral solutions.

- Medicinal appliances

  ACDIMA also is to help the eleven Arab countries without indigenous pharmaceutical production to start a formulation industry; and help those now in possession of such industry to upgrade it and make better use of facilities.

ACDIMA aims to increase the percentage of local drug manufacture in the Arab world from the present 44 percent (1977) to 60 percent by 1985. This is a gigantic ambition. It means that the current local manufacture of $528 million will have to be tripled to $1,560 million to meet the needs resulting from the present 15 percent annual increase in consumption. For the next seven years, this will mean that present production capacity must be augmented by four new factories yearly, each with a production capacity of $20 millions.

Already this year, the countries of the Arabian Gulf are building two new factories — one in Iraq and the second in Ras El Kheima. The Gulf countries' health ministers have decided to add two more: one in Kuwait and the other in Saudi Arabia. ACDIMA is executing these plans. Egypt is also building a new formulation plant with participation from

ACDIMA. However, ACDIMA, despite its noble and humanitarian aims to make drugs available more easily and cheaply to the 160 million Arab citizens the company was created to serve, is meeting great difficulties due to international rises in prices of drugs and raw materials, and the growing difficulty and expense of technology assessment and transfer in the manufacture of raw and packaged materials.

A factory for manufacture of antibiotics, previously estimated to cost about $40 million, will now require an investment of $90 million; worse, the pharmaceutical glass factory projected to cost a maximum of $45 million, is now estimated to require an investment of $128 million These costs are almost prohibitive for anyone, even for a group of developing countries wishing to embark on the manufacture of raw or packaged drug materials

What can be done by the United States and the American pharmaceutical industry? I cannot add much to what Dr. Krause has said. I second all his suggestions. The fact, as mentioned by another speaker, that more than 50 million dollars have to be spent before a new medicine can be marketed essentially precludes such research by developing countries. Therefore, please carry out your research on tropical diseases in the developing countries concerned. It is much cheaper, and there are enough people with advanced degrees, and enough laboratories and research facilities for the purpose.

As we were told by previous speakers, the world suffers from having more than half its 4,300 million population afflicted with ill health. This is reflected in unrealized productivity and production, poverty and low purchasing capacity, in addition to being a reservoir of illnesses, many of which are endemic or epidemic, and which pose the risks of periodic flare-up and spread. If this were to continue unchanged, I cannot believe the world would be able to cope with a population of 7,000 millions in the year 2000, only 22 years from now, especially if more than half would -- as now -- have less than the minimal acceptable level of health. I believe this situation would be very harmful to developed and developing countries alike.

I claim that, in the long run, it will be to the benefit also of the developed countries to struggle against ill health anywhere in the world, and to devote a maximum effort to improve this situation. This cannot be done if technological achievements and advances in the health fields -- including pharmaceuticals -- remain confined to the developed countries. It is not only inhuman to deprive the poor of the benefits of scientific advances in prevention and treatment of disease because of their prohibitive cost; this is also against the interests of the owners of the technology, and of the world as a whole.

On the other hand, we were told that the pharmaceutical industry is not a charitable organization, and should not be expected to invest more in research on diseases of the developing countries to find drugs

that cannot be profitably marketed because of the prevailing poverty and low purchasing power of those countries. There is no guarantee that they will get a return on their investment.

What can be done?

From the platform of this shrine of science at "The National Academy of Sciences," I am launching a plea to all scientists of the world. It is time that scientists and the United Nations devote more serious thought and action to improve dramatically the present state of ill health in the world. Health improvement should become of central concern to the world. No sick person should be deprived of the benefits of scientific advancement. Sickness should not any longer be a source of excessive wealth to anybody.

All discoveries and scientific advances in the health field should belong to the world and become the world's property, but without harming or impairing research in any way. The discoverer or technology owner should be compensated generously for his efforts and expenses. He can be repaid doubly or triply for his work.

The idea of world ownership is neither fancy nor new. UNESCO already regards temples, monuments, historic buildings, and other treasures as part of the human heritage, and pools money to preserve them as a source of enjoyment and nourishment for mind and soul; it is time for the world also to pool money and raise a fund through WHO, UNIDO or a new "International Bank of Health". In this way, the world can own discoveries and technologies in the health field, and make them available especially to developing countries, not gratis, but at prices adjusted to each country's purchasing power. A revolving fund of perhaps $50-100 million would be enough to achieve this noble, essential, and long hoped-for objective. UNIDO has already been thinking along such lines, buying the technology for chloroquine manufacture to make it easily available to India to enable her to control recurring malaria. Unfortunately, I learned only last week in the UNIDO Conference held in Cairo -- on the same subject, "Pharmaceuticals for Developing Countries" -- that this objective could not be achieved.

It is a race with time, and this is the only hope for achieving a healthier world in the year 2000.

In summary, and as a citizen of a developing country, let me express my deepest respect, appreciation, and gratitude to the American government, scientists, and industry for the care and interest they devote to developing countries and the health of their populations. What I have heard from Mr. Kennedy and the other American speakers at this Conference permits me to return home much more pro-American than I ever was before I came.

# C. PROBLEMS OF DISTRIBUTION, AVAILABILITY AND UTILIZATION OF AGENTS IN DEVELOPING COUNTRIES: AN ASIAN PERSPECTIVE *

Sanjaya Lall

This paper represents an economist's view of the main problems in providing adequate medication to the populations of poor countries. In taking the "Asian perspective," there is of course considerable latitude in what one can cover, from the problems of OPEC countries in digesting their vast wealth to those of Mainland China in providing socialized medicine on meager resources. I shall only pick on the experience of two South Asian countries -- India and Sri Lanka -- with which I have some familiarity. Even these offer a wide range: Sri Lanka with a relatively unindustrialized but socially advanced economy, endowed with a good educational infrastructure, but suffering from a long period of economic stagnation and dependent on imports for most of its medicinal needs; and India with its impoverished masses, poor social facilities and enormous size, on the one hand, and advanced industrial capabilities, strong indigenous entrepreneurship and increasing penetration of world pharmaceutical markets, on the other. Between them, these two countries furnish a fairly broad range of drug provision problems in developing countries.

In this brief space I cannot hope to deal with the whole array of relevant issues.1/ I shall, therefore, concentrate on a few which the recent experience of the South Asian countries has revealed as particularly significant. Furthermore, I shall only discuss problems of drug distribution and availability: it is beyond my competence to deal with problems of utilization.

I shall proceed as follows. First, thumbnail sketch of recent policy developments in the pharmaceutical sector in India and Sri Lanka; second, a discussion of the main problems as far as the availability of drugs is concerned; third, problems of drug distribution; last, the main conclusions.

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## Recent Pharmaceuticals Policies in India and Sri Lanka

The Indian Government has traditionally followed a policy on pharmaceuticals composed of these elements:

- a heavy emphasis on import substitution in all stages of manufacture, down to the basic stages of manufacturing fine chemicals;
- the promotion of "Indianization" in the ownership of the industry, with exceptions made only in cases where very advanced technologies are involved;
- the promotion of public-sector manufacturing activity in bulk drug manufacturing; -
- a reduction of patent protection and a liberal interpretation of patent laws to favour domestic imitators of foreign technology;
- strict price controls on drugs; and
- encouragement of research and development locally, especially for plants and herbs.

In recent years, especially following upon the official Hathi Committee Report on the industry,2/ the government has increased its emphasis on "Indianization" of foreign drug companies, though more extreme demands for nationalization have been rejected. The overriding concern of the government continues to be promotion of local production, and to this end increasing attention is given to attracting advanced technology from abroad, by licensing where feasible and by direct foreign investment where necessary. The last two or three years have witnessed the following significant developments.

The Hathi Committee's recommendation on gradual abolition of brand names has been accepted, though initially it will be implemented (in the teeth of fierce industry opposition) on only five drugs; it is not clear how far and how fast this will be extended.

The emphasis on self-sufficiency in drug production continues, but with greater attention placed on the 117 "essential drugs" identified by the Hathi Committee (it is not, however, clear how the essential drug program fits in with a 5-year plan (for 1978-83) to boost production and exports). Production has registered sustained growth recently, and reached $1.3 billion in 1977-78, an increase of 25 percent over the previous year (formulations grew by 27 percent and bulk drugs by 9 percent 3/); however, the Indian government identified the "non-availability of certain technologies" as a major barrier to fuller future development of the industry.

Exports are increasing as rapidly as production. In a three-year period (March 1975 to March 1978) the exports of bulk drugs and formulations doubled, and in the first six months of the current fiscal year (i.e., March-September 1978) they have increased over 40 percent compared to the corresponding period last year.4/ On an annual basis this yields total exports of some $80-90 million, directed mostly at the United States, Eastern Europe, Japan, and the Soviet Union. The government is putting a major effort behind its export drive, especially to increase bulk drug exports to Europe and to other developing countries. A planned development of special interest is "offshore formulation" of Russian bulk drugs for re-export to Russia and third countries.5/ This is the first time, at least in India, where such activity (common in electronics and transport equipment) has been found to be economical in pharmaceuticals, and this has important implications for the course of development of the industry in the Third World.

Development of local technology is being promoted both within the foreign and local sectors. For foreign firms, only firms which produce "high technology" drugs will be allowed to retain majority equity participation.6/ Furthermore, the government is planning to require all foreign firms to invest at least 4 percent of local turnover in research and development in India.7/ At the same time, the Central Drugs Research Institute in Lucknow is proceeding with its research, mainly into plants and herbs, and has taken out several patents. Several Indian firms (public and private) have been successful in process innovation: improving imported processes, making new processes and adapting processes to use locally available materials.

India has, in a modest way, become an exporter of pharmaceutical technology. It has set up its own "mini multinationals" which are investing in neighboring Asian countries; the IDPL (Indian Drugs and Pharmaceuticals Limited, a large public sector firm) is selling turnkey plant technical assistance and training services to Arab countries, Sri Lanka, and Bangladesh; Sarabhai Chemicals (a private firm) is setting up a turnkey multi-purpose plant in Cuba, under a contract awarded by UNIDO; and several possibilities of technical cooperation with Latin America are being explored, again under UNIDO auspices. A few drug patents have been sold abroad for commercial exploitation.

The Hathi Committee commented extensively on the serious problems raised by poor quality control and lack of adequate testing and inspection facilities in certain parts of the country. Surveys have shown that the proportion of poor quality and 'spurious' drugs on the market is unacceptably high. There is little doubt that the foreign firms have excellent records in this respect, as do most of the larger units in the 'organized' sector. Most of the difficulties arise with the myriads of small firms, especially formulators, but they must not all be tarred with the same brush: many of them are extremely efficient producers. However, several are incompetent, ill-equipped or simply corrupt, and, despite efforts to eradicate them, grave deficiencies in

this respect still persist.

Let us now consider Sri Lanka. In 1972, Sri Lanka set up a State Pharmaceuticals Corporation (SPC) to centralize all drug imports, to economize on their purchase and to replace the sale and use of drugs by brand names to generic names.8/ Sri Lanka was, and continues to be, dependent upon imports for the bulk of its drug needs; local production, by a few small local firms and five affiliates of foreign firms, was confined to the relatively simple formulation and packaging of a few imported pharmaceutical chemicals. The main features of Sri Lanka's reform were:

The number of drugs imported was reduced to 600 from several thousand brand named versions of 2,100 drugs. This rationalization in purchase of drugs, implemented by a committee comprising pharmacologists and medical practitioners, sought to delete imitative drugs, "irrational" combination drugs and drugs of high toxicity or unproved efficacy. It was implemented gradually, and its progress depended on the resistance emanating from the medical profession. The experience of the United States Food and Drug Administration in checking the safety and efficacy of drugs proved to be of major significance in guiding this aspect of policy.

It was sought to economize on the costs of drug purchase by buying in bulk, by buying generically and by "shopping around" world markets, subject to the overriding consideration of getting drugs of adequate quality and bioavailability. Many drugs continued to be purchased from the multinational firms which had traditionally supplied Sri Lanka; others were substituted for by small firms in developed countries, East European producers and other developing countries (mainly India). The savings achieved were considerable (over 40 percent in 1972), depending on the extent of competition before the reform and the source of purchase;9/ the benefits accrued automatically to the consumer in terms of correspondingly lower prices. While some problems were encountered with the quality of a few drugs -- and these were seized upon and publicized by opponents of the reform -- there is little doubt that the overall benefits far exceeded its (probably inherent) risks even in the early stages.

The process of rationalizing the imports of finished drugs proved easier than those of pharmaceutical chemicals for local formulation, because of the resistance put up by local affiliates of foreign (British and United States) enterprises. The government found itself unable to make some of them formulate chemicals imported by the SPC, both because of pressures exerted from abroad and because of its own deteriorating political position.

The SPC succeeded in achieving a considerable, but not total, switch in use of drugs by brand names to their use by generic names. This move was strongly resisted by the medical profession (for reasons

well known to everyone familiar with the industry); nevertheless, a process of re-education and re-information, coupled with careful control on quality of generic drugs, did succeed in rationalizing prescribing practices to some extent, and in providing more objective information on use of drugs than is normally provided by market mechanisms.

Clearly, the Sri Lanka case is valuable for study of the problems of drug availability and distribution in developing countries. Its main interest lies in the sweeping nature of the reform in terms of defining need for drugs, identifying source of supply and rationalizing the information and distribution system. The Indian experience, on the other hand, serves to highlight issues of industrial and technological development, since Indian policies have not dealt with problems of drug proliferation, brand/generic names (except marginally), or information dissemination.

While the achievements of reform in Sri Lanka were impressive, resistance from multinational affiliates, drug importers, and the medical profession continued, and the change of government in 1977 led to some emasculation of the activities of the SPC. Detailed information on the most recent developments are not available but indications are that a private market, with brand-named drugs, will be restored,10/ and that the SPC will continue to function as the major importer for the state health services and possibly also (like CEME in Brazil) for the poor sections of the population. It is also likely that more drugs will be bought by the SPC from the multinational companies and that product patents (which were never abolished) will be observed more strictly.

## Problems of Availability

The problems of drug availability may be discussed under three general headings: imports, local production, and the range of drugs to be provided. Let us take them in reverse order.

1. The problems concerning number and types of drugs to be provided by developing countries are currently receiving a great deal of attention in discussions of the WHO's work on "Essential Drugs." Because this will be taken up in detail by another participant, I need not go into details here; I would, however, like to make a couple of points in passing.

First, some confusion exists about what a list of "essential drugs" contains. The WHO seems to interpret it, as does India, as a list of most commonly needed drugs for primary health care, a sort of "priority" list, which must be filled (in the large quantities needed) before the other drugs are provided, but which coexists with a free market unrestricted supply of drugs elsewhere in the country. Others interpret it as a "rationalized" list of all drugs provided in a country, similar to

the SPC's list in Sri Lanka; of these, allocations are made according to need and cost between the major requirements of drugs at the primary care levels and the minor, but perhaps more expensive, requirements at the secondary and tertiary levels.

Second, these two concepts of "essential drugs" are directed at different problems and entail different sets of policies. The "priority" drugs concept is concerned mainly with the fact that primary health care in developing countries is gravely deficient and that the drugs required are expensive in relation to available resources. It thus aims to bypass the market mechanism by obtaining increased quantities of essential drugs at reduced prices in world markets (e.g., the WHO scheme in cooperation [so far] with German, Swiss and a few French firms), or by stepping up domestic production and subsidizing prices to the consumer (the scheme proposed in India).11/ The "rationlized" drug list concept, based on formularies used in most hospitals, is concerned with the fact that the free market throws up a tremendous proliferation of branded drugs, backed by powerful and expensive promotion, and on average priced much higher than generic equivalents. Thus, it seeks to reduce some of the confusion in information flows inherent in the present system, to improve prescribing practice, to reduce prices and obtain all drugs at competitive rates. The second scheme is far more sweeping and difficult to implement than the first, but I believe that a good case can be made for thoroughgoing "rationalization" in poor countries.

Third, there are several problems in trying to implement any sort of essential drug scheme. Not only is there great resistance from large, multinational drug firms 12/ and from the medical profession, there are two real risks which have to be faced: (1) a bureaucratically determined list may be too inflexible to provide the best therapies, and (2) cutting of prices on brand-named drugs may have an adverse effect on innovation. These subjects are beyond the scope of my brief, so I will not discuss them further.

2. The area of local production of drugs contains a host of difficult issues, most of of which are general to the whole problem of industrialization in the Third World and not peculiar to this industry. However, they do arise here as much as anywhere else, and, in view of the fact that most developing countries have identified pharmaceuticals as an important area for industrial growth, it may be worth taking them up.

Most developing countries confine local manufacturing of drugs to simple formulation and packaging activity, where skill requirements are narrow (mainly for quality control), scale economies absent and capital investment relatively low. A few, like India, Argentina, Brazil, Mexico, and Egypt, have gone beyond this stage to production of drugs from first stages, with India having the most diversified and vertically integrated structure, supported by a large research establishment. Since Sri

Lanka's problems are much more elementary as far as local production goes, I shall confine myself to India.

The problems in promoting the availability of drugs through local production may be divided into four headings:

(1) Technology: The major constraint on further development of the pharmaceutical industry in India now is availability of new and complex technology. There are three ways to resolve this constraint: direct investment by foreign firms in production of bulk chemicals; licensing of technology by foreign firms of local enterprises, public and private; and indigenous development of process technology. All three are, as indicated above, being actively pursued by Indian government. Multinational firms are being encouraged, and pressed, to invest in high technology areas of bulk drug production in the country; local firms are entering into joint ventures and licensing agreements with foreign holders of technology, in the Eastern as well as Western blocs; and development of local technologies has achieved a certain degree of success. There is, however, some conflict between the desire of multinational firms to exploit proprietary technology themselves, and that of the Indians to buy it outright for their own use. While such conflict is natural in an R&D based industry with high rents accruing to innovators, it has been exacerbated, on the one hand, by reluctance of the multinationals to enter bulk drug production in a big way and to part with their technology, and, on the other, by price controls and "Indianization" requirements of the government. No doubt this conflict over technological ownership between foreign firms and local ones has led to a weakening of the patent system to accommodate the growing capabilities of the latter.

(2) Public and private sectors: A different sort of conflict has simmered in India between the public and private sectors in pharmaceutical production. Though the public sector has devoted most of its activity to bulk drug manufacture in areas where private firms were reluctant to invest, the conflict has focused around, first, the fact that private formulators were required to use bulk drugs made in the public sector (allegedly at small scales and consequent high costs), and, second, exclusion of private firms from areas where they did want to enter. It is difficult to assess the merits of these debates. There is an inevitable ideological element in the public-private controversy which makes an objective evaluation of arguments very problematic. It can hardly be denied that most public enterprises in India have had "running in" problems, especially in industries where new, complex, and often unsuitable technology was imported. On the other hand, it is clear that recent performance of the public sector in general, and IDPL in particular, has shown remarkable improvement, with a professionalization of management, investments in in-house R&D and aggressive attacks on export markets. I do not myself see the public-private conflict as an important source of problems in drug availability in India.

(3) Poor quality control: This problem afflicts mainly the thousands of small scale producers whose promotion is a strong plank of government industrial policy. The Hathi Committee identified several causes of this phenomenon: poor technical and mechanical facilities, inadequate inspection facilities, corrupt practices, the attractions of imitating high-profit branded drugs, and so on. Clearly, none of them admits to easy solutions. As noted previously, the experience of several excellent small-scale producers leads us to believe that they can serve a very useful economic purpose. However, the incidence of substandard drugs on Indian markets (about 20 percent according to one estimate) is too high to contemplate with any complacency.

(4) Price control: The Indian government operates, like most others, a pervasive and strict system of price controls on drugs, and producers complain, as they do elsewhere, of the detrimental effects on profitability. The price control formula is complex, with differential incentives built in for R&D, bulk drug production, exports and so on, and with some prices frozen over long periods. In view of recent investments by local and foreign companies, and their consistently high recorded profitability, it is difficult to believe that the system is as much of a straitjacket as the trade associations claim; on the other hand, it is also difficult not to believe that the system is cumbersome, often rigid, and sometimes inimical to the stated aims of the government to promote investment and innovation.

3. The issue of drug imports can best be considered for the case of Sri Lanka, and may be subdivided into two components: import of finished pharmaceutical products, and that of intermediate pharmaceutical chemicals.

Problems facing developing countries in the import of finished drugs are in essence an international extension of problems facing the U.S. Food and Drug Administration in promoting generic prescribing, or of European authorities in introducing a two-tier price structure for new and imitative drugs. Problems of quality and bioequivalence are, however, much more serious for a small country "shopping around" on world markets, for obvious reasons, than for a national authority promoting generic sales from domestic manufacturers. To counterbalance this, the developing country has the option of renouncing patent legislation, or at least implementing patents "flexibly", which is not open to a national drug authority like the FDA.

The general problems of substituting generic for branded drugs, of ensuring equivalence, or winning doctor/consumer acceptance, are too well known to repeat here. It should suffice to point out that there is, on the one hand, considerable scope for safe, desirable, and economical substitution (especially within the framework of an essential drug list), but that, on the other, there do exist serious problems which call for very cautious, gradual, and well-planned reform. The

United States leads the developed world in promotion of drug substitution and in fostering of a dynamic generic market: what developing countries need to do is to create such a market on an international scale. Such a policy is clearly very difficult for an individual country like Sri Lanka. Its experience shows that its tendering procedures did not reach the main generic market in the United States, that its limited resources forced it to refuse bids from, say, Italy where it could not evaluate the manufacturing practices of the firms concerned, that its quality control procedures were not fully effective and that the pressures brought by brand-name manufacturers on doctors could, for these reasons, slow down reform. A more broadly-based scheme, comprising a group of developing countries, or an international body like WHO, or a North-South cooperative venture of regulatory bodies in rich and poor countries, has obvious advantages in countering these problems. The most significant developments in this context are the WHO-Certification scheme for drugs sold to developing countries and the Swiss-German scheme of providing a few basic drugs at preferential prices through WHO -- in effect launching a competitive generic mini-market for multisource drugs.

As far as new patented drugs are concerned, the problems are more difficult. Should poor countries, facing acute shortages of medicines, observe patents on drugs innovated mainly for rich countries? What is the "right" rate of return on drug innovation? How long is the "right" life for a drug patent? How should the burden of financing innovation be shared between rich and poor countries? There cannot be straightforward answers to these questions, for three reasons: (1) institution of the patent system as such is controversial, and debate will always continue on the correct balance between private monopoly and public interest; (2) there is a fundamental value judgment involved about sharing of costs of innovation between nations; and (3) patents may enable a broadly-based monopoly position to be built up which provides returns often in excess of a "just" reward for innovation, and it is practically impossible to separate these two elements. The best solution here may be for both sides to recognize that compromise is required. Drug companies should accept that poor countries constitute a special case in that their need for innovation is low (except for specific tropical diseases), their ability to pay is limited and their propensity to renounce patents is high. The developing countries, for their part, should recognize that some form of adherence to patents is desirable in the interests of innovation, and that a stable legal framework may help to promote investment and transfer of technology.

A brief note on pricing of intermediate chemical imports: the main problem in this context is that of transfer pricing of imports by affiliates from their parent companies, and the pharmaceutical industry has received the greatest amount of exposure over this issue. As with patented finished drugs, pricing of intermediates involves immense difficulties in evaluating correct rates of return on risky innovation. However, given the flexibility inherent in pricing of intra-firm trade,

and limitations of government monitoring, there is little doubt that the firms concerned use such trade to minimize tax burdens and reduce exposure to other types of risks. The Sri Lanka experience shows the large reductions in prices of intermediate chemicals which could be obtained by bargaining and "shopping around" (83 percent on ampicillin was offered by Beecham, and Hoechst was prepared to supply tetracycline at 80 percent below prices charged by Pfizer).

In general, however, it is the developed countries that have gone furthest in regulating possible transfer-pricing abuses by multinational enterprises. Developing countries tend to veer between excessively restrictive regimes and overly liberal ones on controlling intra-firm prices, but they lack resources to mount a continuous, sophisticated and comprehensive survey of transfer prices.13/ While richer countries progress towards information exchange between tax authorities and even international joint tax audits (being started by Canada and the United States), poorer ones are in danger of being excluded from a privileged club of efficient tax administrations. The problem stretches far beyond the drug industry, of course, but this industry is the one where it comes up most frequently.

## Problems of Distribution

Problems of drug distribution may be discussed under three headings: drug information, drug pricing, and the physical distribution of drugs.

Under the general title of "information," we may place the range of vexing but well-known problems concerning high costs of promotion, brand versus generic names (which have been discussed above), and labelling and information provision, which are familiar fare for everyone dealing with the industry in the United States. It is also widely recognized that these problems may be worse in developing countries because doctors are even more dependent on companies for their information on drug use, and because authorities are more lax in controlling advertising and claims by the companies.14/ A strong case can be made that an alternative system of information provision can work more cheaply and effectively to promote rational (and economical) prescribing.

Few developing countries have attempted to install such a system. India has, by and large, tended to ignore problems in this broad area. Sri Lanka has launched a thorough reform, with tremendous resistance from the medical establishment, but it is as yet impossible to evaluate the success of its attempt. Some other countries, like Afghanistan, are banning advertising of branded drugs altogether, but it is not clear what alternative channels of information dissemination will replace it. One interesting proposal by Drs. Andrew Herxheimer and N. D. W. Lionel, for "minimum information" data sheets (MIDS), deserves

serious consideration in this context.15/ The MIDS are supposed to counter deficiencies in the present system of providing information to doctors in the United Kingdom and elsewhere, by providing concise and easily digestible information on clearly validated uses, more controversial uses, serious and less serious side effects, and so on. An internationally harmonized MIDS system, provided as a counter to the existing system, can be greatly beneficial in developing countries, and may serve as a basis for rationalizing the whole information system in the longer term.

The problem of drug pricing is so complex that it would be impossible to do it justice here. The central difficulty arises from pricing of innovations relative to other drugs, and we may refer to attempts of various European countries (mainly France) to set up a system which encourages innovation while forcing down the price of imitation drugs. India has, as noted above, a system with four categories of drugs, each with different markups over cost, but I am not equipped to discuss it in detail. While it is feasible to generate any number of pricing systems with different incentives for different kinds of drugs, the inherent problem of reconciling private incentive with public interest is difficult to resolve, especially when risky innovation is at stake, and each society must strike its own balance. Developing countries may tend to strike it on the side of economy rather than innovation, and perhaps this is justifiable given their needs and resources.

Physical distribution of drugs raises several problems: location of pharmacies, their accessibility, storage facilities, stocking practices, control over drugs with short shelf-lives, refrigeration, transportation, and so on. It is almost a definition of underdevelopment that distribution is much worse in rural areas than in urban ones, and that the best facilities are centralized where rich elites live. It is difficult to see how drug distribution can be radically improved without a tremendous upgrading of the primary health care delivery system; and this, in turn, may require a much greater emphasis on social equity than many developing countries are prepared to give. Within the given structure, however, there may be substantial gains possible by improving transportation, storage, and pharmacy facilities, but discussion of these is not the task of the economist.

## Conclusions

In this paper I have touched on a vast array of problems. It is beyond my present brief to discuss policy requirements to remedy them, but several recommendations have naturally been implicit in the discussion of difficulties facing developing countries. In another recent paper, I have tackled more directly what multinational drug companies may do to meet the aspirations and needs of the Third World.16/ The most general conclusion I arrive at is that the "free market" system as it now exists is incapable of resolving the various conflicts that

exist between drug multinationals and developing countries without substantial modification. It needs reform in terms of the number and prices of drugs it provides, of the assistance it gives to local production capabilities of less-developed nations, of the system of drug promotion and information dissemination, and of the importation and distribution of drugs. To some extent, developing countries can achieve improvements on their own, but clearly they run up against barriers after a short distance: and here assistance from abroad, even in terms of an acceptance of their objectives and policies, would be very helpful. At the same time, a massive structure of controls and regulations should not be recommended lightly to the administrations of developing countries. It is to be hoped that some flexible and pragmatic compromise will emerge which achieves progress with minimum cost and conflict.

## REFERENCES AND NOTES

1. I draw upon some of my earlier work, in particular "The International Pharmaceutical Industry and Less-Developed Countries, With Special Reference to India," Oxford Bulletin of Economics and Statistics, August, 1974; "The Political Economy of Controlling Transnationals: The Pharmaceutical Industry in Sri Lanka 1972-1976," (with S. Bibile) International Journal of Health Services February 1978; and The Growth of the Pharmaceutical Industry in Developing Countries: Problems and Prospects, Vienna; U.N. Industrial Development Organization (ID/204), 1978.

2. Report of the Committee on Drugs and Pharmaceuticval Industry, Ministry of Petroleum and Chemicals, Government of India, 1975, Chaired by Mr. J. Hathi.

3. Of the total value of production of $980 million in 1976-77, bulk drugs accounted for 18 percent (of which 33 percent was produced by two public sector units, 60 percent by large private units and 7 percent by small-scale units) and 82 percent by formulations (7 percent public sector, 76 percent large private and 17 percent overall-scale units). Data from Scrip, 17 June 1978, p. 16. The successful participation of some 2,500 small-scale units in bulk drug and formulation production is worth notice -- on the positive side because of their flexibility and employment creation and on the negative because of the greater risk of poor quality.

4. Scrip, 4 November 1978, p 12

5. Scrip, 23 September 1978, p 21. Indian firms are, according to information received privately, also subcontracting from the United Kingdom for the manufacture of capsules; their advantage lies in their willingness to meet specific requirements.

6. Scrip, 8 April 1978, pp 20-21

7. Scrip, 8 July 1978, p 24. In 1975, of 36 foreign companies surveyed 26 invested less than 2 percent in local R&D; the top four R&D spenders (in India) were Uni-Sankyo (10.6 percent) CIBA-GEIGY (6.8 percent), May and Baker (6.4 percent) and Wyeth (4.1 percent). (Scrip, 28 January 1978, p 15)

8. The experience is discussed in greater detail by Lall and Bibile, op cit, and S Bibile. A Case Study of Pharmaceutical Policies in Sri Lanka, UNCTAD, TD/B/C.6/21, 1977

9. For a statistical analysis of the Sri Lanka savings on drug purchase see S. Lall, Price Competition and the International Pharmaceutical Industry, Oxford Bulleting of Economics and Statistics, February 1978, pp 9-22

10. See Scrip, 31 December 1977, p 18

11. It may be noted that obtaining essential drugs at the lowest possible prices may conflict with the objective of increasing local production, at least in the short-term until local enterprises are able to assimilate the technology and achieve economies of scale. This conflict arises, of course, only for large countries like India with well-developed local industry.

12. Recently, for instance, all the large drug firms in Argentina have decided to boycott a scheme to buy drugs at preferential prices for the social security. Scrip, 1 November 1978, p 13

13. Some of these problems are reviewed in my "Transfer Pricing and LDCs: Some Problems of Investigation," World Development, January 1979.

14. It appears, however, that the problem of excessive claims and suppressed adverse reactions publicized by Professor Milton Silverman has been overcome in Latin America by the companies themselves controlling their marketing practices (Scrip, 8 July 1978).

15. See the British Medical Journal, 21 October 1978, and Scrip, 4 November 1978, p 14

16. Emerging Trends and Future Prospects in the Less-Developed Countries. Medicines for the Year 2000. Edited by G Teeling-Smith. London: Office of Health Economics (forthcoming).

## D. DEVELOPING COUNTRY PERSPECTIVES - AN OVERVIEW

Vittorio Fattorusso

Over the past few years, as Director of the WHO Division dealing with pharmaceuticals, I have become deeply involved in the issue of "Pharmaceuticals for Developing Countries" and delivery of health care to large segments of the world's population. I have visited several of these countries in different parts of the world to gather first-hand information on problems of pharmaceutical supply and of drug utilization in health care and in disease control.

What the absence of basic drugs can mean in daily life was eloquently described by Dr. F. Johnson-Romuald in his presidential address at the opening of the discussions at the World Health Assembly last May. "You really only become aware of how essential is water when you are in a desert," he noted, "and you only fully understand the vital importance of drugs for health care when you see the long queues of the sick in front of a little dispensary out in the bush which has nothing on its shelves, not a single tablet of an antimalarial or a flacon of antibiotic. Yet this is the situation in entire regions of the world."

The subject under discussion at this Conference is very complex. As I was asked to give an "overall view of problems and constraints," I should like to concentrate on what I consider are some key issues in the less developed among developing countries.

Pharmaceuticals cannot be separated from health care systems. In many developing countries, health services are overwhelmingly Western-styled, based on city hospitals which use 80 percent of the national health expenditure, but cater to the needs of a mere 20 percent of the population.

However, the whole approach to health care in the world is on the brink of far-reaching changes. The developing countries have come to realize increasingly that the conventional approach inherited from the industrialized countries is hopelesly inappropriate when it comes to meeting, within a reasonable period of time and from available resources, the basic health needs of their vast populations.

The problem is not just to extend the existing medical infrastructure, which is generally very limited. It is to begin building at the other end, in villages and city slums. This is the concept of "primary health care", of essential care made universally accessible to individuals and families in the community by means acceptable to them, through their full participation and at a cost the community and the country can afford.

While these new ideas on primary health care, already implemented in a few countries, take root in other countries and help to break the present log-jam in extending medical care from the urban, elitist minorities into the vast rural populations, the whole problem of an adequate supply in the public sector of pharmaceuticals indispensable to meet the basic health needs of large populations is assuming a new social dimension.

Already, in a consultation on drug policies held in Geneva in 1976, with participation by representatives of the pharmaceutical industry, the question was raised of whether the "free market" system existing in the international trade of pharmaceuticals could meet the health needs of the world's poor without concerted, corrective measures. The following was stated in the report of the consultation:

"In many areas of the world, there are insufficient quantities of essential drugs and severe problems of distribution. To resolve these difficulties, countries must examine their real health needs, determine which of their health problems should be given the highest priority, and then relate their drug supply with these needs and problems."

"The consultation, appreciating the urgency of the growing problems of ensuring that resources are adequate to meet the basic needs of the populations of developing countries, considered that the fulfillment of their health and drug needs in particular will soon demand a completely new approach. It is worth embarking now on an exploration of special considerations and arrangements for drugs on lines similar to those already followed for food (e.g., The World Food Program)."

The operation of a country's medical and health services requires three main components:

- qualified personnel (doctors, pharmacists, auxiliaries);
- adequate infrastructure (hospitals, dispensaries, warehouses);
- medical supplies including pharmaceuticals of adequate quality and in sufficient quantity suitable to meet the needs of different levels of the health services.

Let me first comment on the third component -- the pharmaceuticals -- and come later to trained personnel and infrastructure.

In the less developed countries, the problem of pharmaceuticals can be summed up in a word: shortage. There are two main causes for this shortage:

- an economic cause: the purchasing power of most of the people of developing countries is too limited to allow them to buy modern drugs at the current market price;

- a geographic cause: many developing countries are far away from the main centers of pharmaceutical production and, particularly for landlocked countries and the small islands, transport is difficult, long, and costly. Within the developing countries themselves, the remoteness of large population groups from the distribution centres in urban areas is the main constraint.

The shortage of pharmaceuticals in developing countries is evident, and economists can measure it: pharmaceutical expenditure may be less than one dollar per capita/per year, or three dollars or ten dollars, compared to an average of up to U.S. $70 in certain industrialized nations.

I may surprise some of you by stating that, at present, I personally do not think our attention should be focused only on this disparity, real as it is, nor do I think that the average amount spent on drugs necessarily reflects the quality and effectiveness of health care of the whole population of a country. We should be much more concerned about the types of pharmaceuticals available to the population, their quality, their distribution in rural areas, and proper use by health personnel. These qualitative elements cannot be measured by economists; nevertheless, they are crucial issues in the modernization of health care in developing countries.

In this connection, the position of WHO on selection of essential or basic drugs is unequivocally clear, as stated in a resolution adopted by the World Health Assembly last May. As this position does not seem to have been properly explained at large, I should like to provide some information. The concept of the selection of essential drugs to meet basic health needs of the population is so closely linked with the concept of primary health care, and so important, that you must forgive me for repeating some of these obvious statements.

1. As medical scientists, we can agree that health needs of a particular population can best be determined by epidemiological studies or, in their absence, by whatever health information is available and that, once identified, these needs should be reviewed regularly.

2. Having determined priority needs, we should determine which modern drugs are most suitable to meet these needs within available resources. The less developed countries will be in no position to meet basic needs of the vast majority of their populations without a series

of concerted measures, one of which will have to be some kind of selection of the most essential drugs at different levels of their health care systems, with particular emphasis on needs at the primary health care level.

3. Again, as scientists, we would like to see that this process of selection of the drugs most suitable to meet basic health needs under severe economic constraints is, as far as possible, unbiased and based on adequate scientific data obtained in controlled clinical trials and/or epidemiological studies. Furthermore, information on the proper use of the selected drugs should be made available. This is the whole concept behind selection of essential drugs which created heated debates when publicized two years ago. It is now gaining wider acceptance, although some confusion still exists.

4. Another important point -- preparation of a list of essential drugs of uniform and general acceptability is not possible because of the great differences among developing countries with regard to the pattern of prevalent diseases, type of health personnel available and genetic, demographic, and environmental factors. There is not, and probably there will never be, a WHO List of Essential Drugs. There are only principles and criteria recommended to developing countries willing to follow this approach.

5. It follows that selection of essential drugs to meet basic health needs of a given population can only take place locally, at different levels of the health care network, taking into account financial resources and product availability. The process should directly involve doctors and pharmacists responsible for delivery of health care and drug procurement, with advice from pharmacologists, particularly clinical pharmacologists, and epidemiologists. The process of selection should be dynamic and flexible, to avoid a rigid approach which would be counter-productive and would prevent therapeutic progress.

6. A limited selection of pharmaceuticals cannot provide for the needs of every person, but should certainly meet those of the vast majority. Therefore, exclusion does not mean rejection, or that no other drugs are useful, but simply that in a particular situation and under certain constraints, the selected drugs are the most needed and should be available in the public sector to health services in adequate amounts and in proper dosage forms. Information on proper use of selected drugs must be available.

Last month, I attended a meeting in Suva in the Fiji Islands, where representatives of the South Pacific countries (or areas) adopted, in accordance with the above-mentioned principles, a South Pacific List of Essential Drugs for combined bulk purchasing by governments (this does not affect the private sector). The meeting brought together, for

the first time, doctors and pharmacists who are involved with procurement, distribution, and use of drugs in the region. It also offered an opportunity for exchange of information relating to sources of supply, sales prices, drug utilization, drug toxicity, and related pharmaceutical matters.

The meeting considered each drug and its dosage presentation and, on the basis of therapeutic relevance, pharmacological justification, cost/effectiveness ratio and suitability for collective bulk purchasing by governments, adopted the South Pacific List of Essential Drugs, which will be revised regularly.

Among the essential drugs included in the list were those which would provide orders of sufficient size to be economically attractive to suppliers only if orders from individual countries were pooled. The relatively large turnover of other drugs on the list would enhance the collective bargaining position and, therefore, reduce drug costs. Some drugs included in the list may not be suitable for bulk purchasing, but are life-saving or essential for health care and, as such, should be made available. It was understood, however, that drugs which are not on the list might well be used by individual member countries, according to their special needs.

Having adopted the South Pacific List of Essential Drugs, which will be published shortly, the meeting made a proposal to be considered by a Conference of Ministers of Health, to be held later this year, for establishment of a joint South Pacific pharmaceutical service which might include a quality control laboratory. This is just an example of the practical application of the concept of selection of essential drugs.

Before leaving the subject of selection of essential drugs, I should like to say that there are great numbers of other pharmaceuticals widely used in both developed and developing countries, for which well-documented toxicological, pharmacological, and clinical studies are lacking or are inconclusive. The market for many of these products is considerable as demand by consumers is high. Most are considered to be safe, in that toxic effects have not been recorded in widespread use, but their efficacy in influencing specific health conditions in a predictable fashion is dubious, to say the least, their use being mainly to satisfy hopes and expectations of the patient.

In the public sector, expensive, imported pharmaceuticals of this type, irrelevant to basic health needs, may become a wasteful drain on a developing country's scarce resources for health care and could be replaced by cheaper items of local production, particularly herbal remedies.

Finally, in developing countries there is also a growing demand

for psychotropic drugs liable to abuse. Some pharmaceuticals containing dependence-producing active substances are essential for health care, but there is also a demand for non-medical uses of such drugs, and they may constitute a public health problem in some developing countries.

There are many other aspects of pharmaceuticals in developing countries where problems and constraints should be mentioned in an overall view. I shall comment on these very briefly in presenting to you an outline of the new WHO Action Program on Essential Drugs, as approved by the WHO Executive Board on 24 January 1979. This new program has broad objectives and is distinct from the Special Program on Research and Training in Tropical Diseases.

The aim of WHO is to stimulate, through the new program, broad international cooperation among governments, both of developed and developing countries, interested United Nations agencies, development aid organizations, and pharmaceutical industries, in order to alleviate the situation in the public sector of those developing countries where large segments of the population do not have access to the most essential drugs, including vaccines, that are indispensable to ensure even a minimum of health care. The resolution of the WHO Executive Board indicates that high priority should be given to the urgent needs of the least developed countries, among them especially the landlocked countries and small islands.

For many diseases affecting millions of people, effective drugs and vaccines already exist, but are not available in sufficient quantities, are too expensive, and are not effectively distributed or utilized. Without such essential drugs, effective health care cannot be provided, no matter what efforts are made to train health workers and to develop an infrastructure.

It is also recognized that such essential drugs for which reliable scientific, clinical, and epidemiological data on efficacy, safety, and quality are available, are mainly produced in the industrialized countries. While it is expected that in the coming decades more developing countries, having reached an advanced stage of industrial development, will produce more of such drugs, most of the less developed countries (LDCs) will continue to depend on imports.

Where programs are implemented in these countries to extend health care coverage of the population, pharmaceutical supply is becoming an important constraint because countries cannot afford current prices of essential drugs on the international market. In most cases, these drugs must be paid for in scarce convertible currencies and, in some cases, the import of unnecessary, expensive pharmaceuticals causes a wasteful drain. Lack of information, education, and training in selection, control, storage, distribution, and proper use of drugs is also a major problem in these countries.

In coming decades, development of primary health care systems in the developing world will require a concomitant development of pharmaceutical supply systems adapted to needs of large populations, and new forms of international cooperation.

The objectives of the new WHO program can be stated as follows:

1. To strengthen national capabilities of developing countries in selection, procurement, supply, distribution, and proper use of essential drugs to meet health needs of the majority of the population.

2. To strengthen, whenever feasible, quality control and local production of such drugs.

3. To make available to the less developed countries (LDCs) essential drugs, including vaccines, under favorable conditions in order to extend health care coverage and disease control programmes to larger segments of the population.

WHO should give careful consideration to the proper balance of actions in developing countries necessary, on the one hand, to achieve urgent improvements in the supply position and, on the other hand, to build up national capabilities. Otherwise, results could be counterproductive. For example, in some countries, provision of finished products could inhibit or delay the step-by-step expansion of local production, starting with the simplest operations and moving to more complex ones.

It is envisaged that, at the request of a government, the Action Program could provide immediate help to improve the supply position where lack of essential drugs is the main constraint for development of a national program of primary health care. At the same time, adequate support could be provided for a comprehensive survey of the country situation which, in turn, could lead to further cooperation in strengthening national technical and managerial capabilities, in training personnel, in transfer of information and in building up infrastructures in the following six main areas:

1. Drug selection and requirements. As already mentioned, epidemiological surveys, drug utilization studies and clinical pharmacological expertise are required for selection of essential drugs and to determine the quantities required at different levels of health services, particularly at the primary health care level, taking into account local conditions and plans for extension of health care coverage of the population.

2. Quality assurance. Proper training of personnel for drug procurement and building up of regional quality control laboratories, linked with laboratories in the more advanced countries, are required

for developing countries that cannot afford an efficient national control laboratory. There is a need for transfer of information on national drug legislation, on implementation of good manufacturing practices in producing countries, on trends in international prices for essential drugs, and on possible sources of supply.

Ensuring the quality of drugs and vaccines was one of the points most frequently raised at the World Health Assembly as a main concern of national health authorities of developing countries. It is evident that a country gains nothing, or may even lose, if it buys cheap drugs or starts to produce them locally and then discovers that these drugs are either unsafe or ineffective because of poor quality. The WHO Certification Scheme on Quality Control of Pharmaceutical Products moving in International Commerce may provide a partial quality assurance of essential drugs. However, when bioavailability of a drug is of crucial importance, a reliable product may be the easiest answer and such information may be obtained by the drug regulatory agencies of some producing countries.

3. Distribution and logistics. This is a very important component, as already mentioned. I have no time to dwell on it and can only say that building up of an efficient drug distribution system, parallel to the health care network, is vital to ensure that the "right" drugs are properly stored and are constantly accessible to those who need them, particularly in rural areas.

4. Local production. Having ensured adequate control facilities, there is a need for improvement of existing formulation units or for establishment of new units for processing of imported intermediates or raw materials, or for production of parenteral solutions or vaccines. Feasibility studies should determine the capital investment required and annual operating costs in order to compare cost of local production to cost of equivalent imported products.

5. Natural resources. Use of herbal remedies may, as already mentioned, replace many expensive imported products. Trained personnel and adequate equipment are required for collection and processing of medicinal plants.

6. Research and development. Almost everything has been said on research and development of better tools for control of tropical diseases, but this discussion should not obscure other areas, such as clinical and epidemiological studies on safety and efficacy of existing drugs used under local conditions, development of appropriate technologies for drug formulation and packaging, including stability of the products under tropical conditions, and development of more heat-resistant vaccines, etc.

While research and development of new and better drugs is crucial to progress in health care -- and the outstanding contribution of the

pharmaceutical industry in this respect is fully recognized — I should like to return to the fundamental question:

Is it real progress if most people in the world continue to be excluded from the benefits of modern drugs?

The industry tells us that many effective drugs developed in recent years for control of diseases prevalent in developing countries are not in widespread and effective use. Perhaps the new Action Program on Essential Drugs, outlined above, coupled with development of primary health care efforts in developing countries, could increase effective use of modern drugs, open new markets in the public sector for such drugs and, by the same token, provide incentives for research and development efforts of the industry more relevant to particular needs of developing countries.

This new program of WHO is in its initial stages, and its success will largely depend on the political will of the governments of developing countries to tackle the problems in their own countries, and on the readiness of more affluent countries to work together in true partnership with the less affluent to define and implement a plan of action as part of social and economic development. It will also depend on new visions and new initiatives of the major drug industries. In this respect, I should like to say that the first reactions coming from European companies are very encouraging. Some of these companies have pledged their participation in the program through the provision, to governments of less developed countries, of selected products suitable for use in extending and in improving the health care coverage of the population.

These companies, which are among the major drug manufacturers, have stated that selected products would be made available under specially favorable conditions in economic packages, taking into account the requirements of primary health care and tropical climatic conditions, with uniform labelling, including generic names and possibly an emblem indicating the special character of the Action Program, since these products should not move into the private commerical sector or be re-exported. Conditions would be even more favorable if requirements could be planned ahead for periods of 3 to 5 years. The products fall into the following categories: amebicides, analgesics, antipyretics, antibiotics, anti-infectives, antimalarials, antischistosomals, antitrypanosomals, antituberculosis drugs, cardiovascular drugs, and vaccines, etc.

I should like to add that some pharmaceutical companies have also expressed interest in providing services to the least developed countries, including training of technical personnel and building the infrastructure required for provision of essential drugs on the basis of an assessment of the basic health needs of the population. We hope that major American companies, to whom we have not yet had an opportunity

to explain the new program, might consider participation.

Obviously, these are matters to be decided by individual manufacturers, in agreement with the governments concerned, because the challenge is not intended to fall solely on the shoulders of the pharmaceutical industry. But it is a challenge to see if industry and governments can work together on urgent problems whose solutions require pooling of talents and resources -- public and private. Perhaps the new WHO Action Program on Essential Drugs can stimulate this approach.

Let me close by making a pledge to those of you working in the pharmaceutical industry who, I realize, deal with reality instead of hopes and theories. We shall do our best to stimulate mutual understanding and cooperation between governments and private industries in order that the fruits of your technology -- modern drugs, vaccines, diagnostic products and all the rest -- which are indispensable for modernization of health care and effective disease control in developing countries, get into the hands of more health workers for the benefit of a larger proportion of the world's population who, at present, are denied access to them. In this effort, your understanding and cooperation will be of immeasurable help in striking a fair balance between economic constraints of the industry and acute needs of developing countries, between investment by industry in drug research and reasonable opportunities for a fair return. This requires search for pragmatic solutions, rather than prolonging dissent, and a more sober dialogue in a climate of mutual confidence.

# INNOVATION AND AVAILABILITY IN THE UNITED STATES OF DRUGS FOR TROPICAL DISEASES

Jean DiRaddo and William M. Wardell

This report presents analyses of objective data describing the environment for, and the rate of, development of new drugs for treatment of parasitic and other tropical diseases by the United States-owned pharmaceutical industry. Data on drugs already approved for use in the United States, or available from the Center for Disease Control (CDC), are also presented. Although the relevant data base is small, this examination of the past and present situation has clear implications for the future of American research and development (R&D) in this field.

## Current Concerns in Drug Development for Parasitic and Tropical Diseases

Drugs currently available for treatment of parasitic diseases have limitations due to problems of toxicity, development of resistance to the drugs, and the fact that they are generally expensive.1,2/ In addition to better distribution of existing therapies, less developed countries (LDCs) need new drugs that are safer, more effective, and more easily administered for treatment of these diseases. Development and availability of such compounds represent problems of high priority for LCDs. It has been stated that industrial research directed toward development of such drugs has decreased over the past decade.3/ The large scale of the scientific, technological, and financial resources necessary for developing new drugs means that, with the exception of Phase II and III clinical trials, the discovery and development process is limited to a very small number of developed countries -- essentially the United States, Western Europe, and Japan.

Not only are local health needs and priorities in developed countries very different from those in LDCs, but also pharmaceutical firms in developed countries are subject to increasingly stringent systems of drug regulation to ensure that drugs approved for marketing are safe and effective and, in some cases, safer or more effective than other available therapies. A significant investment of resources is

required to meet these regulatory criteria. For example, the average cost to a United States-owned firm for developing a new chemical entity (NCE) to the point of marketing approval in the United States is approximately $54 million (in 1976 dollars).4/ Furthermore, the average length of time from initiation fo clinical testing in the United States to marketing approval for all NCEs approved in 1976 was more than six years,5/ and preliminary data from a more recent study suggest that for those NCEs discovered wholly within the United States industry this span of time was approaching nine years in 1976.

Despite these apparent disincentives, certain pharmaceutical firms continue to be actively involved in research on drugs for parasitic diseases. The World Health Organization (WHO) initiated a Special Program for Research and Training in Tropical and Parasitic Diseases in 1976. One objective of the Program is development of new agents for control of six diseases: malaria, schistosomiasis, trypanosomiasis, filariasis, leprosy, and leishmaniasis. Several companies are cooperating with WHO in this Program.6,7/

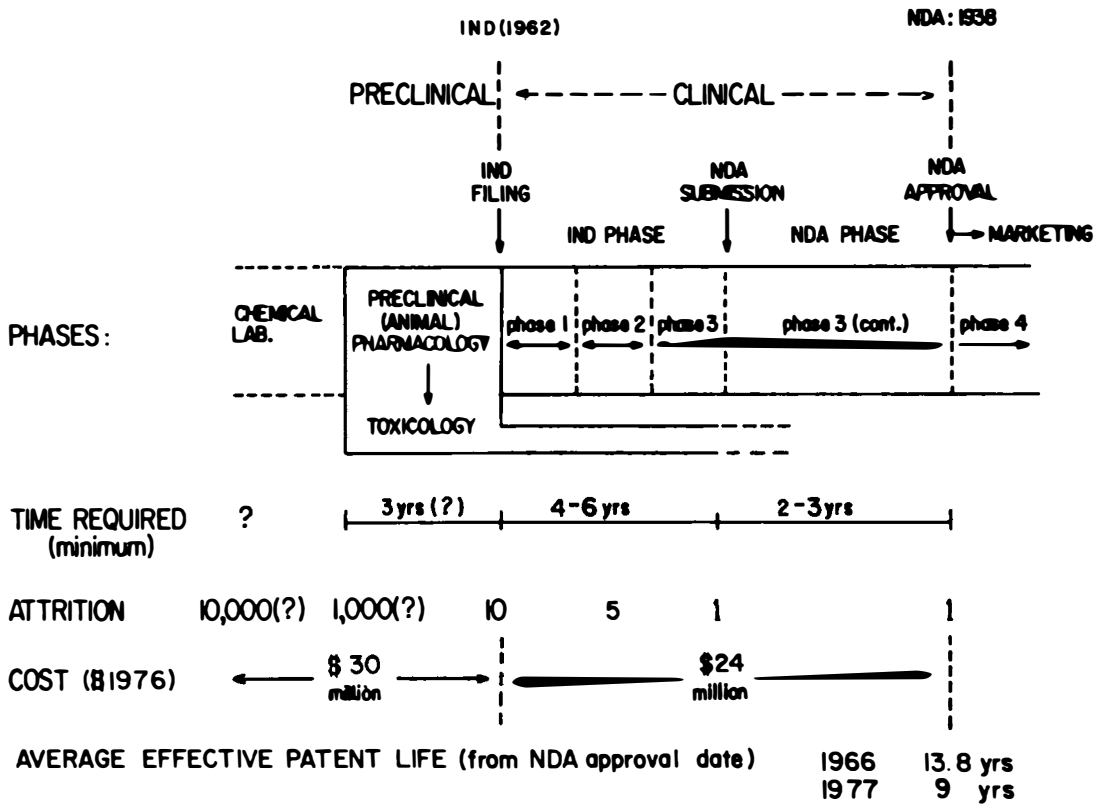
## The New Drug Approval Process in the United States

The upper portion of Figure 1 depicts the various stages through which a new drug must pass before it can be marketed in the United States. After the preclinical testing phase and initial toxicological studies, a manufacturer must file with the FDA for an investigational new drug exemption (IND) prior to initiating human testing. Clinical investigations are divided into three phases. During Phase I, a drug is given to a small number of healthy human volunteers with the principal objectives of looking for evidence of toxicity and determining basic properties of the drug in man. In Phase II studies, the drug's effects on a small population of patients with the appropriate disease are examined to determine its therapeutic value and to detect any adverse effects or possible toxicity. Phase III consists of larger-scale testing to uncover less common side effects and to approximate more closely the type of drug utilization (e.g., in patients of varying disease severity) that would occur in medical practice if the drug were marketed.

When a manufacturer believes he has adequate evidence to demonstrate safety and effectiveness of the compound (after clinical trials that last from four to six years), a new drug application (NDA) is submitted to the FDA. When and if the NDA is approved (an assessment process that usually takes two to three years) the drug can be marketed in this country.

Certain drugs without NDAs, including several drugs for parasitic diseases, are made available under the IND procedure in the United States from the CDC. These may be termed "therapeutic INDs" because licensure and commercial production and distribution in the United

FIGURE 1. DRUG DEVELOPMENT (U.S.A.) a/




a/The following aspects of the United States regulatory process are particularly relevant to development of drugs for parasitic and other tropical diseases.

1. Since export of non-IND drugs from the United States is prohibited, a United States IND is required before a drug can be tested in man in the United States or abroad.

2. A drug cannot be exported for marketing without an approved United States NDA.

3. In part because of the high attrition rates shown in Figure 1, the cost of filing sufficient compounds at the IND level in the United States to obtain one successful NDA is $30 million; to obtain one approved NDA requires a total of six to nine years from the time of IND filing and a further $24 million (in 1976 dollars).4/

4. The "effective patent life" (the time from NDA approval to expiration of the patent) has fallen from a mean of 13.8 years for those drugs with NDAs approved in 1966 to nine years in 1977 8/ -- the difference being largely accounted for by the increase in development time between those years.

States are not generally being sought by the manufacturer due to limited demand for these drugs.9/

### Export Restrictions: Relationship to IND and NDA

If a drug synthesized in the United States can only be tested clinically for a tropical disease in the country in which that disease occurs, then the drug needs to be exported from the United States in order to be properly evaluated. Therefore, the effects of regulatory restrictions on export of drugs from the United States, whether for clinical investigation or for sale, are important in the case of drugs for conditions such as parasitic diseases that do not usually occur in the United States. Present regulations stipulate that no drug may be sent abroad for clinical investigations unless it has at least a United States IND, and no drug can be exported for marketing unless it has an approved United States NDA. Legislative revisions of this policy that would allow for export under certain conditions of compounds not approved for use in the United States are currently being considered and will be commented on in the Discussion.

## METHODS

### Measures of Innovation in Pharmaceuticals

There are several possible ways of measuring pharmaceutical innovation, but all present technical problems.10,11/ Among possible criteria that may be used to measure innovative output are the number of new molecular structures (new chemical entities, or NCEs) synthesized, novelty of their molecular structure, novelty of their pharmacologic action, number of patents issued, number of NCEs tested in man, number of NCEs marketed, and qualitative measures of the value of marketed NCEs.

The measure we have recently developed in some detail is the number of NCEs taken into human testing, and their subsequent progression through clinical and regulatory stages of drug development. This is a useful measure, since the point of entry into human testing represents a firm's decision that a compound is worth further testing and investment. It also represents the first appearance of innovative output outside a firm and, in the United States, it marks the entry of the compound into the regulatory pathway.

### Investigational NCEs

Data on investigational NCEs presented in this paper are a subset taken from a comprehensive study of development of NCEs in all therapeutic categories in the United States. This study is based on responses

to two surveys: the overall results of our 1975 survey have been reported 12/ and we do not yet have a complete response to our expanded 1977 survey.

The present study is an analysis of our current data from United States-owned firms on NCEs for treatment of parasitic and tropical diseases, those that were classified by responding firms in that survey as antiamebic, antimalarial, antischistosomal, antitrypanosomal, antiprotozoal (otherwise unclassified), and anthelmintic agents. Antileprotic drugs would also have been included, but no NCEs were listed as being developed for leprosy. Because only the initial therapeutic category is given for each NCE, drugs useful for a parasitic disease but that were first tested for another indication (e.g., rifampin, which was tested first for tuberculosis and subsequently for leprosy) cannot be included in our analysis.

The information provided on the 1975 and 1977 investigational NCE surveys, and analyzed in this study, includes for each compound the date and country of first administration to man; dates of IND filing, IND closure, NDA submission, and NDA approval; reason(s) for termination of IND research; and the country in which it was first synthesized. Response to the 1977 survey is nearly complete and all available information on drugs in the parasitic disease categories is reported here. Since data requested in the surveys are not publicly available and were provided under a confidentiality agreement with responding firms, results of the surveys are expressed in aggregate form without identifying any individual company or compound.

Although the contribution of foreign-owned pharmaceutical firms to new drug development in this field is known to be substantial, complete data on the experience of these firms were not obtained in our investigational NCE survey; the investigational NCEs described in this paper represent only those developed by United States-owned pharmaceutical companies.

## Marketed NCEs

Publicly available data on NCEs marketed in the United States have been obtained from the FDA,13/ pharmaceutical companies, and market research organizations.14/ Information on those "therapeutic INDs" available thorough the CDC was also obtained. A survey currently in progress will provide detailed information on development of those drugs that have successfully passed through the United States regulatory pathway.

## RESULTS

### Part I: Investigational NCEs for Parasitic Diseases*

Of approximately 900 NCEs studied in man by United States-owned pharmaceutical firms from 1963 through 1976, 20 were candidates primarily for tropical or parasitic diseases. These 20 NCEs came from 11 of the 41 United States-owned pharmaceutical firms and affiliates from which data are currently available. These NCEs were classified according to a single therapeutic category provided by the firms: one antiamebic, one antimalarial, five antischistosomal, one antitrypanosomal, three antiprotozoal (otherwise unclassified), and ten anthelmintic agents. (It cannot be determined from the data available but it is possible that some of these compounds may fall within more than one therapeutic category.) Because of the small number of compounds in each specific category, all categories ar combined in this initial report.

#### Countries in which NCEs were First Synthesized

Table 1 lists the countries where the investigational NCEs for parasitic diseases were first synthesized. Where the information is known, one-third of the United States-owned firms' drugs in this area were synthesized abroad, including those originated in foreign laboratories of United States firms.

#### Location and Time Trends of First Human Administration

Nine of the 20 NCEs were first administered to man in the United States. Of the 11 given to man abroad, six were first tested in Western Europe.

Table 2 shows the location of first human administration (United States versus foreign) as a function of time. From the mid-1960s to the early 1970s, more NCEs were first tested in man in the United States than abroad. However, no NCE for parasitic disease therapy has been first introduced into clinical study in the United States since 1972, although four have been studied abroad. Considering NCEs in all therapeutic categories combined, we previously observed a trend toward

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* Very few United States-owned companies have not yet provided data and we believe those firms are not likely to have taken many tropical disease NCEs into human testing. The distinction between this study and Sarett's observations of the number of firms engaged in research in this area (also reported in this volume) is that we have included only information from United States-owned firms and have considered only those NCEs that have reached the stage of clinical investigation.

TABLE 1. COUNTRIES IN WHICH INVESTIGATIONAL NCEs FOR PARASITIC DISEASES WERE FIRST SYNTHESIZED

| | Total 20 NCEs |
|---|---|
| United States | 9 |
| United Kingdom | 2 |
| Belgium | 1 |
| Italy | 1 |
| South Africa | 1 |
| Not Supplied | 6 |

an increasing proportion of NCEs being first given to man abroad over time.12/ The pattern observed for parasitic disease NCEs represents an extreme case consistent with that trend.

IND Filings

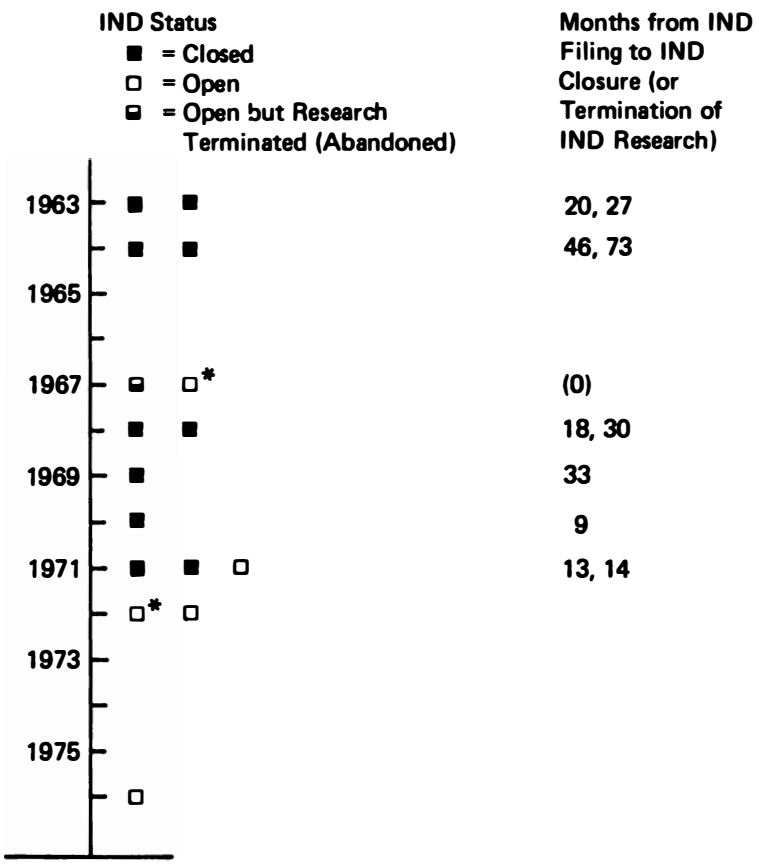
INDs have been filed on 16 (80 percent) of the 20 NCEs. These represent those NCEs that have been cleared for United States study and that may therefore be transferred abroad for clinical study. The remaining four NCEs, tested in man abroad between 1968 and 1975, do not have INDs, and so presumably originated in foreign subsidiaries or affiliates of United States firms and have not been developed within the United States regulatory system.

Of the 16 INDs, 10 have been formally closed and one has been abandoned (clinical research under the IND has been terminated). Two reached the point of NDA submission and were approved, leaving only three unmarketed compounds on which research was still proceeding under the United States IND at the end of 1976.

The IND filings are shown in Figure 2 as a function of time. The rate of IND filings by United States firms and their affiliates was fairly constant (i.e., a total of one or two per year) except for the periods 1965-1966 and 1973-1975, when there were no IND filings.

The life in months of each of the 10 closed INDs and of the one abandoned IND is also shown in Figure 2. If one can generalize from

FIGURE 2. IND STATUS AND DURATIONS OF CLOSED AND ABANDONED INDs BY YEAR OF IND FILING




*These compounds had received NDA approval by the end of 1976.

TABLE 2. LOCATION AND TIME OF INTRODUCTION OF NCEs INTO HUMAN TESTING BY THE UNITED STATES-OWNED PHARMACEUTICAL INDUSTRY

| | United States | Abroad |
|---|---|---|
| Total | 9 NCEs | 11 NCEs |
| Date Unknown | 0 | 2 |
| 1963-64 | 1 | 2 |
| 1965-67 | 2 | 1 |
| 1968-70 | 3 | 1 |
| 1971-73 | 3 | 1 |
| 1974-76 | 0 | 4 |

the admittedly small number of cases, decisions to terminate research on compounds are being made considerably sooner after IND filing in the 1970s than was true in the 1960s.

Reasons given for terminating research fell into two major categories (Table 3). Six of the reasons given pertained to commercial or apparently related problems, while three pertained to safety or efficacy problems.

## NDA Submissions

NDAs were submitted for only two of these antiparasitic drugs; both NDAs were approved. This observation is consistent with our previous finding, based on NCEs in all therapeutic categories, that only 10 percent of INDs filed reached the stage of NDA submission. Once a company has decided that a drug is worth submitting for an NDA, that drug has high likelihood (88 percent) of eventually obtaining NDA approval.12/

For each of these drugs the IND phase was shorter than the NDA phase, in contrast to the pattern seen for NCEs in all therapeutic areas, for which the average IND phase was longer than the average NDA phase. 12/

TABLE 3. REASONS GIVEN FOR TERMINATION OF IND RESEARCH a/

| | |
|---|---|
| Total | 6 NCEs |
| Commercial or Related Problems: | |
| Commercial Market Too Limited | 2 |
| "Not Commercially Feasible" | 1 |
| "Studies Outside United States Since Drug for Tropical Disease Treatment" | 2 |
| "Analog" | 1 |
| Total | 3 NCEs |
| Safety or Efficacy Problems: | |
| Lack of Efficacy | 1.5 |
| Human Toxicity | 1 |
| Human Pharmacokinetics | 0.5 |

a/ Two reasons were given for one NCE so each is counted as 0.5. Some possible responses were listed in the survey and respondents were asked to specify any reasons other than those listed; these additions are noted by quotation marks. Reasons were not provided for two NCEs.

## Part II: Marketed NCEs for Parasitic Diseases

This part deals with NCEs that have received NDA approval and are marketed in the United States by United States-owned or foreign firms.

Within our data base of all NCEs that have received NDA approval in the United States from 1940 through 1978, 35 of the approximately 850 drugs are in the parasitic and tropical disease categories.*

*Drugs with more than one parasitic disease indication are listed, for this analysis, in the category of their earliest approval. Since the original approved indications for the older (pre-1963) drugs are not uniformly available, it was necessary for us to classify the drugs into disease categories.

(Drugs used topically are excluded from this list but are given in Reference 15.) The breakdown by disease category is as follows: ten antiamebic, three antileprotic, nine antimalarial, one antischistosomal, one antitrypanosomal, eight anthelmintic, and three otherwise unclassified antiparasitic drugs.

The specific drugs are listed by category in Table 4, together with the year of NDA approval and duration of the NDA phase (i.e., interval from NDA submission to NDA approval) for each NCE. (There was no IND filing, and hence no IND phase, prior to 1963.)

Comparing the NDA phase for parasitic disease drugs with those for drugs approved over all therapeutic categories,12/ the NDA phases for antiparasitic drugs approved in the 1960s were generally longer than average whereas those approved in the 1970s were similar to the average values.

It will be noted that out of the 35 drugs, only three have been developed since the present IND/NDA system was instituted in the United States in mid-1963; the others had been in clinical investigation prior to that time. The IND phase for pyrantel pamoate (IND filed in 1967*) was 27 months, compared to an average of about 34 months for all NCE NDAs approved in 1971; the IND phase for trimethoprim-sulfamethoxazole (for the earliest IND filing) was 35 months, compared to an average of about 42 months for all 1973 approvals; and the IND for mebendazole (filed in 1972) was 11 months, versus an average of about 40 months for all 1974 aprovals.

## Part III: Antiparasitic NCEs Available from the CDC

Because of the special position of the CDC with respect to drugs for tropical and parasitic diseases, the distinction between investigational and marketed drugs, and hence the significance of IND filing and NDA approval, is not as meaningful as for NCEs developed by industry. Information from CDC on their INDs in this area indicated that none were first testd in man in the United States. Sources of the INDs were United States-owned firms or their affiliates for 30 percent of the NCEs and, considering only those on which this information was available, 14 percent were synthesized in the United States.

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*The data of IND filing for these approved NDAs were obtained through correspondence with the FDA.

TABLE 4. ANTIPARASITIC NCEs APPROVED FOR U.S. MARKETING SINCE 1940

| Category and NCE a/ | Year of NDA Approval | Duration in Months of NDA Phase b/ |
|---|---|---|
| Antiamebic | | |
| Carbarsone (Carbarsone) | 1944 | Not Available |
| Glycobiarsol (Milibis) | 1949 | 0 |
| Arsthinole (STB) | 1949 | 5 |
| Thiocarbarsone (Enseals Thiocarbarsone) | 1950 | 1 |
| Diiodohydroxyquin (Bacta) | 1952 | 9 |
| Fumagillin (Fumidil) | 1953 | 1 |
| Bialamicol (Camoform) | 1954 | 1 |
| Chlorbetamide (Mantomide) | 1955 | 2 |
| Glaucarubin (Glaucarubin) | 1957 | 25 |
| Paromomycin Sulfate (Humatin) | 1960 | 10 |
| Antileprotic | | |
| Glucosulfone (Promin) | 1944 | 1 |
| Sulfoxone (Diasone Sodium Enterab) | 1946 | 2 |
| Dapsone (Avlosulfon) | 1955 | 1 |
| [Rifampin (Rifadin, Rimactane)] c/ | | |
| Antimalarial | | |
| Quinacrine (Atabrine) | Not Available | |
| Chloroquine (Aralen) | 1946 | 1 |
| Chloroguanide (Chloroguanide) | 1947 | 5 |
| Pentaquine (Pentaquine) | 1948 | 7 |
| Amodiaquin (Camoquin) | 1948 | 1 |
| Primaquine (Primaquine) | 1951 | 0 |
| Pyrimethamine (Daraprim) | 1953 | 6 |
| Hydroxychloroquine (Plaquenil Sulfate) | 1955 | 3 |

Table 4 - Cont'd

Table 4. (Cont'd)

| Category and NCE a/ | Year of NDA Approval | Duration in Months of NDA Phase b/ |
|---|---|---|
| Amopyroquin (Propoquin) | 1966 | 50 |
| **Antischistosomal** | | |
| Lucanthone (Lucanthone) | 1960 | 5 |
| **Antitrypanosomal** | | |
| Stilbamidine Isethionate (Stilbamidine Isethionate) | 1953 | 4 |
| **Anthelmintic** | | |
| Diethylcarbamazine (Hetrazan) | 1948 | 1 |
| Piperazine Citrate (Antepar) d/ | 1953 | 13 |
| Pyrvinium | 1955 | 10 |
| Dithiazanine Iodide (Delvex) | 1958 | 2 |
| Bephenium Hydroxynaphthoate (Alcopara) | 1967 | 87 |
| Thiabendazole (Mintezol) | 1967 | 30 |
| Pyrantel Pamoate (Antiminth) | 1971 | 28 |
| Mebendazole (Vermox) | 1974 | 14 |
| **Other** | | |
| Amphotericin B (Fungizone) | 1957 | 5 |
| Metronidazole (Flagyl) | 1963 e/ | 34 |
| Trimethoprim-Sulfamethoxazole (Bactrim, Septra) | 1973 f/ | 11 |

a Each NCE is listed, by generic (and trade) names, with the category and date of its earliest NDA approval where this information is available. Otherwise, we have assigned the NCEs to these categories.

b/This is the difference between the dates of NDA submission and approval.

c/Rifampin is available in the United States but has not been approved for leprosy.

d/Piperazine itself was available previously (approved in 1940 as Urolizine) but its early indication appears to have been for the treatment of gout.

e/Metronidazole was approved in 1963 for trichomoniasis and was subsequently (1971) approved for amebiasis.

f/This approval date is for its use as an antibacterial.

Table 5 lists antiparasitic drugs available for therapeutic use in the United States under INDs from the CDC.8/ Seven of the drugs listed have trade names and presumably are marketed abroad by foreign-owned companies.

TABLE 5. ANTIPARASITIC DRUGS AVAILABLE FOR INVESTIGATION FROM THE CDC a/

| Drug | Disease |
|---|---|
| Bayer 2502 | Chagas' Disease |
| Bithionol | Paragonimiasis |
| Dehydroemetine | Amebiasis |
| Melarsoprol (Mel B, Arsobal) | Sleeping Sickness |
| Niclosamide (Yomesan) | Tapeworm Infections |
| Niridazole (Ambilhar) | Schistosomiasis |
| Pentamidine Isethionate (Lomidine) | Pneumocystis Pneumonia, Gambian Sleeping Sickness |
| Sodium Antimony Dimercaptosuccinate (Astiban) | Schistosomiasis |
| Sodium Antimony Gluconate (Pentostam) | Leishmaniasis |
| Suramin | Rhodesian Sleeping Sickness, Onchocerciasis |
| Diloxanide Furoate (Furamide) | Amebiasis |

a/This information is primarily from: Johnson RH, Ellis RJ, Immunobiologic agents and drugs available from the Center for Disease Control. Annals of Internal Medicine 81:61-67, 1974

## DISCUSSION

The data presented show that for parasitic and other tropical diseases, few NCEs from United States-owned firms and their affiliates are being studied in the United States and fewer still have made it to the United States market. Since there are only three open INDs that have been filed since 1967 (excluding the two INDs on drugs with NDA approvals), and the IND plus NDA phases require an average of more than six years before a new drug can be approved for United States marketing, these represent the probable limit of what can be approved in this country over the next several years. Because there are so few INDs, and because a drug needs an IND or an NDA in order to be transferred abroad for clinical study or marketing, the results indicate that few NCEs of United States origin are being studied worldwide.

Current United States export requirements have received considerable attention in hearings concerning FDA's decision not to approve Depo-Provera® (medroxyprogesterone acetate) for use as a longacting injectable contraceptive in the United States.16/ Revision of current policy has been proposed to permit export of an unapproved drug when the government that is importing the drug indicates its awareness of the drug's status, and when the drug is not thought to represent a danger to the public health (i.e., provisions of the Drug Regulation Reform Bill of 1978). It must be recognized, however, that even if United States export requirements are revised, many countries have a "country of origin" rule whereby a drug can only be imported if it is approved in the country where it is put into the final dosage form. Export considerations may thus influence extent and location of R&D activities on drugs for parasitic diseases.

J. Richard Crout, Director of FDA's Bureau of Drugs, has said that FDA policies on regulations pertaining to acceptance of foreign data are not responsible for lack of any recent NDA approvals in this field since drugs for tropical diseases that do not occur in the United States could be approved on the basis of foreign data.17/ In addition to the current export policies referred to above, however, othe United States regulatory procedures may influence the level of R&D activity in antiparasitic drugs and drugs for other therapeutic areas. In addition to the time and cost requirements involved in developing an NCE to the point of approval for marketing in this country that were cited previously, the average effective patent life (time remaining on a drug's patent when the NDA is approved) has declined from 13.8 years for NDAs approved in 1966 to nine years for those approved in 1977 (Figure 1).8/ The Bioresearch Monitoring Program regulations that are being proposed and implemented by the FDA may in the future also serve as additional disincentives for research. Components of this program include regulations pertaining to good Laboratory Practices;18/ proposed regulations regarding sponsor/monitor obligations;19/ clinical investigator obligations;20/ the role of institutional review boards;21 and proposed regulations on informed consent procedures.

Another possible change in United States regulatory policy, disclosure of data submitted to the FDA, may influence submission of NCEs for NDA approval. For example, it has been alleged that some companies developing antiepileptic drugs abroad do not intend to submit these drugs for approval in the United States regulatory system because of the possibility of release of data under future revisions of regulatory policies. Provisions requiring release of data were discussed in hearings on the Drug Regulation Reform Bill of 1978.

The activities and policies of several major United States and foreign pharmaceutical firms in regard to research on drugs for parasitic and other tropical diseases have recently been described by Behrman.6/ One of the points made by the firms, and by Crout, is that lack of market potential in many Third World countries is one of the major reasons for the low levels of activity in this area.17/ This is in general supported by our data (Table 3). In this regard it has been suggested that further efforts are needed to ensure effective distribution and use of existing therapies.

An expansion of the present study would be needed to provide a more complete picture of the state of new drug development for antiparasitic therapy. One source from which new therapies may reach the market is new antiparasitic indications discovered for existing drugs. One drug that followed this pathway is rifampin, which was approved for tuberculosis and subsequently found effective for leprosy (although not approved for this use in the United States). Another example is approval of metronidazole for amebiasis eight years after its approval for trichomoniasis. Information on supplemental NDAs was only obtained from our surveys for NCEs marketed since 1963, so complete data are not available on investigational use of existing drugs for new indications. An additional pathway that may provide new drugs for human use is drugs first approved for veterinary use.

The analyses described here do not include data from any non-industry sources other than CDC; data from the United States Army's antimalaria program, for example, would be useful. An international expansion of this study to include comparable worldwide activities of foreign-owned pharmaceutical firms is being contemplated when the data are available. The status of new drug development for these diseases is important because of the long interval between discovery and availability of any new compound, and the current picture indicates that few new therapies will become available in the next five to ten years. The potential contribution of new drug development in this field must be considered in regard to the unmet needs for improved systems of health care delivery in the LDCs.

## CONCLUSIONS

1. The number of NCEs brought to the point of human testing for tropical and parasitic diseases by United States industry over the past 14 years is small. By the end of 1976, 20 of the approximately 900 NCEs tested in man were for these diseases; 16 had been filed as INDs in the United States, while four had been developed outside the United States system. Of the 16 INDs, two had reached the stage of approved NDAs, and three others were still being investigated clinically as drug candidates.

2. The requirement for obtaining a United States IND prior to export is a deterrent that prevents more United States-discovered drugs from being studied abroad clinically at an earlier stage of their development. The FDA should be supported in its efforts to lessen export restrictions for investigational drugs; a recommendation from Third World recipients of such drugs would be a useful contribution to these efforts.

3. The requirement for an approved NDA before a drug can be exported commercially from the United States would be expected to encourage United States-owned firms to bypass the United States regulatory system completely by conducting all tropical disease drug development work abroad. This would tend to restrict research in tropical and parasitic diseases to those few companies large enough to have a foreign subsidiary or affiliate that is completely equipped to handle all stages of drug development.

4. A further deterrent to drug development in this area is the cost of developing enough drugs to the IND stage to find one that will reach the point of NDA approval (this cost averages 430 million for drugs in all therapeutic areas).4/ This factor must be taken into account when society considers creating incentives for the private sector to continue research in drug development for tropical diseases.

5. Among steps that would facilitate the process of drug development for these diseases are:

   a. less restrictive standards for introduction of these drug candidates into human testing. Perhaps these standards should be determined by developing countries themselves since they are directly concerned with these diseases and drugs, instead of by developed countries; and

   b. expedited international transfer of molecules discovered in developed countries to LDCs for clinical testing.

## ACKNOWLEDGEMENTS

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# THE SCIENTIFIC BASE: OPPORTUNITIES FOR RESEARCH

# INTRODUCTION

Joshua Lederberg

In his introduction, JOSHUA LEDERBERG indicated that the panel presentations are intended to elaborate rational scientific and technological approaches to the health problems of developing countries. He noted that never before in history have the opportunities been so great, yet so poorly exploited for human benefit. Despite the very substantial breakthroughs in basic biological knowledge, which can be labeled as the new molecular biology, relatively little has been exploited to further the understanding of host-parasite interactions.

Biological specificity is the basic approach to therapy and prophylaxis. Scientists are challenged to find the means to destroy the parasite without destroying or harming the host. This concern can be traced to Paul Ehrlich and his search for "magic bullets," using the general principle of specific action as exemplified by the staining properties of micro-organisms. Today, there is still much to be learned of the biochemical bases of specificity, even for the arsenicals and antimonials used extensively in the past. Currently, investigators have focused their concerns on the metabolic pathways of parasites and hosts. They have mounted a search for wedges that can be driven between these pathways toward development of effective therapies. This concern is the subject of several papers that follow.

Another source of specificity, which illuminates our understanding of host-parasite interactions, are the immunoglobulins: to exploit the host capacity to protect itself against parasitic invasion. Dr. David will report about his investigations in this field.

Specificity can also be examined with the tools of contemporary biology to exploit advances in genetics and molecular biology. DR. LEDERBERG indicated that his presentation would elaborate further on this approach.

The range of topics for discussion could easily have encompassed other exciting fields, e.g., studies on the morphology and life cycle of the parasite as sites for other wedges to be driven between parasite

and host. Thus, Sidney Brenner has pointed out how the water excretion mechanism of trematodes, embodied in a single cell, constitutes a highly specialized physiologic target for specific pharmaceutical development.

# COMPARATIVE BIOCHEMISTRY AND THE DESIGN OF CHEMOTHERAPEUTIC AGENTS FOR INFECTIOUS DISEASE

Seymour S. Cohen

## Introduction

In an earlier paper in this Conference, Janssen described three strategies for control of infectious disease.1/ In this paper we shall discuss only one of these, that of chemotherapy for the treatment of disease, and shall focus on the problem of the design of new drugs that are disease-specific. It is assumed that:

(1) new and better drugs are necessary, as stated recently in a discussion of the chemotherapy of trypanosomiasis;2/

(2) research to discover new pharmaceuticals can be carried out; and

(3) new promising drugs can be tested in humans and can be delivered to needy patients.

All of these assumptions have been challenged in this Conference, but it seems more useful to follow the lead of the sponsors of our meeting at this time.

As the title of this paper suggests, we shall consider a general strategy in approaching chemotherapy of infectious disease. This strategy is considered applicable to all infectious disease,3/ and not only for parasitic diseases of major importance in the developing world. The strategy stems in significant measure from our perception of the history of all chemotherapy in the last 70 years and our understanding of the present state of biomedical science and technology.

Briefly, the strategy rests on the following facts:

1. All infectious agents differ in major biological and chemical properties from their mammalian hosts.

2. Major chemical differences stem from differences between genetic nucleic acids of parasite and mammal. The definition of these

differences constitutes one advanced aspect of the study of comparative biochemistry.

3. These differences in nucleic acid composition and sequence between organisms compel differences in structures of essentially all proteins and enzymes of the parasites and their hosts.

4. The existence of specific differences between these proteins of two organisms establishes the possibility of the synthesis of agents capable of inhibiting or inactivating proteins essential to multiplication of the parasite.

5. During the last decade improvements in technology of protein isolation and characterization have made definition of specific areas in a specific crucial protein of a parasite a feasible undertaking.

6. Improvements in design and synthesis of inhibitors permit exploitation of the definable differences between proteins.

It is suggested then that specific chemotherapeutic agents can be designed to inactivate proteins essential to multiplication or survival of an infectious agent, whether it be bacterium, virus, protozoan, fungus, or worm. This paper will now elaborate aspects of the history of the development of these facts and indicate some particular applications of the strategy to some of the major parasitic diseases in developing countries.

By 1907, Paul Ehrlich had observed cure of trypanosomiasis in mice by trypan red and had formulated a goal of a specific chemotherapy, i.e., the selective elimination of a parasite from a diseased animal without major damage to the host.4/ His subsequent efforts towards such a goal led to development of Salvarsan for syphilis, but as we now know, the arsenical is toxic in important respects. Thus, Ehrlich's goal was not realized before 1936 with the discovery of the chemotherapeutic efficacy of Prontosil and of its essential component, the relavitely nontoxic sulfanilamide. This finding and the demonstration that sulfanilamide competes with p-aminobenzoic acid and inhibits synthesis of essential folic acid in bacteria opened the era of a potentially rational chemotherapy.

At most, the compounds that were made then were designed to emulate substrates and cofactors of essential reactions at the active sites of enzymes. Many of these substances, though inhibitory, are not sufficiently selective between active sites of enzymes of the parasite and those of the host. Nor have inhibitors been tailored generally to complement essential regions other than active catalytic or regulatory sites in the crucial protein.

Nevertheless, in attempts to inhibit some enzymes, of which dihydrofolate reductase is an outstanding example, this approach has

led to development of discriminatory chemotherapeutic agents. Agents that successfully inhibit dihydrofolate reductase include pyrimethamine, trimethoprim, and methotrexate, some of whose properties are presented in Table 1. As shown in this table, selectivity of those compounds active on dihydrofolate reductase demonstrated that enzymes of similar (analogous) function from many cells may be distinguished by their widely different reactions to various inhibitors. Thus, this table demonstrates that structures of these proteins differ sufficiently to permit development of inhibitors selective for analogous bacterial, protozoan, and mammalian enzymes.

Shortly after discovery of sulfanilamide, and with the advent of World War II, work on penicillin was resumed. The development and efficacy of this antibiotic led to further investigations to discover other therapeutic agents produced by organisms. An antibiotic was detected initially by its antibacterial action, and the selectivity of its toxicity was explored relatively late in the sequence of studies seeking therapeutic efficacy.

This search has also produced major new substances, and creative synthetic modifications of antibiotics have been introduced, e.g., penicillin-like derivatives to improve stability, distribution, and antibacterial spectrum. Nevertheless, new antibiotics have been sought empirically and have generally been found to take advantage of unique structural and metabolic properties of bacteria, as compared to the mammalian hosts. In these respects, discovery of antibiotics has not only been of enormous import in the progress of therapy and in preventive medicine but also has demonstrated that clear structural and metabolic differences exist between antibiotic-sensitive organisms and their hosts.

## Selective Chemotherapy and Comparative Biochemistry

By the 1950s, these differences were accepted as important elements of evidence of the major division between procaryotic and eucaryotic cells. Thus, penicillin had led to detection of the characteristic peptidoglycan in many bacterial cell walls, and streptomycin, chloramphenicol, erythromycin, and others led to demonstration of important differences between procaryotic and eucaryotic ribosomes.

In the following decade, observations indicating that few serological cross reactions were detectable between the proteins of procaryotic and eucaryotic organisms began to be understood in terms of transcription and translation of specific nucleotide sequences into unique proteins. These structural specificities exist despite functional similarities among the proteins. Thus, an E. coli enzyme, such as the phosphofructokinase active in bacterial glycolysis, is very different from the human phosphofructokinase. Indeed, Mansour and Bueding had demonstrated twenty-five years ago that a schistosomal

TABLE 1. CONCENTRATIONS ($x10^{8}$M) OF ANTIFOLATES NEEDED FOR 50 PERCENT INHIBITION OF DIHYDROFOLATE REDUCTASE, ISOLATED FROM SIX SOURCES 5/

| Substance | Human liver | Rat liver | Mouse erythrocyte | Pl. berghei | Tryp. equi-perdum | E . coli |
|---|---|---|---|---|---|---|
| Pyrimethamine a/ | 180 | 70 | 100 | 0.05 | 20 | 2500 |
| Trimethoprim b/ | 30,000 | 26,000 | 100,000 | 7.0 | 100 | 0.5 |
| Methotrexate c/ | 9 | 0.2 | (not done) | 0.07 | 0.02 | 0.1 |

a/Antimalarial
b/Antibacterial
c/Antineoplastic

phosphofructokinase differed from the mammalian enzyme, and was selectively inhibitable by an appropriate antimony derivative.6,7/ Thus, it was already known two decades ago that bacteria and other parasites contained unique essential proteins theoretically sensitive to specific inhibitors. At that time, however, it was not known how to design an inhibitor capable of reacting specifically with particular proteins.

## Seeking a Penicillin for Virus Infection

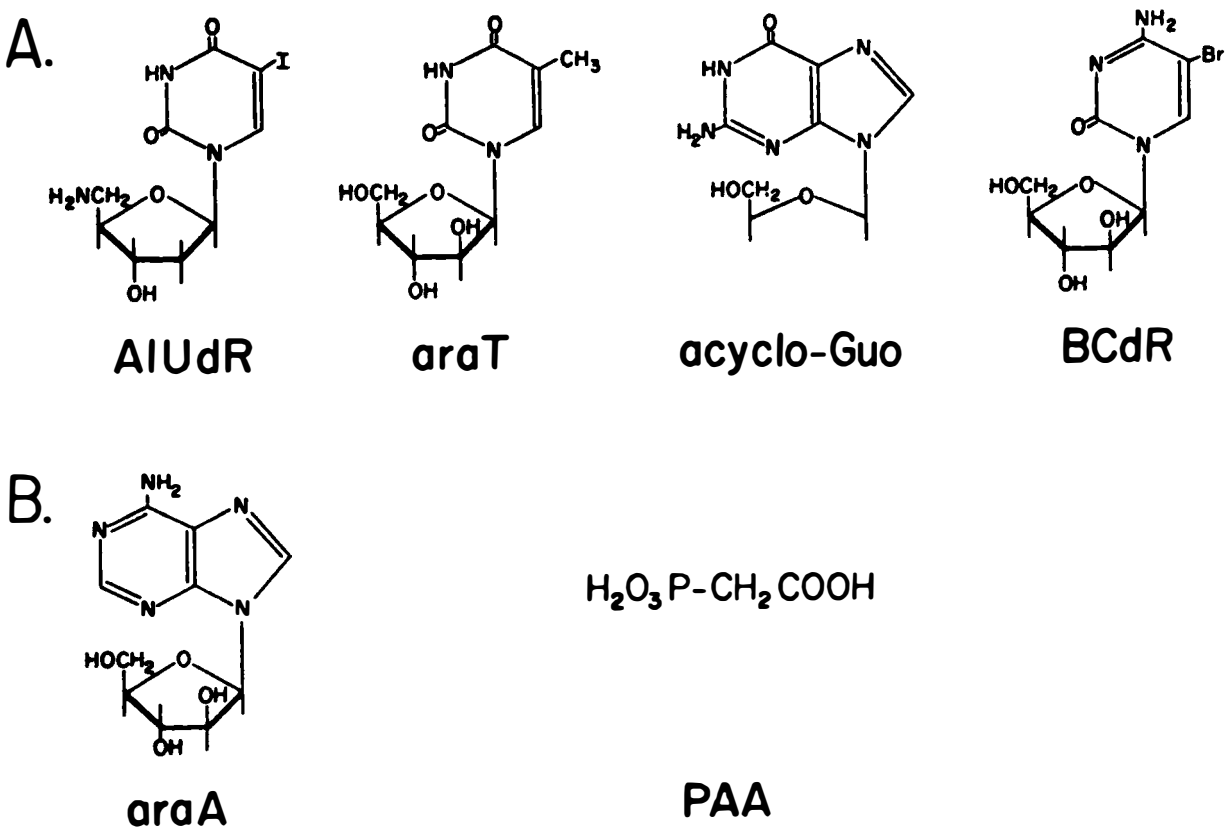
Although the synthetic and antibiotic-screening programs of pharmaceutical laboratories generally do not deliberately take advantage of these opportunities to utilize specific protein inhibitors, many effective antibacterial agents have been obtained by a variety of other efforts encompassing brute screening or enlightened empiricism. However, in applying these methods to virus infections, these extrapolations have generally failed, despite improved screening procedures adapted to viruses or virus-infected cells. After 30 years of such efforts and the expenditure of large sums, the problems of selective chemotherapy presented by virus infections have for the most part not been amenable to screening procedures. For example, the importance of nucleic acid synthesis in virus multiplication led to testing many analogues of bases and nucleosides. With few exceptions, inhibitory compounds so developed proved similarly inimical to the multiplication of viruses and to growth of normal cells.

Nevertheless, it is relevant to examine the sparse harvest of the few antiviral agents that do possess some selectivity. Figure 1 shows some agents active in inhibiting infections with herpes simplex virus. Compounds in Group A are activated to the nucleoside monophosphate by the unique deoxypyrimidine kinase determined by virus DNA. These activated nucleotide analogues have been the true inhibitors of virus multiplication. Compounds in Group B affect the unique virus-induced DNA polymerase. Thus, the few substances found to have promising selectivity in inhibiting virus-infected cells specifically support the generalization described for antibacterial agents. The virus-induced thymidine kinases and DNA polymerases differ from the host enzymes, and these differences can be exploited.

In fact, with the exception of viroids, all viruses code for specific enzymes and structural proteins essential to virus multiplication, stability, and survival. A large body of information on multiplication of various viruses suggests identity of specific proteins induced by the viral etiological agents of herpes, influenza, foot and mouth disease, and some tumors. Many of these are essential to virus multiplication, and the essentiality of these proteins should be noted. Thus, the deoxypyrimidine kinase induced by herpes virus is not believed to be an essential enzyme, and selection of kinaseless mutants

in infected cells by analogue-substrates of the kinase may lead to resistance to the drugs of Group A in Figure 1.

FIGURE 1. RELATIVELY SPECIFIC INHIBITORS OF HERPES VIRUS MULTIPLICATION




A. Compounds whose antiviral activity requires phosphorylation by the herpes-induced deoxypyrimidine kinase: 5'-amino-5-iodode-oxyuridine (AlUdR), ara T, 9-(2-hydroxyethoxymethyl)guanine (acycloGuo) and 5-bromo-deoxycytidine (BCdr);

B. Compounds that do not utilize the herpes-induced deoxypyrimidine kinase: ara A and phosphonoacetic acid (PAA).8/

## On the Technology of Protein and Enzyme Characterization

Until recently, knowledge that proteins induced by etiologic agents differed from those of the host was mainly of academic interest. Protein purification and characterization were slow and difficult, requiring relatively large amounts of material. Advances in the past decade have made it possible to use relatively small amounts of organisms for rapid purification and characterization of proteins and enzymes. For example, as a result of such advances:

1. One gram wet weight of trypanosomes has permitted isolation and purification to homogeneity of the protozoan glutamate dehydrogenase, which was then shown to differ from the mammalian enzyme.9/

2. Picomole quantities of myoglobin have been sequenced.10/

3. Proteins of more than 1,000 aminoacids, such as β-galactosidase, have been completely sequenced.11/

4. Immunochemistry, crystallography, and organic chemistry have helped define sensitive regions of proteins, as have combinations of genetic and complementation techniques when applied to subunit assembly.

5. These techniques have been used to direct synthesis of polypeptides capable of combining specifically with defined protein regions, e.g., lysozyme.12/

6. New inhibitors have been developed capable of specific irreversible or reversible reactions with defined proteins.13/

Some pharmaceutical companies are keeping pace with modern science and technology by attempting to exploit these developments, for instance, in the improvement of inhibitors of dihydrofolate reductase, but most companies are not. Although major pharmaceutical companies usually have the multidisciplinary capability to synthesize and screen new agents, and to take important leads through studies of the mode of action, toxicology, clinical pharmacology, and clinical trials, few appear to possess the requisite skills in protein chemistry, or to have incorporated such skills into their programs. On the other hand, although academia is providing most of the basic scientific information, including that on protein structure, academic institutions cannot organize the requisite multidisciplinary approach necessary to exploit the basic science and technology in this field. It is possible that such integration may be effected through interactions between industry and academia, but it is not yet clear how such integrating efforts might be accomplished.

## Application of Comparative Biochemistry to Drugs for Developing Countries

Many drugs used to treat tropical diseases are highly toxic and have other shortcomings.1/ Nevertheless, we do not wish to minimize possible effects of improvements in delivery systems on drug toxicity. For example, recent experiments have demonstrated that some otherwise highly toxic trivalent arsenicals encased in liposomes can be delivered effectively to leishmaniae-infected liver with relatively little toxicity.14,15/ However, assuming the need for new and better drugs, how shall we consider treatment of tropical parasitic diseases?

Parasites causing such diseases fit very well within the scientific generalizations presented above:

1. The parasites contain characteristic and specific DNA which determines synthesis of unique essential proteins.

2. They possess essential metabolic systems sensitive to discriminating inhibitors.

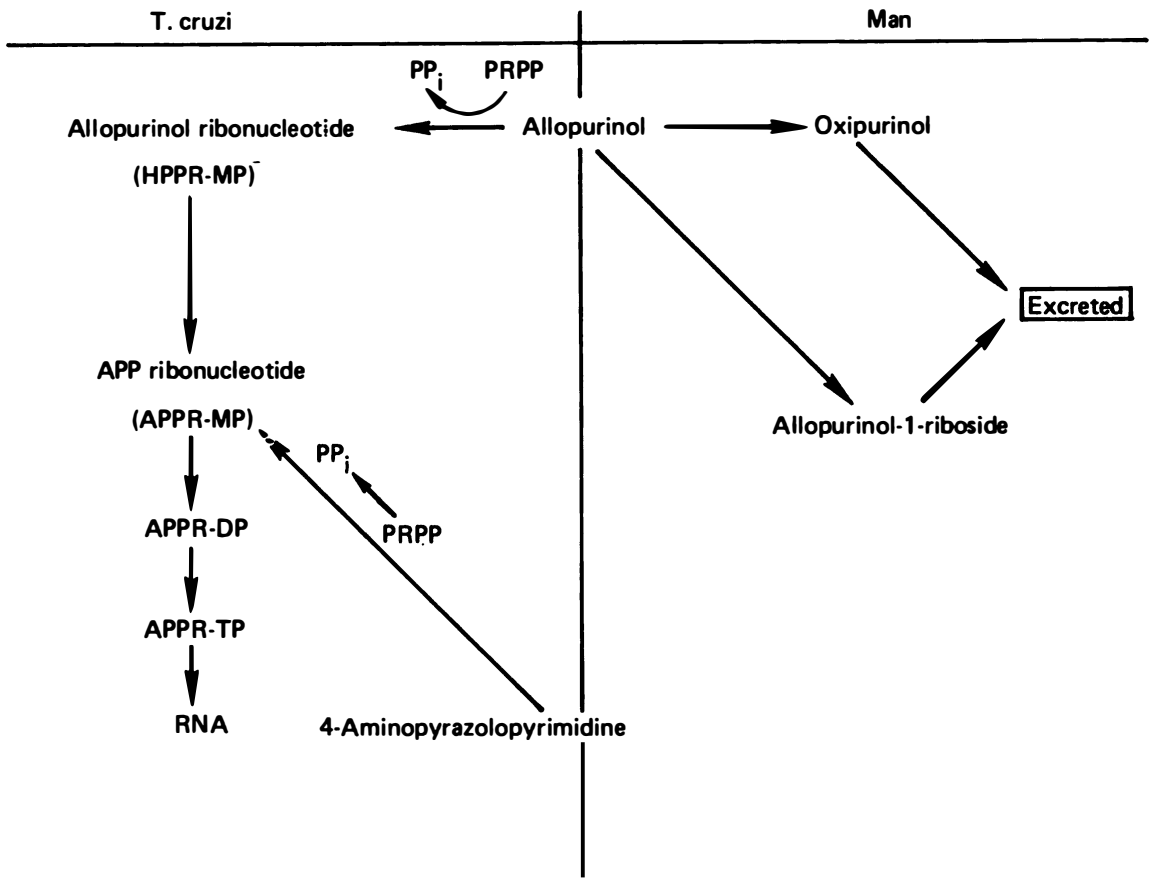
### Some Protozoan Diseases

As noted earlier, the dihydrofolate reductase of malarial parasites, such as Plasmodium berghei, differs from that of mammalian and avian hosts in numerous properties.16/ As presented in Table 1, these differences permit a substance such as pyrimethamine to exhibit selective toxicity towards the parasite. It would be of great interest to determine if inhibition of this enzyme leads to thymineless death in the parasite, as appears to be the case in other organisms.17/ If this is so, the apparent deoxycytidine requirement and purine metabolism of Plasmodia 18/ may possibly be manipulated to exacerbate a deficiency for essential thymine.

The effects of allopurinol on some Leishmaniae and trypanosomes have pointed to the existence of unique enzymes in these protozoans that can convert the analogue within the parasite to an adenine-like nucleotide, as in Figure 2. This newly synthesized analogue can then be inserted into parasite RNA, which leads to inactivation of the parasite.19/ This situation is reminiscent of the effects of inhibitors of herpes virus multiplication activated by virus-induced deoxypyrimidine kinase (Figure 1).

In the trypanosomiases, it has been known for some time that several African trypanosomes, for example T. brucei and T. rhodesiensis, depend entirely on glycolysis as their energy source. Unlike anaerobic yeasts, however, the organisms accumulate pyruvate, as shown in Table 2, and must devise new mechanisms to convert NADH to oxidized NAD essential for maintenance of glycolysis. Several such unique

FIGURE 2. METABOLIC TRANSFORMATION OF ALLOPURINOL IN T. CRUZI AND MAN*




*Human erythrocytes, when incubated with allopurinol, will synthesize trace amounts of 1-allopurinol-5'-phosphate. Small amounts of oxipurinol-7-riboside are found in human urine. The major metabolic pathway of allopurinol in T. cruzi is to allopurinol ribonucleotide (HPPR-MP). This is converted by the adenylosuccinate synthetase to the adenylate analogue, APP ribonucleotide (APPR-MP), which is phosphorylated to the diphosphate (DP) and triphosphate (TP) and incorporated into RNA.19/

TABLE 2. END PRODUCTS OF AEROBIC GLUCOSE METABOLISM IN BLOOD-STREAM TRYPANOSOMES 16/

| | $CO_2$ | Glycerol | Ethanol | Lactate | Pyruvate | Acetate | Succinate | Citrate |
|---|---|---|---|---|---|---|---|---|
| T. rhodesiense | ± | + | - | - | ++ | - | - | - |
| T. gambiense | - | + | - | - | ++ | - | - | - |
| T. brucei | - | + | - | - | ++ | - | - | - |
| T. evansi | - | + | - | - | ++ | - | - | - |
| T. equinum | - | + | - | - | ++ | - | - | - |
| T. equiperdum | - | + | - | - | ++ | - | - | - |
| T. vivax | + | + | - | ± | + | + | - | - |
| T. congolense | + | + | - | - | - | + | + | - |
| T. cruzi | ++ | - | - | ± | - | + | + | - |
| T. lewisi | ++ | - | - | ± | - | + | + | - |

-, none; ±, trace; +, small quantities; ++, substantial quantities

reactions are known, and these sites are inhibited by antitrypanosomal agents. Thus, ethidium inhibits the unique glycerolphosphate dehydrogenase,20/ and reacts with kinetoplast DNA. The $\alpha$-glycerophosphate oxidase and glycerol dehydrogenase of the protozoans also regenerate NAD enzymes. A combination of an Fe chelator, salicylhydroxamic acid, and glycerol prevents this regeneration sufficiently to cause selective damage to the parasites in infected animals.21/

## Comparative Biochemistry and Schistosomes

Over many years, Dr. Tag Mansour has contributed to our understanding of the many unique biochemical features of helminths. Glycolysis is an essential energy source for survival of the parasite in the mammalian host, although oxygen appears to be required for egg production.22/ As noted earlier, Bueding and J. M. Mansour clarified the special properties of phosphofructokinase 23/ among other enzymes participating in essential glycolytic reactions, but the search for specific inhibitors does not appear to have been viewed as a problem in protein chemistry.

It has also been reported that schistosomal eggs contain chitin, a non-mammalian substance.24/ The presence of eggs in the human urethra and bladder provokes various pathological reactions. Antibiotics which inhibit chitin synthetase and chitinases are known, but experiments with these agents in affecting the course of the disease have not been described. Of course, inhibition of the many reactions related to egg production should be examined.

## On Leprosy and Mycobacteria

We know little of the biological and chemical properties of the etiologic agent causing leprosy. The microorganism is believed to be a very slow-growing mycobacterium, and few workers have successfully cultivated the organism *in vitro*. Cultivation of the organism in a host other than man is an important advance, and its growth in a host even as exotic as the armadillo has facilitated many otherwise impossible studies, particularly serological and immunologic investigations. Despite some advances in these directions, at present we must consider development of chemotherapeutic agents without much solid information about the specific properties of the organism.

In this situation we have assumed that the etiologic agent possesses a relatively specific characteristic of *Mycobacteria*, which is in fact shared with *Corynebacteria* and *Nocardia*, *i.e.*, the presence of a cell wall polysaccharide in which about half the sugar residues consist of D-arabinose. This sugar is made in bacteria by an enzyme not found in mouse fibroblasts or in yeast,25/ and is considered strictly of procaryotic origin. Absence of this enzyme is lethal in *E. coli* 26/

which contains the essential derivative of D-arabinose, 2-ketodeoxy-octonate. Thus, it can be imagined that unique and inhibitable metabolic steps exist in M. Leprae, and in related microorganisms, which are essential for synthesis and insertion of the sugar into the cell wall polysaccharide of the Mycobacterium. Indeed, at least four such unique enzymes should exist, if the synthesis and insertion steps are comparable with the mechanisms known to exist for insertion of sugars into polysaccharides.

## Conclusions

It appears that biochemistry has identified unique metabolic steps essential to survival and multiplication of important parasites. The science and technology applicable to analysis of the origin and structure of essential proteins is ready for a major new direction of attack on the chemotherapy of all infectious disease. The desired methodology is such that, contrary to current approaches by funding agencies, the research budget for tropical disease should be viewed as related also to budgets for research on bacterial and viral disease.

The nature of the problem and the approach outlined in this paper require an integrated multidisciplinary attack on parasite-determined proteins, scarcely being attempted at present. A concentration on inhibitors specifically reactive on proteins might well avoid problems of mutagenicity and carcinogenicity of compounds designed to affect nucleic acid metabolism. The time required for such an effort should not be greater than the time usually needed for drug development in a pharmaceutical company. Although the nature of the approach will identify therapeutic leads relatively late in a development process which requires considerable study of the unique essential target protein, search for specificity in the inhibitory process should minimize waste arising from discovery of nonselective toxicity in animal or clinical studies. The funds to be expended might well be much smaller than those spent in futile empirical approaches, as employed in the search for antiviral agents. Finally, a well-organized multidisciplinary effort would provide excellent opportunities to train groups of investigators who must ultimately develop in their own countries the drugs to treat the multitude of bacterial, viral, fungal, protozoan, and worm diseases found uniquely in their countries.

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# CELLULAR REGULATORY PROCESSES IN PARASITIC HELMINTHS: SIGNIFICANCE IN DRUG DEVELOPMENT*

Tag E. Mansour

Cellular regulatory mechanisms of a parasite are essential for maintenance of that parasite's life. For, in addition to adjusting the biochemical machinery of the parasite to meet its needs for energy and reproduction, these control mechanisms must harmonize parasitic biochemical and physiological processes with those of the host. Fifteen years ago, I reviewed the pharmacology and biochemistry of parasitic helminths.1/ The purpose of that review was to emphasize metabolic differences between these organisms and their hosts. Investigations in the field of cellular regulatory biology have since enhanced our knowledge of many basic principles in enzyme and hormone control among diverse organisms. Progress in understanding control mechanisms in parasites has been meager, because of difficulties in cultivating these parasites in well-defined media, and in the identification and isolation of mutants. I shall focus this discussion on three main regulatory mechanisms: parasite motility, control of metabolism, and chemotaxis. An important purpose of this article is to draw the attention of persons interested in chemotherapy of parasitic diseases to the action of diverse drugs at various regulatory sites, and possible utilization of these sites for selection of new antiparasitic agents.

## Regulation of Motility in Parasitic Helminths

A parasitic helminth maintains itself at its specific host site through coordination of its movements. Rhythmical movement of the parasite influences movement of ingested food in the parasite's intestinal tract, and its excretory system functions. The important role of motility in maintaining a successful parasitic life has spurred pharmacologists to use it as a biological parameter for rapid identification of potentially effective new chemotherapeutic agents. In some of these

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experiments, the approach taken with isolated organ systems of vertebrates was also used to study parasitic helminth motility. Kymographic recordings of the motility of Ascaris ,2/ and of the liver fluke Fasciola hepatica,3/ were used to study effects of diverse chemical agents on motility. Recently more elaborate systems for monitoring motility were devised utilizing instruments mounting multiphotocells to measure quantitatively the movement of small parasites such as schistosomes.4/ Acetylcholine and serotonin (5-hydroxytryptamine) are two neurotransmitters that have been extensively investigated in parasitic helminths.

While studying the effects of drugs on the liver fluke Fasciola hepatica 3/ by means of bioassays, we demonstrated the presence of acetylcholine concentrations in extracts of the worms 5/ which were almost as high as those found in mammalian brains. The presence of both the synthesizing enzyme, acetycholine synthetase, and the hydrolyzing enzyme, true cholinesterase, was also reported in Fasciola,5/ and in a related trematode parasite, Schistosoma mansoni.6/ Subsequently, several workers demonstrated the presence of acetylcholine and its two allied enzymes in other trematodes, and in nematodes and cestodes.7/ This evidence, when added to pharmacological data on diverse neuromuscular preparations from these parasites, strongly indicates that acetylcholine or a related compound functions in the neuromuscular activity of these helminths.

Acetylcholine in low concentrations has caused Ascaris preparations to contract. However, these preparations were more sensitive to nicotine, which exerted an effect similar to that of acetylcholine. Cholinergic receptors, therefore, do not appear to be muscarinic since the effect of acetylcholine was antagonized by d-tubocurarine but not by atropine.8/ In the liver fluke, the choline esters -- carbachol, acetylcholine, and methylcholine -- together with physostigmine and prostigmine, relax parasite preparations resulting either in complete paralysis, or in a marked reduction in the amplitude of contraction.5/ The effect of choline esters was reversible. Physostigmine sensitized the preparation to the action of acetylcholine and to carbachol. When added to the fact that acetylcholine, true cholinesterase, and acetylcholine synthetase are present in these organisms, these results strongly indicated the presence of cholinergic receptors in these trematodes. llhese receptors are peripherally located and appear responsible for relaxing or paralyzing the motility of these organisms. The evidence indicates that acetylcholine receptors in trematodes may differ from those found in nicotinic or muscarinic mammalian synapses.5/ This emphasizes an important conclusion; namely, that regulatory processes at the cholinergic receptors of these parasites appear to differ from those of the host.

In 1949, we discovered that rhythmical activity of both intact and degangliated preparations from liver flukes were stimulated by sympathomimetic amines, particularly those related to amphetamine.3/ We

subsequently reported that rhythmical movement of the liver fluke was stimulated by serotonin, and by lysergic acid diethylamide (LSD) and related indoleamines (9,10). The effect was peripheral, and was not mediated through the parasite's central ganglion. Bromolysergic acid diethylamide, an analog of LSD with a bromine atom at the 2' position, depressed rhythmic movement and antagonized the stimulant action of serotonin and LSD. The results suggested the presence of serotonin receptors in these organisms.

Pharmacological evidence that serotonin is a putative excitatory neurotransmitter in the liver fluke 9,10/ raised the question of whether a similar role can be demonstrated in other flat worms. This was in fact indicated by the finding that serotonin stimulated rhythmic movement of the following species: Schistosoma mansoni, Chlonorchis sinesis, and Taenia pisiformis.1/ These findings were further verified in Schistosoma mansoni by two other investigator groups,11,12/ and also apply to the cestode, Mesocestoides corti.13/

Serotonin is an ubiquitous indoleamine in invertebrate tissues. 14,15/ Erspamer and Welch 14,15/ demonstrated its presence in several invertebrate nervous systems. From our laboratory, and based on results from a bioassay procedure 1,16/ and fluorometric methods,17/ we reported that the indoleamine is present in the liver fluke, Fasciola hepatica.1,16,17/ Andreini et al.18/ published data suggesting that the indoleamine in the fluke differs spectrophotofluorometrically from serotonin. The failure of Chou et al.19/ to demonstrate indoleamine in the liver fluke may be due to their use of unstarved parasites which contain large amounts of caecal contents that include lysine. The same group of investigators noted that this amino acide gives a spectrofluorometic signal similar to that of serotonin.20/ Intact liver flukes were capable of synthesizing the indoleamine from 5-hydroxytryptophan but not from tryptophan.1,16,17/ The presence of 5-hydroxytryptophan decarboxylase and its activation by pyridoxal phosphate was further demonstrated in cell-free extracts from the flukes 1,16/ using bioassay procedures. The presence of serotonin and of an uptake mechanism was reported in schistosomes.21/ The data implicate serotonin or a related indolamine as a putative neurotransmitter in the regulation of neuromuscular activity in parasitic flat worms.

## Chemotherapeutic Agents that Affect Parasite Motility

Several studies indicate that particular chemotherapeutic agents are effective because they modify one or another regulatory mechanism involved in motility. Santonin, an obsolete anthelmintic once used exclusively against nematodes, was found by Baldwin 2/ to paralyze only the anterior neuromuscular preparations in Ascaris at low concentrations, and to stimulate intermediate preparations. Santonin may, therefore, deprive the worm of coordinating impulses which come from the central nerve ring. This action is presumed to result in the

parasite's not being able to maintain its normal position in the host's intestine, and therefore becoming subject to expulsion. More recent studies on the mode of action of piperazine on Ascaris add evidence to the idea that effective chemotherapeutic agents may act upon regulatory mechanisms of neuromuscular function. Standen 22/ showed that Ascaris were paralyzed when incubated with piperazine. Subsequently, Norton and DeBeer 23/ showed that acetylcholine-induced contractions in Ascaris preparations could be blocked by piperazine and by d-tubocurarine. Piperazine may cause paralysis of Ascaris by blocking at the neuromuscular junction. The anthelmintic agent may be a pharmacological analog of a natural inhibitory neurotransmitter. The molecular identification of such a natural transmitter is an important problem that deserves further investigation.

Methyridin (2-B-methoxyethylpyridine), an anthelmintic with high activity against nematodes, was reported by Broome 24/ to act on the neuromuscular junction of Ascaris. According to this finding, methyridin and acetylcholine cause rapid paralysis of rehythmic movement. The effect of both compunds was reversed by d-tubocurarine and by piperazine. Methyridin may therefore produce a depolarizing effect on nematode muscle closely resembling that produced by acetylcholine. A similar effect was demonstrated in mammalian tissues, but only at very high drug concentrations. The selective effect of this drug as a chemotherapeutic agent seems to depend on a differential sensitivity of nematode neuromuscular receptors to its action.

Hycanthone is a new and highly schistosomicidal agent. Chou et al. 25/ reported evidence implicating serotonin receptors in the chemotherapeutic effect of this agent. Hycanthone treatment of the host results in a loss of the ability of the parasite to store serotonin in neuronal structures and, consequently, in its ability to coordinate its motility. Accordingly, hycanthone may interfere with a regulatory mechanism that is essential for maintenance of the parasite in its normal habitat.

Among anthelmintics effective against cestodes, arecoline may be used as a classical example. This muscarinic cholinergic agent, although not currently in clinical use, was the drug of choice a quarter of a century ago. Because of its muscarinic effect on the host, it was thought that the drug exerted its anthelminitc action as a result of its purgative effect. Batham 26/ showed that this was not the case since, when the drug was injected subcutaneously, it caused purgation but not worm removal. Using neuromuscular preparations of Taenia, Batham showed that it causes relaxation and eventual paralysis of the worm at low concentrations.

In vivo experimentation supports the view that some anthelmintic drugs owe their effectiveness to a primary action on motility. In 1944, Rogers 27/ showed how tetrachloroethylene, a drug that was extensively used against Ancylostoma, caused the nematode parasite

Nippostrongylus muris to leave the mucus of the rat's intestinal wall, after which they were expelled while still alive by movement of gut contents. A closely related phenomenon was observed by Standen 28/ in his early studies on antischistosomal agents. This is referred to as "the parasite shift effect." It can be demonstrated to follow treatment of infected mice with an antischistosomal agent. A "shift" can be observed in the distribution of the parasites from the mesenteric vessels to the liver. Standen explained this as due to interference by these agents with the muscle tone of the parasites. The end result is that they are unable to hold on to the walls of the blood vessels, and are gradually swept into the liver with the portal blood. Death of the schistosomes then occurs in the liver, according to Standen's histological studies.28/

## Serotonin Regulation of Metabolism in Flukes

Although information on hormonal control of metabolism of parasites is scanty, the evidence indicates that control of metabolism in parasites may be mediated through hormones that differ from those of the host. The involvement of cyclic 3',5'-AMP as a second messenger has already been reported in some parasites.

The liver fluke Fasciola hepatica is being used in our laboratory as a model to study regulation of carbohydrate metabolism in trematodes. Fasciola is an anaerobic organism that metabolizes glucose at a high rate, and converts it almost quantitatively to volatile fatty acides and CO with formation of only small amounts of lactic acid.29/ Incubation of the organism with serotonin causes a marked increase in lactic acid production.30/ In addition to its stimulatory effect on glycolysis, serotonin increases glycogen breakdown when glucose is omitted from the fluke medium, and activates glycogen phosphorylase and adenylate cyclase.30,31/ None of these effects can be mediated by epinephrine or norepinephrine.

The effect of serotonin on glycolysis does not seem restricted to Fasciola. The indoleamine, and its agonists methylsergide and dihydroergotamine, increases lactic acid production by schistosomes.32/ Furthermore, Higashi et al.33/ reported that adenylate cyclase from schistosomes is activated by serotonin. Thus, serotonin affects carbohydrate metabolism and adenylate cyclase in the liver fluke and in schistosomes similarly to epinephrine in some mammalian tissues. This is a very good illustration of a difference between the parasite and the host that can be utilized for planning the search for a chemotherapeutic agent.

## Serotonin and Cyclic AMP in the Liver Fluke

Adenylate cyclase in the liver fluke 31,34-36/ is a membranous

enzyme with multiple components for its control. While basal activity (without activators) is low, it is markedly activated in the presence of serotonin. Activation by serotonin 35/ is dependent on the presence of GTP.35/ Such a requirement is also seen with activation of adenylate cyclase by mammalian hormones. The specificity of serotonin activation of the enzyme was recently confirmed from studies on structure-activity relationships with diverse analogs.35/ Serotonin appears to activate adenylate cyclase. Although LSD and its derivatives are poor agonists compared to the indoleamines, they demonstrate greater affinity to serotonin sites.35/ D-LSD was the most potent derivative. Any substitution other than of the diethyl group on the amide nitrogen decreased the potency of the derivative. Either D- or L-LSD act as antagonists of serotonin activation with very low affinity for L-LSD. Thus, both activation of adenylate cyclase and antagonism of 5-HT are stereo-specific processes. BOL, which is not an agonist to adenylate cyclase activation, competes for the 5-HT activation and inhibits basal (non-activated) enzyme activity. BOL was the most potent antagonist with a $K_i$ value in the nanomolar range.35

Cyclic 3',5'-AMP phosphodiesterase is the only enzyme known to hydrolize cyclic AMP to 5-AMP. Both adenylate cyclase and phosphodiesterase regulate the concentration of cyclic AMP in the cell. Phosphodiesterase was found in fluke homogenates,37/ and appears to be involved in regulation of cyclic AMP concentrations in this organism. Phosphodiesterase inhibitors increase motility like serotonin and its analogs.37/ The molecular basis for this effect does not appear to be simple inhibition of the phosphodiesterase, thus raising the concentration of cyclic AMP. Only one of these inhibitors, isobutyl methylxanthine, increaed the concentrations of cyclic AMP in the flukes. Indeed, many of these agents antagonized serotonin-mediated rises in concentrations of endogenous cyclic AMP. While direct participation of cyclic AMP in fluke motility has not been demonstrated, phosphodiesterase appears to offer a site for chemical agents to influence motility of the parasite.

Some effects of hormones are known to be mediated by cAMP through activation of protein kinases which phosphorylate specific proteins. Epinephrine activation of glycogen phosphorylase offers a classic example of such a control mechanism. Recent studies in our laboratory by Gentleman et al.38/ demonstrated the presence of a protein kinase both in the particulate and in the supernatant fractions of Fasciola. The fluke protein kinase was highly sensitive to cAMP. Incubation of flukes with serotonin activated the protein kinase. Under these conditions, the enzyme was highly active without cAMP. Interestingly, and under conditions which favor an antagonistic effect on the adenylate cyclase system in the flukes, LSD also antagonized activation of the protein kinase.38/ The results may indicate that, as in mammalian cells, some physiological effects of serotonin are mediated by cyclic AMP activation of protein kinase. Such an effect may also apply to other trematodes, since S. mansoni was reported to contain this enzyme

together with an adenylate cyclase activated by serotonin.33/ Substrates for the protein kinase have still to be isolated and identified.

## Pharmacologic Manipulation of Phosphofructokinase

Studies have been carried out on enzymes catalyzing rate-limiting reactions to increase understanding of the details of their regulation. Usually, these enzymes are allosteric proteins and exhibit complex kinetics complementary to the metabolic needs of the cell. Phosphofructokinase is one enzyme that has attracted our attention. This enzyme catalyzes the physiologically irreversible phosphorylation of fructose-6-P to fructose-1,6-$P_2$ with ATP as the phosphate donor. The enzyme was shown to regulate glycolytic flux in higher organisms (for references see 39). Evidence was presented indicating that serotonin activates phosphofructokinase in the liver fluke as it activates adenylate cyclase.40,41,42/ Control of the enzyme appears to involve conversion of a low molecular weight inactive form of phosphofructokinase to a high molecular weight active form. The fluke enzyme, once activated, is subject to all the allosteric kinetics relevant to mammalian phosphofructokinase.39,43/ This includes inhibition by one of its substrates, ATP. The ATP-inhibited enzyme can be "de-inhibited" by cyclic AMP and fructose-6-P. Kinetic studies with the active enzyme showed that each of the three ligands (fructose-6-P, ATP, and cyclic AMP) could alter the saturation curve of the others. These kinetics were considered in terms of the Monod-Changeux-Wyman model for allosteric proteins.44. Thus, the parasite enzyme is well endowed with all the control mechanisms necessary for reversible conversion from active to inactive form through changes in the tertiary and in the quaternary structure of the enzyme, a classic example of a regulatory enzyme.

Because of its critical role in regulation of glycolysis, phosphofructokinase has been implicated as the site of action of an important group of antischistosomal agents, the antimonials. Utilizing a cell free extract system for measuring glycolysis, we observed that phosphofructokinase is a rate-limiting enzyme in schistosomes,45,46/ and that its inhibition can account for the effect of these antischistosomal agents. The parasite enzyme is comparatively more sensitive to inhibition by these antimonials than is the mammalian phosphofructokinase.45/

Similarly, selective inhibition by antimonials on adult filariids was recently reported. *Dipetalonema witei* (=viteae) and *Brugia pahangi* were reported to be metabolically similar to the schistosomes in that they are homolactate fermenters.47,48/ Helminths, such as *Ascaris* and *Hymenolepis diminuta*, which are not homolactate fermenters also exhibited phosphofructokinase activities which were susceptible to inhibition by stibophen. This is in direct contrast to phosphofructokinases derived from mammalian tissues which are considerably more refractory to inhibition by antimonials.48/ These findings, when added to our results with schistosomes,45 suggest a broad spectrum of activity by

antimonials against parasitic helminth phosphofructokinases. This enzyme model is amenable to selective inhibition by chemotherapeutic agents.

## Other Regulatory Sites Affected by Anthelmintics

Schistosomes seem to depend primarily, if not exclusively, on preformed purines to satisfy their needs for purine nucleotides.49/ Utilizing this finding, Jaffe 50/ found that the purine analog, tubercidin (7-deazoadenosine), exerted a potent antischistosomal effect due to inhibition of the utilization of adenosine for adenine nucleotide formation.51/

One enzyme system that appears essential for many trematodes, nematodes and cestodes that ferment glucose to succinate or to volatile fatty acids is fumarate reductase, a component of the succinic dehydrogenase complex. Since these parasites are predominantly anaerobes, the enzyme plays an important role in the regeneration of NAD.52-55/ Inhibition of this enzyme markedly suppresses the viability of these parasites.56-59/ Metzger and Duwel 60/ recently demonstrated that the mechanism of action of 2,6-dihydroxy-3,5-dichlorobenz-4'-chloroanilide (DDBA) as a flukicide may be ascribed to a primary inhibition of fumarate reductase within the succinic dehydrogenase complex in the parasite.57/

Studies on the biochemistry of egg formation should be of importance in developing drugs to interfere with parasite egg laying capacity. Bennett and Gianutsos 61/ reported that disulfuran raises the levels of dopamine when given to schistosome-infected mice and then reduces the levels of norepinephrine to almost undetectable concentrations in schistosomes. Although changes in motility of the parasites were not observed, such treatment resulted in abnormal egg production. This effect appears related to inhibition of the enzyme phenol oxidase. This enzyme was first demonstrated in trematodes in Fasciola hepatica, 62/ and was subsequently found in schistosomes.61/ Phenol oxidase has a variety of substrates, and may be involved in the oxidation of an as yet undetermined catechol substrate necessary for egg formation. The effect of disulfuran on egg formation by the parasites may be due to inhibition of the activity of this enzyme. Studies on the biochemistry of egg formation in the parasite may elucidate other sites amenable to selective inhibition by chemical agents.

## Chemotaxis

Chemotaxis is one of the most primitive processes enabling an organism to respond to favorable and noxious agents in the environment. The process is being extensively investigated in prokaryotes,63/ and appears to involve a receptor-mediated stimulus event, a sensing

mechanism that is temporal in nature, and movement of the organism in response to the stimulus. Studies on eukaryotic cells have not advanced as far as those in bacteria. Chemotaxis of leukocytes to various complement-derived factors and byproducts of the inflammatory response,64,65 and to n-formyl methionine-containing peptides has recently been reported. In addition, the process of aggregation in the cellular slime mold, Dictyostelium discoideum, has been shown to be mediated via chemotactic responses to oscillating gradients of cyclic AMP produced by the starving amebae.66,67/

We have recently studies chemotaxis, using the acellular slime mold, Physarum polycephalum.68,69/ The organism provides both an objective and quantitative model for the measurement of chemotaxis, and information on this organism may provide additional insight into the nature of this important process.

Chemotaxis in parasitic helminths appears intricately involved in completion of the life cycle. Migration of trematode miracidia to intermediary snails, and attraction of the motile cercariae to mammalian hosts of some trematodes, are classical examples of chemotaxis in the life of these parasites. A study has been initiated on the details of how miracidia and cercariae find their hosts. Recent work reported by MacInnis 70/ identified chemicals from mammalian skin which initiated penetration responses by Schistosoma mansoni cercariae. Earlier studies by the same group implicated amino acids and other compounds as attractants of S. mansoni miracidia to the snail host.71/ Since eighteen amino acids have been reported to be excreted by the snail, it remains to be seen whether a few amino acids can be identified as the real attractants in this large mixture.

The value of information gained from these studies for development of drugs and other methods for controlling schistosomiasis and other trematode infections 71/ is obvious. Analogs of these amino acids may act as antagonists instead of agonists, and may result in disrupting an important system for completion of the life cycle. Misleading miracidia into migrating to a non-favorable environment may be sufficient to terminate their life cycle.

Research on biology of chemotaxis has been extended to studies on snail vectors of parasites. Recently, MacInnis' group has investigated chemicals emanating from food sources which can attract or trap the snail.72/ Fractionation of lettuce by these workers revealed that the portion containing free amino acids was the primary attractant for Biomphalaria glabrata, the snail host for Schistosoma mansoni. These amino acids have been identified as glutamate and proline. A trapping mechanism, following attraction of the snails, may be devised by providing these attractants as baits. Similarly, molluscicides may be effectively used if they are released in the water following a prolonged release of attractants such as proline and glutamate.

The above overview illustrates that, despite spectacular advances in knowledge concerning chemotaxis in prokaryotes during the last decade, information available on chemotaxis in parasites is very limited. Intricate details of this process may expose sites amenable to pharmacologic manipulation.

The available information concerning cellular regulatory processes in parasitic helminths is scanty, and much research is needed in this important area. Workers in this field may benefit significantly from the recent explosion of knowledge of cellular regulation in bacterial and mammalian cells. Studies on cellular regulatory processes discussed above, and involving motility and metabolism, support the view that the the nature of these regulatory processes in the parasite may be different from that of the host. An important aspect of this thesis is that these processes may be exploited toward a strategy for chemotherapy of the infections caused by these parasites.

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# RATIONAL DEVELOPMENT OF NEW DRUGS FOR TRYPANOSOMIASIS

Anthony Cerami and Steven R. Meshnick

Although development of therapeutic agents for parasitic diseases has been largely neglected in the past fifty years, this has not always been the case. In fact, as is evident from the classical studies of Ehrlich on malaria and trypanosomes, these organisms served as the model for development of chemotherapeutic agents in general.1/ In recent years, however, the pharmaceutical industry lacked incentive to find new drugs for diseases of the developing world. This has been brought about by two factors: the substantial amount of capital necessary to evaluate safety and efficacy of possible new agents; and the limited resources of the developing world.

The new nationalism and awareness of problems of the developing world in the last few years has made it apparent that additional efforts must be undertaken to alleviate this problem. The means for overcoming this impasse, however, are not obvious. In the past few years, both WHO and NIH have launched major programs to study parasitic diseases. But it is doubtful whether university-based research programs can, by themselves, achieve the desired ends, since universities often lack facilities for evaluation of drug safety and experience in this subject. Thus, there is a definite need for participation by the pharmaceutical industry in development and eventual distribution of new drugs.

It therefore becomes imperative to develop a holistic approach which would facilitate application of modern chemistry and biology to understanding parasitic diseases and developing means for their control. One possible solution would be cooperative ventures consisting of governmental, pharmaceutical, and academic groups. This is particularly important since it is doubtful that these new drugs would ever be as important a source of revenue as a new broad spectrum antibiotic.

One of the ways that cost of drug development could be significantly reduced is by applying modern chemistry and biochemistry to rational design of new drugs for parasitic diseases. Rational design of drugs for treatment of orphan diseases is in fact an area of great interest to our laboratory.2,3/ We have recently tried to apply these

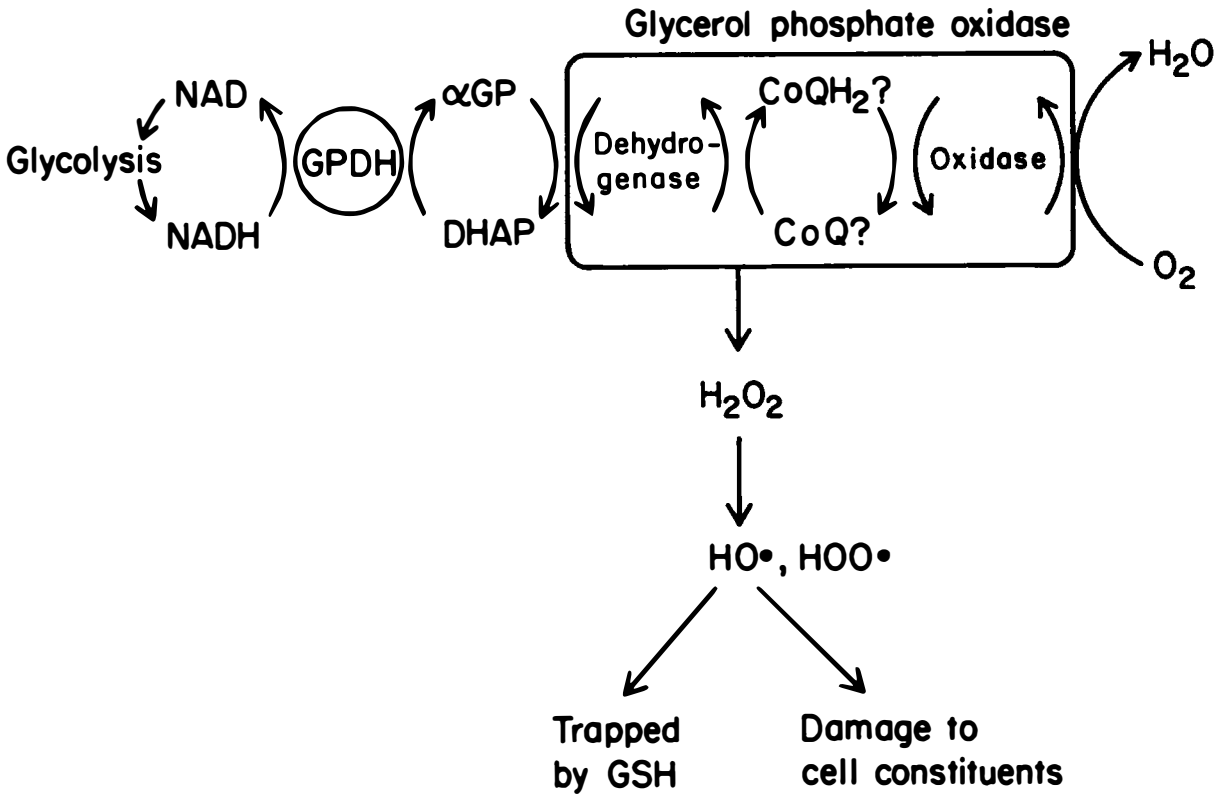
principles to elucidation of new drugs for parasitic organisms and have studied African trypanosomes (Trypanosoma brucei and Trypanosoma congolense) as model organisms.4,5,6/ Our approach was to elucidate a biochemical difference between trypanosomes and their host, and to design drugs which could take advantage of this difference. The biochemical difference we have exploited is inability of trypanosomes to synthesize heme.7/ As a result of this deficiency, and the avid binding of heme to serum proteins in mammalian hosts, the bloodstream form of African trypanosomes has no detectable heme or hemoproteins such as cytochrome or catalase. This in turn leads to an accumulation of intracellular hydrogen peroxide in these organisms which renders them susceptible to killing by agents that promote homolytic cleavage of hydrogen peroxide to yield hydroxy (OH.) or hydroperoxy (HOO.) radicals. These radicals can react with unsaturated lipids and other cell constituents, thereby leading to cell destruction.4/

Intracellular hydrogen peroxide arises in an adventitious manner from the x-glycerol phosphate oxidase complex in the rudimentary mitochondria of the trypanosome. Approximately 1-3 percent of the oxygen consumed by these parasites appears as hydrogen peroxide which leads to a final concentration of approximately 70μM. In addition to lacking catalase these organisms also lack other enzymatic means for destroying this waste product, and depend upon diffusion of this potentially lethal metabolite from the cell to its surroundings where it can be disposed of by mammalian enzymes. Figure 1 shows that portion of the biochemistry of the parasite in which production of hydrogen peroxide is thought to arise, and depicts those sites where we have sought to intervene to increase the concentration of intracellular hydrogen peroxide or its homolytic cleavage products.5/

We have found that hematoporphyrin D and meso-tetra 4-sulfonatophenyl porphine (TPPS4) are free radical initiators, and cure trypanosome-infected mice. It is of interest that neither of these compounds was active in vitro. Analysis of this phenomenon revealed that insertion of zinc was necessary for cleavage of hydrogen peroxide to occur with subsequent killing of the organisms. This conversion was catalyzed by the zinc complex, probably via removal of a $\pi$ electron from the porphyrin ring. This is unlike the reaction of iron porphyrins with $H_2O_2$ where oxidation occurs at the metal atom.

Knowledge of the mechanism of action of the porphyrin analogues permitted further intervention.5/ As seen in Figure 1, methods for increasing hydrogen peroxide should make porphyrin derivatives more effective. It has been possible to increase the rates of both oxygen consumption and hydrogen peroxide production in trypanosomes in vitro by addition of naphthoquinones. Presumably, naphthoquinones act as coenzyme Q analogues and cycle as shown in Figure 2. The naphthoquinones are reduced to the corresponding quinols by the dehydrogenase, and then nonenzymatically reduce oxygen to form superoxide and hydrogen peroxide. Meanwhile, the quinone is reformed and can be cycled again.

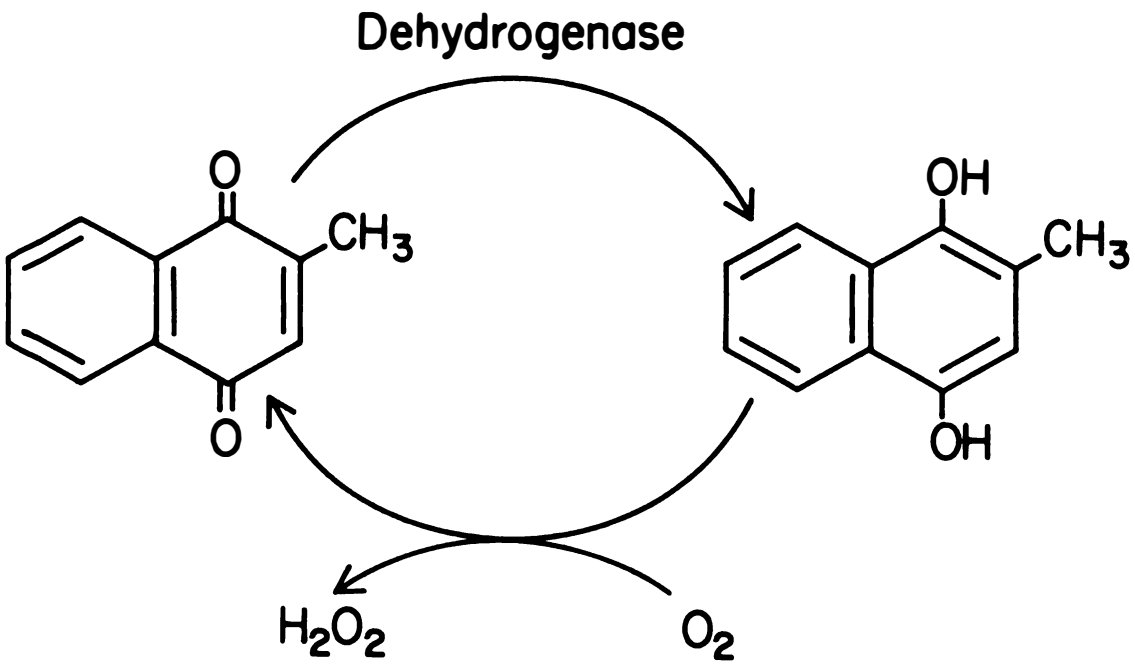
FIGURE 1.




The addition of sublytic concentrations of both napthoquinones and heme leads to a synergistic lysis of the organisms in vitro. Although naphthoquinones are trypanocidal in vitro both alone and in combination with porphyrin analogues, we have not yet been able to identify a naphthoquinone active in vitro either by itself or in combination with various porphyrins. We are continuing a search for potentially active naphthoquinones.

Another method of rendering trypanosomes more susceptible to radicals generated by porphyrin-induced decomposition of hydrogen peroxide would be to decrease the level of intracellular radical scavengers

FIGURE 2.




in the trypanosome. Reduced glutathione is believed to play such a protective role in these organisms. Incubation of isolated bloodstream forms of T. brucei with the trivalent arsenical, melarsenoxide, led to a decreased intracellular concentration of glutathione which imparts to the organisms an increased susceptibility to heme lysis. In fact we have noted synergism between arsenicals and hematoporphyrin D in vitro. Since both hematoporphyrin and Mel B can cross the blood/brain barrier, an evaluation of the combination of both agents in advanced forms of sleeping sickness is warranted.

From our in vitro studies to date, it is apparent that the combination of a series of drugs which can increase hydrogen peroxide

production, cause homolytic breakdown of hydrogen peroxide, and decrease glutathione concentration should be an effective means of selectively killing these organisms. As noted earlier we began our studies with African trypanosomes as model organisms in which to look for biochemical differences between host and parasite. In addition to the African trypanosome, it appears that Trypanosoma cruzi, which causes Chagas' disease in approximately seven million people in South America, also lacks the ability to enzymatically destroy hydrogen peroxide.8/ Furthermore, naphthoquinones have been found which cause increased production of this potentially lethal byproduct in vitro.9/ This, coupled with the fact that hematophorphryin D and TPPS are active against Leishmania donovani,10/ emphasizes the similarity of the trypanosomatids which cause human and animal diseases. New agents, which take advantage of the biochemical differences outlined above, may be useful in several of these diseases.

Further studies, like the one described above, may lead to identification of other biochemical differences which could be exploited to develop new drugs. This kind of investigative process is especially well carried out by academic scientists who are intrigued by basic biochemical studies and who are funded by agencies such as NIH and WHO. Once a biochemical difference is identified, it could perhaps be handed over to organic chemists in the pharmaceutical industry who could best synthesize and identify more efficacious anlogues. Because much of the cost of drug development today is consumed in safety evaluation of the new compound, sharing of these costs between the pharmaceutical industry and public health organizations might achieve this last and important objective. In the next fifty years the number of parasitic diseases controlled through chemotherapy can be significantly higher than it is today.

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# IMMUNOLOGY AND PARASITIC DISEASES*

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In considering some infectious diseases in the developing world that are the subject of this meeting, it became clear that, as in the course of political events, one must know the past to understand the future. And the history of these diseases tells us that we must now make a multifaceted attack if we hope to bring them under control. This is best illustrated by the history of attempts to control malaria, so beautifully set forth in a recent book by Gordon Harrison.1/ For many years immunologic study of malaria was in the doldrums, because it seemed so obvious that insecticides and drugs were the agents which would control this disease. Now that mosquitos are thriving on DDT, and drug resistant strains of malaria are occurring, development of a vaccine seems more reasonable, and work to develop one is underway in several laboratories. Indeed, at a time when one of the scourges of mankind, smallpox, essentially has been eradicated from the world by a vaccine, it is small wonder that one turns to immunology for some help in combatting other infectious diseases afflicting the developing world.

Although three commercial vaccines are available against parasites of animals, cattle and sheep lung worm, and dog hookworm, it is disappointing that there are none for protozoa or helminths infecting man. But vaccines against parasites are not easy to come by, because these parasites have evolved very effective ways of living in their hosts, and of evading their hosts' immune defenses.

Parasites have evolved at least four methods of evading immune attack. Some, like schistosomes, incorporate host antigens onto their surface and masquerade as the host.2,3/ Some, like the African trypanosomes, can change their surface antigens when attacked by antibody, an an amazing biological adaptation.4,5/ Some turn on a subset of T lymphocytes, whose function it is to suppress the immune response.6/ And, finally, there are suggestions that some parasites may develop

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innate resistance.7,8/ In other words, they are still recognized as foreign by the host, but have developed changes on their surface which make them impregnable to attack by the host's humoral and cellular defense mechanisms.

At this point, I should define an important concept relevant to this subject, that of concomitant immunity. When the host is first invaded by a parasite, it has no specific immunity. The parasite induces an immune response, but it also manages to evade effective this response by one of the four mechanisms described above and lives relatively unperturbed in the host. If another parasite of the same species subsequently invades the host, the second invader will be destroyed by the immunity induced by the first infection. In this way, the balance required for parasitism is preserved, the parasite lives on, and the host is not overwhelmed.

I would like now to consider the short-term and long-term goals of immunologic research as it relates to our current problems. There are at least three short-term goals. We must obtain more information on the role and mechanism of immunity in specific parasite diseases, develop better serodiagnostic tools, and obtain more basic information on regulation of the immune response in general. The latter goal I will return to at the end of this presentation. Work in this area is essential if we are to have a rational basis for developing effective vaccines.

Why, you may ask, is there a need for more basic studies when Jenner knew nothing about T or B lymphocytes, let alone macrophages, eosinophils or antibodies? The answer is simple. First, immunity to smallpox, and to many other viruses, is obvious, direct, and long-lasting. Second, the attenuated virus can be grown easily. Neither of these situations pertains in the case of parasites.

If we are to develop vaccines and useful immunodiagnostic tools, and attempt to deal with the tissue damage resulting from the immune response, we must be able to answer certain types of questions. Is there immunity to T. cruzi in Chagas' disease? In that disease, is the first infection responsible for all subsequent damage? Are subsequent infections of trypanosomes by the reduviid bugs eliminated? If the answers are affirmative, a vaccine would be a rational approach to this problem. It is not part of my subject, but we should remember that better housing in this case is an even more rational approach.

To go on, which antigens of a parasite induce positive defense mechanisms and which induce suppressor responses? Does treatment of minimal schistosomiasis diminish subsequent immunity? We do not know the answer to this question, but we should, if we are going to treat patients with low grade infections. What disease manifestations result from immune hypersensitivity? We already know that some pathology in schistosomiasis and filariasis is caused by immune reactions, so we

should be considering the possibility that immunosuppressive drugs may be useful in treatment of the immunopathology of some parasitic diseases.

We need better serodiagnostic tools to use in assessing prevalence of disease and efficacy of drug treatment. We need serodiagnostic tools capable of detecting different strains of parasites and, we hope, some which correlate with parasite burden and can be used to measure intensity of infection.

Having implied by these questions that our present store of knowledge about the immunology of parasitic diseases is limited, let me now move on to describe a recent development in immunology that may convince you that it is worth going on. This development, a method of producing monoclonal antibodies using lymphocyte hybridomas, is revolutionizing the field and already is spreading to other disciplines.9/ The technology has so many applications to development of serodiagnostic tools and vaccines for parasitic diseases that I will take a few minutes to explain it and its potential. It is based on the fact that each antibody-producing cell in the body makes only one kind of antibody, directed at a single antigenic determinant. If it were possible to isolate a single antibody-producing cell and allow it to grow into a huge colony, that colony would produce monoclonal antibody restricted to one antigenic determinant. This is now being done, and here is how to do it.

Two different cells can be fused by a variety of viruses or by polyethylene glycol. Their fusion results in a single cell with two nuclei. Subsequently, the nuclear membrane breaks down, chromosomes divide, and they are randomly distributed into two daughter cells. The daughter cells are hybrids because they contain chromosomes from the two original cells. Kohler and Milstein in England adapted this principle to produce monoclonal antibodies.10/ For one of the fusing cells , they used a myeloma cell produced experimentally in mice and adapted to culture. It can grow forever. For the second fusing cell, a mouse is immunized with any antigen one wishes (it need not be pure), and the spleen cells from this mouse are fused with the myeloma cell. The cells are then grown in a selective medium. Myeloma cells alone cannot grow in this medium because they lack an enzyme which normal spleen cells possess. Thus, the unfused myeloma cells die, and the unfused spleen cells, not adapted to long-term culture, also die. But the hybrids live on, because the myeloma cell gets the chromosomes necessary to provide the missing enzyme, and, in living on, they immortalize the spleen cell's capability to make antibody.

The hybrids are grown and then cloned in microtiter plates. The medium from each clone (derived from a single cell) are tested for antibody to the desired antigen. Positive clones are selected and grown en masse, either in vitro or in vivo. A single mouse carrying these hybrid cells will produce antibody, for example to a lymphocyte marker,

amounting to more than all the antibody to this marker made by hundreds of investigators all over the world. Such antibody can have titers in the millions, unheard of before, and it is directed at a single antigen. It can be used to isolate the antigen by affinity chromatography and to develop specific radioimmunoassays. If there are minor differences between different strains of similar parasites, this is clearly the way to detect them. Presently, we are using this system for schistosome antigens and adapting it to detect strain differences in Leishmania. Adaptation of this system to produce monoclonal human antibodies should have amazing therapeutic potential.

Before leaving this topic, I would like to point out that this incredibly practical and important discovery stems from basic, non-targeted research by scientists in Europe and in the United States who set out to dig deep into the problems of molecular and cell biology and immunology.

The long-term goal of any immunologic approach to parasitic-diseases is development of safe and effective vaccines. Recently, there have been important developments in malaria, and vaccines have been produced that successfully immunize monkeys using sporozoites, merozoites, and gametocytes. Furthermore, irradiated larvae have been used successfully to protect cattle against Schistosoma bovis. Dr. Jordan describes these elsewhere in this volume. For development of vaccines, we need to obtain antigens in quantity and to develop adjuvants that can be used in man to enhance the naturally poor effector immune response to parasites. With respect to the need for antigens, there has been a major breakthrough by Dr. Trager at Rockefeller University, who has successfully cultivated human malaria merozoites in tissue culture.11/ Also, Dr. Hiroumi at ILRAD in Kenya is growing African trypanosomes. These are most promising developments. Obtaining quantities of antigen from helminths, however, is a greater problem. For example, the schistosomula, the stage of the parasite which makes its odyssey through man, does not divide. We are currently attacking this problem by attempting to define antigen or antigens that elicit an effective immune response by generating monoclonal antibodies. The aim is to determine which of these antibodies to schistosomal antigens can transfer immunity to schistosomula in mice, or mediate eosinophil-dependent killing of schistosomula in vitro. These antibodies can then be used to isolate antigens and characterize them. It is not too unreasonable to hope that, if the antigenic determinant is not too large, modern methods of synthesis, or molecular biologic techniques being developed, such as those for production of insulin by bacteria, might be adapted to this problem.

As for adjuvants needed for vaccines, considerable work is being carried out to develop adjuvants safe to use in man. Promising prospects include muramyl-dipeptide, or MDP, an active ingredient from mycobacteria, and synthetic derivatives of MDP. Other products from mycobacteria and from other organisms such as Nocardia are also being

used. Another method for enhancing the immune response is to incorporate antigen and adjuvant into lipid envelopes for liposomes, and this is also being investigated. Hand in hand with this research, it will be necessary to determine which portion of immune responses is enhanced by each adjuvant. The aim here is to be able to enhance a particular cellular or humoral mechanism at will, bypassing suppressor mechanisms.

I should like to stress a point that Dr. Krause made yesterday; namely, that the study of parasite immunology will produce, as it already has, information that will be useful in other areas. He gave the eosinophil as an example. In fact, study of parasite immunology has uncovered an unknown and important function of eosinophils; namely, that these cells can kill antibody-coated schistosomula and other larvae.

Anthony Butterworth was the first to show that human eosinophils, and other cells, kill antibody-coated schistosomula.12,13/ Under the microscope, one can see the eosinophil, with its granules, plastered up against the larvae. The cells then degranulate, and one can see granules on the surface. In recent studies with Butterworth, and in collaboration with Gerald Gleich, we have shown that damage to larvae is mediated by major basic protein, the main protein found in eosinophilic granules.14/ Until this time, there was no known function for this protein.

Probably the most important and exciting area of investigation in immunology today is on the basic control of the immune response. In order to know how to deal with and to alter this complex system, one must know how it works, And this work has produced many surprises.

I would like to end with an example of such a surprise. Although this is not parasite immunology, it is directly related, and contains the germ of an important new concept, You may, understandably, be disturbed that I should pick a recent finding from the field of bone marrow transplantation, certainly the ultimate in sophisticated individual medicine as practiced in superindustrialized countries. But it does bear on our problem, and it illustrates why we must understand control mechanisms.

Recently Drs. Reinherz, Rosen, and Schlossman and their colleagues in Boston gave a bone marrow transplant to a woman, with her identical twin sister being the donor. The transplanted cells caused a definite graft versus host reaction in the twin recipient, manifested by skin rash and abnormal liver function. At first, this would seem to be quite impossible, because in identical twins, the transplanted cells should be identical to the patient's own cells, and according to the dogma of histocompatibility, should not react against her own tissues. On analyzing the recipient's blood, it was found that, at the time of the graft versus host reaction, one subset of T lymphocytes was completely missing. This subset had previously been shown to mediate

suppression. As the subset of T cells returned, the graft versus host reaction disappeared.

Why is this important to us, and what does it mean? It indicates that we normally have autoreactive cells in our systems, and that these are constantly under control by T suppressor cells. If the suppressor cells are absent, the autoreactive cells become manifest. Hence, we must continually have a strong T cell suppressor response to prevent autoimmune disease. This concept has many ramifications. For example, the reason it may be so difficult to mount an attack on cancer cells is that this attack may be suppressed by the same suppressor cells that prevent autoreactions. Furthermore, the parasite, which takes on host antigens, may actually stimulate this suppressor response.

This finding has more than theoretical importance, and should certainly be of interest to the pharmaceutical industry. Several anti-lymphocyte sera made commercially for transplantation programs did not work. In fact, some even enhanced graft rejection. As it turns out, some of these sera were directed against the very subset of suppressor T cells we have been discussing. Thus, it is possible that eliminating these cells temporarily with these antisera could greatly enhance immunity against tumors or parasites. As we learn more about the different antigens of subsets of lymphocytes, identifying cells with different functions, we should be able to favor production of antibodies that can affect certain cell types and thereby modulate the immune response.

All of this points out that there may be similarities in the ways by which tumors and parasites evade immune attack. What is more, parasites appear to be ideal organisms for study and analysis of control mechanisms of the immune response. There is no doubt that much of the information we gain from intensive study of parasite immunology will spin off to directly affect conditions in the industrialized world and in the developing world. Indeed, I would like to leave you with the thought that increases in expenditures by government and the pharmaceutical industry on these projects will result in benefits for the health of people here, a substantial fringe benefit indeed for this humanitarian endeavor.

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# MOLECULAR BIOLOGY AND GENETICS AS BASIC APPROACHES TO THE PROBLEMS OF PARASITISM AND SPECIFIC CHEMOTHERAPY

Joshua Lederberg

I am grateful for this opportunity to offer a few observations on the relationship of fundamental studies in molecular biology and genetics to the world's most urgent health problems.

First of all, there are compelling reasons for biologists to put renewed emphasis on parasitic adaptation. There are innumerable ways in which the study of parasitism has illuminated the biology of the host -- in a sense we are emulating the evolutionary 'learning' by which the parasites themselves have carved out their ecological niches by taking the most subtle advantages of the habits of their host. Fields such as immunology, hormonal control of development, cell biology of phagocytosis and endocytosis are rich in such contributions.

Studies of the most primitive parasites, bacterial viruses, would alert us to expect that there may be quite specialized adaptations, at the genetic level, between parasite and host -- the direct chemical exhibition of DNA sequences, and indirect methods of exposing homologies of parasite and host DNA, will tell us soon enough. These sophisticated advances thus enable us to leapfrog fortuitous gambles in the quest for obscure biological relationships.

Exploiting similar precedents, we should be looking for phenomena like plasmid-determined, viz. 'infectious' drug resistance, in eukaryotic parasites which may pose important complications in chemotherapy of parasitic, as they do in bacterial diseases. To be sure, parasites do not often congregate densely and in mixed company, as bacteria do, and these ecological differences may engender quite different genetic systems. On the other hand, it is hard to believe that parasites that spend a large part of their life cycle within the host cell, in intimate contact with its DNA, will have no trace of alien sequences which can have played an important role in accelerating their evolution.

Turning now to practical applications, long established methods in microbial breeding should certainly be exploited for production of attenuated live vaccines. Surely, Mycobacterium leprae, though still eluding cultivation in artificial media, can be made to exchange

genetic information about its antigens with other mycobacteria more amenable to laboratory manipulation -- and the world's armadillos will not breathe easily until we do these studies. Similar approaches have already been applied to enteric pathogens, like V. cholera. New ways of cultivating malarial plasmodia should encourage cognate approaches that could also exploit the host-specificity for virulence of known species. Indeed, these approaches have been technically available for the last 25 years.

Somewhat more modern methods of enzymatic analysis of DNA, eventually capped by explicit sequencing of whole (virus-sized) genomes, will be invaluable for working out the taxonomy of difficult groups like leishmania. In fact, the genetic polymorphism of hosts (like people with Hb-A versus Hb-S) is also accessible now to exhibition of DNA differences. These methods having been worked out for visible markers, we can now look forward to comprehensive mapping of the entire human genome. On such a map, it will be easy to locate polymorphisms for genetic susceptibility/resistance to parasitic and infectious diseases, and in turn to the physiological controls that can be exploited for hygienic ends.

The most exciting opportunities stem from new technologies of DNA-splicing or genetic engineerig. Enzymatic tools are now available that can cut DNA segments at specified locations, and others that can rejoin and splice segments into viral or plasmid carriers. These in turn can be grown, if necessary in tank lots, in cultures of bacterial or yeast hosts, often with expression of the genetic information that had been spliced in.

This new technology is already extensively exploited for the deeper understanding of cellular phenomena. We are just beginning to see efforts at its technical exploitation, which will surely include:

- Production of specific parasite antigens, for diagnostic and prophylactic uses.
- Manufacture of proteins identical to, or carrying the essential specificities of human immunoglobulins: first for diagnostic and then for therapeutic use (passive immunization and 'sero'-therapy).
- Production of specific receptors (like the Duffy factor) that can be expected to interfere with the natural life cycle of a parasite.
- Discovery and manufacture of other host factors that interfere with a parasite (in the fashion that high-density lipoprotein lyses trypanosomes.)

These extensions have been impeded by the regulatory apparatus which has proliferated in response to hypothetical fears about proliferation of laboratory DNA hybrids. The unanalyzed concept of pathogenicity is applied in a way that would distinguish between lion and pussycat, as DNA source, in the containment measures imposed on experiments transferring such DNA to frogs. Fortunately, the enormous benefits of DNA research are being more widely perceived as part of the policy equation; and in many countries we can expect rapid resumption of research of the utmost human utility.

At still another level, it must be cautioned that safety of a prospective pharmaceutical can no longer be regarded as a side issue, to be worked out at a late stage in development and validation of a compound. Almost any compound with significant effects on any organism must automatically be suspected of latent human toxicity, and in the present climate must be assumed guilty until proven otherwise. The plan for demonstrating safety of a drug in practical application should be part of the whole R&D design, and in many cases will dominate the overall cost of development. The insights of molecular biology -- having already generated such powerful and valuable tools as the AMES test -- may very well also give us more effective policy criteria for predicting effects in human application of suspect agents having irreplaceable therapeutic value. This remark is essentially a call for establishment of a sorely needed new discipline, a comparative toxicology that can call in all of the tools and wisdom of traditional fields of comparative biology, genetics, and evolution.

# METHODS OF DRUG ADMINISTRATION

John Urquhart

This Conference on Pharmaceuticals for Developing Countries addresses means for improving health in areas of the world where economic resources are most limited and health problems are most pressing. Pharmaceuticals play a key role in both therapy and prevention of disease, and thus constitute key technological resources for improving health. Pharmaceuticals have to compete for limited economic resources both with other means for health improvement and among themselves. Consequently, economic and political pressures are strong to minimize the costs of pharmaceuticals. These forces have impact not only on utilization of today's pharmaceuticals but also on priorities for research and development of tomorrow's pharmaceuticals.

One immediate consequence of these economic and political pressures is the move to class pharmaceuticals of recognized value in developing countries as chemical commodities, emphasizing least cost for a total treatment.1/ Naturally, this often means emphasis on least cost per unit quantity, though it is preferable to focus on therapeutic/prophylactic outcome and the cost required to achieve that outcome -- in those circumstances in which outcome is assessable. One deficiency in viewing pharmaceuticals as chemical commodities stems from the fact that, to be utilized as practical therapy or prophylaxis, pharmaceuticals have to possess more than just chemical and pharmacological attributes. The additional attributes relate to the methods by which drugs are administered to people.

## Drug Administration: Basic Considerations

From the outset, confused semantics vex discussion of drug administration. Almost everyone, with the exception of the organizers of this Conference, uses the word "drugs" synonymously with pharmaceuticals. In fact, a pharmaceutical is one or more pharmacologically active chemical substances compounded with other substances into a form -- in pharmaceutical language, a dosage form -- that allows the active substance(s) to be administered to a patient. Thus, a single active substance may be prepared in various dosage forms: tablets,

capsules, ointments, drops, injectables, and others.

The pharmacology of an active substance teaches its therapeutic potential. That potential is translated into practical therapeutic value when the active substance is prepared in a dosage form and the regimen is defined for its use in that form. If the regimen is too complex, too productive of unpleasant side effects, or too expensive, the therapeutic potential of the active substance goes unfulfilled because people shun its use.

The life-saving hormone, insulin, illustrates the practical value of dosage forms. Everyone recognizes what a problem it is that the only effective dosage form of insulin is the injectable, and how much we could improve both therapy and the quality of life for diabetics if a better dosage form existed for the active substance, insulin. Furthermore, many pieces of indirect evidence suggest that the outcome of therapy is degraded because insulin is always administered unphysiologically and often administered unreliably.2/

Man has employed every natural orifice of the body as a portal for drug entry, and sometimes we create orifices temporarily just for that purpose, as for injections of I.V. infusions. My purpose in this paper is to describe opportunities through research for improving therapeutics and prophylaxis by improving methods for administering drugs. My thesis is that improvement and simplification go hand in hand, because making something simpler to use makes it more reliable.

The reliability of a method of drug administration has both technological and human elements; either or both elements may limit realization of a drug's potential therapeutic value. Use of an unreliable method to administer a proven drug can be expected to result in an outcome degraded in relation to that attainable when the same drug is reliably administered. A degraded outcome obviously has an adverse effect on any cost/benefit reckoning one might employ in comparing means for improving health. A clear example of how unreliability in drug administration degrades outcome is seen with oral contraceptives: when reliably administered in a closely monitored clinical trial, pregnancy rates are ca. 0.1 percent per year 3/ but, in actual everyday use, the element of unreliability in unsupervised self-administration degrades this outcome to pregnancy rates of 2 percent 4/ to 6 percent 5/ per year -- 20 to 60 fold higher than those pharmacologically attainable. As Ryder 5/ pointed out in his seminal work in this area, "it ... (is) most important to recognize the extent to which the outcome of use is the joint consequence of method characteristics and user characteristics."

To place primary emphasis on creating new methods for administering active substances, and secondary emphasis on creating new agents, reverses an historic gradient in pharmaceutical research. Both academic and industrial research have always focused most intently on the

search for new active substances, with methods for their administration taken for granted. Yet, in the past decade, the creation of new methods to administer active substances has attracted growing interest, research, and product development efforts. Analyzing the therapeutic significance of these efforts for developing countries is the focus of this paper.

## Logistics of Chemotherapy

Between the worlds of pharmacology and of therapeutics lies a series of distribution and delivery systems. Their role is to convey an active substance, with its potency preserved, to appropriate drug receptors in patients throughout the world.

With suitable packaging, shipping, transfer through customs, local distribution and transport, and with preservation from temperature extremes and excessive moisture, a pharmaceutical can travel, and remain within specified potency, from a plant in Kalamazoo, Michigan, to a dispensary in El Golaa, Tunisia. The last step in the distribution/delivery sequence occurs when the package is opened and a patient contemplates a pharmaceutical whose administration someone has deemed desirable. At that moment the pharmaceutical must pass a final gauntlet of hope, fear, resignation, indifference, anger, and/or suspicion before it enters the patient. If taken, the dosage form disappears, usually within minutes, as the active substance passes, generally by dissolution or leaching, into soluble form in body fluids. Thence, molecules of active substance proceed by diffusion into the blood, distribution via circulating blood, and diffusion through capillary and perhaps cellular membranes, to reach sites of therapeutic action: the end of a long journey from factory to receptor.

Unfortunately, one-time administration of a pharmaceutical rarely suffices, because most active substances are metabolically inactivated and/or excreted within a few hours to a day or two. Thus, the key step of dosage form administration has to be repeated. The practical maximum rate of self-dosing is four times daily. Of course, a highly motivated patient or health worker could repeat dosing 10-20 times per hour in the face of great need for continuous presence of agent. There are a few instances of such high frequency dosing, e.g., in the topical treatment of severe infectious ophthalmias,6/ but high frequency dosing is exceptional. At the other end of the spectrum, only a few pharmaceuticals can provide adequate therapy/prophylaxis on a once- or twice-weekly schedule -- for example, very useful prophylactic regimens vs. malaria. Still fewer products can be effective when given every few weeks to months (e.g., the Depo-Provera R injectable contraceptive and the injectable enanthate of fluphenazine), though one of the limiting features in the long-acting injectables is ambiguity of their duration. Finally, a few immunizations provide adequate protection on a once-a-lifetime basis. Leafing through any good formulary, however, will demonstrate that the vast majority of useful active substances

are in dosage forms that have to be taken 1-4 times per day.

Repetition of the conceptually simple, widely accepted acts of pill swallowing, eyedrop instillation, ointment application, or injection creates a logistic problem of some magnitude. In Western medicine, the problem is reflected in what is called patient noncompliance. In developing countries, the same problem is a major cause of extensive underutilization of available medicines that is so widely commented upon.

Underutilization has both macro- and micro-aspects, and only when both are addressed satisfactorily can the problem be solved. At the macro-level, it can stem from such factors as unevenly distributed health care personnel, faulty channels for distributing products, economically constrained procurement, and so forth. At the micro-level, patients overtly accept, but in many instances covertly reject or erratically execute, regimens whose perceived impact on well-being may be substantially at variance with what scientific, medical, or political authority may teach or wish. My focus here is the micro-level problem of noncompliance with scientifically valid regimens for administration of proven drugs. I take it as axiomatic that poor compliance results in degraded outcomes of therapy or prophylaxis; when that is not the case, then good compliers are at a disadvantage of being overmedicated, and the regimen is ipso facto scientifically invalid.

An extensive literature, complied and analyzed by Sackett and Haynes,7/ teaches that noncompliance is disappointingly common in Western medicine. It prevails in the face of literacy, technological awareness, health consciousness, and ready access to pharmaceuticals costing no more than consumer products such as cosmetics, cigarettes, and alcoholic beverages. Most studies of Western patients' compliance with regimens of chronic medication show that only about one-half to two-thirds of prescribed amounts are taken. Moreover, it is apparent that timing of self-medication is often erratic, as Kass has shown with his recent work using an ingeniously microcomputerized dispensing monitor for eyedrops in treatment of glaucoma.8/ The conclusion is inescapable that noncompliance is a major worldwide problem with today's pharmaceuticals.

It logically follows that improving methods of administering active substances -- old or new -- to make them far simpler to use could improve therapeutic outcome. The goal is to minimize dependence of therapy upon repetitive acts by patient and/or health workers. Moreover, it is essential to accomplish this with no added risk -- and preferably with less risk -- compared to that incurred using conventional dosage forms.

## A New Class of Pharmaceuticals

A basic strategy in improving on conventional dosage forms has been to develop a wholly new class of pharmaceuticals. These have the characteristic that -- instead of rapidly disappearing by dissolution or disintegration -- they preserve both form and function, delivering drug at specified rates for an extended and specified duration. Such rate-specified pharmaceuticals are variously called controlled or advanced drug delivery systems, or therapeutic systems.9-13/ The term therapeutic systems will be used here. The physical-chemical principles of membrane-controlled diffusion and osmosis are the basis for many of these developments.

A key distinction between a therapeutic system and a conventional pharmaceutical is the manner of specifying strength: for conventional pharmaceuticals, strength is specified only by quantity of contained drug; for therapeutic systems, strength is specified not only by quantity but also by the rate at which they deliver their active agent(s) and the duration for which they do so. Specification of strength by rate of drug delivery is noteworthy from a technical point of view, but clearly has to demonstrate its value in practical therapeutic consequences.

## Therapeutic Rationale of Rate-Specified Pharmaceuticals

Two major ideas intersect in assessing the value, in practical therapeutics, of rate-specified drug delivery. The first major idea is that a therapeutic system, precisely because it is a rate-specified dosage form, should maintain uniformity of drug action with little or no side-action throughout the system's functional lifetime. In many ways this point is obvious, yet it has revolutionary implications in pharmacology, as will be discussed below, and in therapeutics, where reduction of unpleasant side effects minimizes these disincentives to compliance. The second major idea is that, by controlling rate, the interval between acts of self-medication can be prolonged, in some instances to an unprecedented extent, thus simplifying regimens of chemotherapy. One might note there that the technical capability of specifying delivery rate *in vivo*, with concomitant reduction in drug level-related side effects, will lift such rate-specified pharmaceuticals above the long and acrimonious debate about bioequivalence inequivalence of various conventional forms of the same active substance.14-16/

Let us examine the principles upon which the second major idea rests. Conventional dosage forms -- including sustained-release tablets and capsules -- deliver their active substance(s) in what is called first-order fashion: delivery occurs at rates that are highest initially, and then decline steadily thereafter. This pattern approximates that of exponential decay, *i.e.*, first-order kinetics.

The result of repetitive dosing with such dosage forms is a saw-tooth pattern of peaks and valleys in the concentrations of agent in blood and tissues. After any particular dose, the concentration of agent at some critical site ultimately becomes too low to be effective; the need then arises to remedicate. The elapsed time from dosing until loss of effect can be prolonged by putting more active substance into the dosage form: the initial rate of release will then be higher, and drug concentration at the critical site will take longer to fall below its minimum effective level; however, the penalty of such prolongation is a more widely fluctuating concentration of drug in blood and tissues, and thus more widely fluctuating effects and side effects. Using first-order dosage forms, one sees the first-order pharmacology of drugs: a time-dependent mixture of side effects and desired effects, with side effects tending to predominate early in the interval following the dose.

For some agents, effect and side effect occur at widely different concentrations in blood or tissues, but for many others the difference in these levels is small. With the latter category of active substances, controlled delivery is particularly valuable in separating desired from undesired actions 17/ and, at the same time, extending duration of desired action.

## Some Principles and Examples of Zero-Order Pharmacology

The most astute pharmacologists have now recognized how much conventional pharmacology rests on arbitrary pulse or drench methods of administering active substances. Over the next several years, we can expect to see -- under the rubric of steady-state, or zero-order pharmacology -- very substantial rethinking and research on old agents, with discovery of new therapeutic values in some of them. A teaching case is provided by theophylline, largely through work of Weinberger and associates:18/ plasma concentrations of this agent can rise a factor of only two above its minimum effective level without causing troublesome side effects. Controlling delivery of theophylline within this narrow range makes this old agent very much more useful than it has ever been, and competitive with the newest broncho-dilating agents. Because this new value in theophylline is so markedly concentration-dependent, it is delivery rate-dependent. Thus, it is dosage-form dependent, and merely listing theophylline in a formulary will not suffice, for in conventional dosage forms this agent is difficult to use, often inefficacious, and occasionally dangerous.

Understanding a drug's zero-order pharmacology is to know the rank order of its actions elicited during delivery at a series of constant rates ranging from the lowest rate sufficient to elicit any detectable effect, to the highest rate allowed by common sense and ethics of experimentation. As one progresses stepwise upwards through that range of delivery rates, successively more actions of the drug appear, and sometimes an action in one direction is replaced by its opposite.

Table 1 illustrates the rank ordering of actions of three familiar agents: pilocarpine given topically to the eye, and scopolamine and theophylline, both given systemically. As may be inferred from Table 1, zero-order pharmacology teaches a new basis for finding selectivity in drug action, by utilizing zero-order drug delivery to "peel" the top-most action -- or top several actions -- from the stack of delivery rate-dependent actions, excluding the rest.

TABLE 1. THREE EXAMPLES OF ZERO-ORDER PHARMACOLOGY

| Drug Delivery Rate | Pilocarpine a/ | Theophylline | Scopolamine |
|---|---|---|---|
| lowest | ocular hypotension | bronchodilation | slight bradycardia |
| | | | inhibition of motion sickness |
| | miosis | | |
| | | | dry mouth |
| | myopia | nausea & vomiting | inhibition of drug-induced nausea |
| | | tachycardia | |
| | | slight insomnia | |
| | | | slight tachycardia |
| | ciliary spasm, browache | | |
| | | | drowsiness |
| | | | cycloplegia |
| highest | systemic effects, e.g., salivation, intestinal cramping | greater tachycardia, cardiac arrhythmias, seizures | amnesia hallucinations |

a/Topical, to the eye.

This principle is basic in endocrinology: the specificity of a hormone's physiological actions is partly due to chemical structure, and partly due to control of its secretion. This is a physiological lesson of fundamental importance to pharmacology. The demonstrable actions of various hormones include not only their physiological

actions but also others that simply never occur unless normal secretory control mechanisms are deranged or the hormone is administered exogenously at unphysiological rates or in pulse drench mode (see, for example ref. 19). The lesson should be clear for pharmacology: control complements chemistry in the quest for specificity of drug action.

To be sure, there is considerable oversimplification in the sharp distinction I have drawn between first- and zero-order pharmacology. For example, actions of certain agents are known to wax or wane gradually with time, e.g., tolerance to narcotic analgesics, adrenergically induced "down" regulation of adrenergic receptors, and others. The zero-order rubric cannot accommodate nonstationary actions, but neither can one claim that conventional first-order dosage forms optimally deliver agents with such properties. Instead, agents with nonstationary actions merit research specifically to determine what temporal pattern of rate-controlled administration is optimal for each agent. Such considerations and exceptions notwithstanding, zero-order delivery can improve therapeutic values of many agents, old and new.

Principles of zero-order pharmacology have been reduced to practice in development of an ocular therapeutic system form of the widely-used antiglaucoma agent, pilocarpine.20-23/ This was the first therapeutic system to become a pharmaceutical product. It has a functional lifetime of one week, replacing four-times-daily eyedrops; it reduces the total amount of drug required by four-to-eight-fold; it virtually eliminated the side-effects of pilocarpine -- miosis and induced myopia -- that interfere with vision. Conventional, first-order pharmacology classes pilocarpine as a miotic agent; yet this vision-disturbing side-effect has no relation in the steady-state to the drug's desired ocular hypotensive action.

A complementary value of automatic, rate-controlled delivery technology is to make it feasible to administer agents that are very rapidly metabolized or excreted. An example is the first utilization of the physiological ovarian hormone, progesterone, in a contraceptive product. 24,25/ Progesterone is so extensively metabolized by liver that it cannot effectively be administered orally save in gram quantities. In contrast to some man-made progestational steroids, such as norethisterone and norgestrel, progesterone has relatively low potency-by-weight and is not a practical agent for parenteral systemic contraception. Yet its continuous deployment at controlled rates into the uterine cavity has been achieved for a period of one year, and a recent technological advance has made it possible to extend this duration to three years. Contraception at the 2 percent per year failure rate has thus been achieved with intrauterine delivery of progesterone at a rate of 65 µg per day and less, a miniscule increment to the 20-30 mg per day secretion rate of progesterone by the ovarian corpus luteum. In this fashion, the principles of rate-specified delivery have been applied to make practical the pharmaceutical use of a physiological substance that is the gestational hormone of every mammalian species,

produced by corpora lutea and, in many species including man, by the placenta as well. In this sense, the toxicologic and teratologic record of the safety of progesterone is the evolutionary history of the class Mammalia.

Most endogenous substances that chemically mediate physiological actions are, like progesterone, rapidly metabolized and thus short-lived. Rate-controlled delivery technology opens new opportunities to utilize these uniquely efficacy and safety-verified substances in therapeutics.

## New Path for Pharmacology

The demonstration of multiday, continuous, controlled drug delivery has thus opened up a new path for pharmacology, which is illustrated by another example from ocular pharmacology in treatment of a parasitic disease. Instead of regarding the eye as the subject of a somewhat arcane specialty, let us regard it as a tissue model for the whole body, having the useful property of allowing direct visual observation.

The example is the work of Jones, Anderson, and Fuglsang,26/ which has great potential significance for prevention of blindness due to onchocerciasis (river blindness). They showed that intensity of adverse inflammatory sequelae to the long-recognized microfilaricidal agent, diethylcarbamazine (DEC; Hetrazan(R)), administered by eyedrop, related to the temporal pattern of drug concentration reaching target tissues. They found distinctly different effects at different rates of DEC administration: at low rates, DEC caused death of microfilariae; at higher rates an undesirable inflammatory response accompanied death of the organisms. Results indicate that zero-order delivery of DEC at the proper rate could lead to gross reduction in microfilarial load without endangering critical tissues by inflammatory responses.16/

Jones and his colleagues further point out that, if ocular manifestations of the disease can be regarded as a model for the disease in other parts of the body, then the ocular reactions they have seen also suggest the value of zero-order systemic delivery of DEC. Human skin appears sufficiently permeable to DEC that zero-order systemic delivery of this agent should be possible via the transdermal route. Langham reported what may be interpreted as a favorable feasibility test of this idea, using a simple DEC lotion.27/ If, however, it is indeed true that satisfactory therapy requires carefully maintained control, then it would be desirable, as Jones et al. suggest, to develop a specific transdermal therapeutic system for DEC to reduce the systemic load of microfilariae with little or no adverse inflammatory reaction.

This work with diethylcarbamazine in onchocerciasis is another case study of how new technology can beget new thinking. In this

instance, recognition of the potential application of therapeutic systems technology to controlling DEC administration led Jones and his colleagues to examine, with very simple tools, the zero-order pharmacology of DEC under conditions that simulated continuous, controlled delivery. In fact, their work is the first fruition of the recommendations of a PAHO/WHO meeting on onchocerciasis, held in December 1974,[28] which called for just such studies in recognition of the coming revolution in dosage form technology:

> "The existing chemotherapeutic agents deserve careful re-evaluation from the standpoint of improving their safety and efficacy by searching for optimal treatment schedules. The schedule dependency of the efficacy of potent chemotherapeutic agents is exemplified in the field of cancer chemotherapy, in which the careful and painstaking study of different combinations of dosage and dosing schedules has made it possible to achieve effective regimens with agents that initially seemed to offer only modest promise. This has been the case, for example, in acute myelogenous leukemia in adults, acute lymphocytic leukemia in children, Burkitt's lymphoma, and Hodgkin's disease. The effort to optimize dosage and dosing schedules is quasi-empirical, and its inception need not await the conclusion of extensive studies of mechanism of action nor of animal models of the disease. Instead, the search for optimal schedules can proceed in parallel with supporting studies of drug action in vitro and in animals."

> "Clinical pharmacologic studies on the schedule dependency of drugs for onchocerciasis should be designed with a view to developing schedules that are possible and practicable in the field. In addition, recent developments, in membrane, polymer, and elastomer technology applied to continuous controlled drug delivery give promise of broadening the scope of practical dosage schedules beyond those that have been possible with traditional formulations."

## Developmental Status of Rate-Specified Dosage Forms

Many advances in therapeutic systems technology are still in the developmental phase, but some noteworthy achievements or work in progress include:

- One-week-duration ocular therapeutic systems in the form of a thin elliptical film, worn beneath the eyelid for delivery of an antiglaucoma drug;[21-23]

- One- and three-year-duration therapeutic systems, in the form of a T, providing intrauterine delivery of progesterone for contraception with concomitant reduction of

menstrual blood loss; 24,25,29,30/ it also appears uniquely well-suited to immediate post-partum insertion,31/ permitting institution of an automatic contraceptive regimen at the time of confinement;

- Half-year-duration injectable therapeutic system, under development for systemic delivery of a progestational steroid for contraception;32/*

- Three-day-duration therapeutic system in the form of an adhesive patch, worn on a few square centimeters of skin surface, for transdermal systemic delivery of a drug for motion- or drug-induced nausea;33-35/

- Multiday-duration therapeutic system of the same adhesive patch, under development for transdermal systemic delivery of an anti-hypertensive drug;

- Day-long-duration, osmotically actuated tablets, under development for oral administration of many rapidly metabolized/ excreted agents, so that they can be administered once daily instead of 3-4 or more times daily; 17,36/

- A multiweek-duration ocular therapeutic system under development for antibiotic treatment of the blinding communicable ophthalmias and trachoma;37/

- One- and two-week duration miniature osmotic pumps, designed so that they can be loaded with solutions of bioactive agents, and implanted in laboratory animals;38/ these are basic tools for research in zero-order pharmacology in animals;39-43/

- Multiday duration, self-powered, lightweight, and thus portable,44/ or ultralight and thus wearable 45-47/ infusion pumps; these are basic tools for zero-order clinical pharmacology and, in tropical medicine, could conceivably find specific field application where none but the parenteral route can do.

General technical descriptions of these systems can be found in references 10, 12, and 48, and the entire book by Robinson (ref. 48) is an excellent compendium of diverse efforts now underway in the development of improved means of administering drugs. Their potential value in therapeutic problems of developing countries is discussed in references 26, 28, 37, and 49.

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## Economic Considerations

Unfortunately, the first therapeutic systems products are expensive compared to conventional forms of the same agent. We should hold in abeyance, however, judgment that unfavorable economics foredoom zero-order drug delivery technology to providing products only for an affluent minority. Virtually every major new technology enters the marketplace with product cost at an historic high, for translation of a new technology into its first products involves much breaking of new ground -- with costly false starts. At the same time, opportunities for applications of first products are often poorly defined.

The electronic pocket calculator illustrates these points. The first scientifically oriented pocket calculator entered the marketplace about seven years ago with a price of $400 -- 10-20 times the price of a good slide rule. Today's version of the same product is simpler to use, technologically more advanced, and costs one-eighth as much (Table 2).

TABLE 2. COMPARATIVE COSTS OF POCKET CALCULATORS (1971-1978)

| | General Purpose a/ | Scientific b/ |
|---|---|---|
| 1971 | $150 | $395 |
| 1978 | $ 10 | $ 50 |

a/Datamath, Texas Instruments.
b/HP-35 and its contemporary equivalent, HP-31, Hewlett Packard.

The first general-use calculator has undergone a 15-fold price reduction in the same time. There has been great diversification from single product to a multiplicity, designed to meet diverse needs of users from many callings. Needs of potential users of these products grew and diversified as technology demonstrated what was possible. Slide rules have been driven from the market in this seven-year period. Moreover, orders of magnitude more people now use pocket calcuators than ever used slide rules, and there exists not only one, but many markets that even the greatest optimist could not have foreseen in 1971.

This seven-year old technological revolution, with its diversification and cost reduction, did not have to contend with the distraction of government regulation. Such regulation, however well-intended, is anti-innovative. Perhaps one day regulation will be deemed desirable

for calculators when someone traces a fallen plane, a fallen bridge, or a miscalculated dose to a malfunctioning pocket calculator, but up to now this industry has advanced its technology with astounding alacrity. Its progress recalls the first decade of antibiotic development, and is humbling to today's pharmaceutical industry, which, in response to safety concerns, has become bureaucracy-ridden both from without and within. Yet as slow and costly as we have allowed ourselves to become in research and development leading to new active substances, it appears possible to achieve significant improvements in dosage form design and methods of drug administration much more rapidly. The economics of large volume production can prevail no less in manufacture of rate-specified pharmaceuticals than they do in other industries generally.

## Conclusion

The therapeutic systems revolution aims at simplifying chemotherapy. To make something simpler to use makes it more reliable. Achieving this simplicity for the user, however, requires technological sophistication in the researcher, the developer, and the producer. It is a complex process to make something simple.

Technical developments in controlling administration of active substances have fundamental significance for the science of pharmacology, both animal and clinical. The prospect of having controlled delivery dosage forms for a wide variety of active substances should increase the priority of research on zero-order pharmacology of many older, basic agents. In the search for new drugs, controlled delivery offers a whole new basis for profiling the actions of compounds in the drug screening process. Concepts of zero-order pharmacology should be introduced into the screening process at the earliest opportunity, for the simple reason that control complements chemistry in the quest for specificity. Until screening is done from the perspective of zero-order pharmacology, therapeutically useful opportunities will be missed.

The analogous concept of zero-order toxicology should be examined with great care by academic, industrial, and regulatory people. It may offer a rational path out of the current confusion prevailing in the safety evaluation of drugs given in pulse or drench modes.

New methods of drug administration begin to lead one's thinking away from seeing pharmaceuticals merely as chemical commodities. The therapeutic systems revolution brings improved pharmaceuticals that share many attributes of medical devices. These attributes preclude such new pharmaceuticals from being understood and described wholly from the chemical perspective that has dominated the pharmaceutical field.

There are, therefore, two strategies for making research yield practical consequences relatively rapidly in the form of improved

pharmaceuticals for developing countries. The first is to evaluate zero-order pharmacology of the many agents that have been used and found active, but in one way or another have also proved troublesome. If, as with DEC, theophylline, pilocarpine, scopolamine, and doubtless many other basic agents, controlled delivery can dissociate troublesome activities from useful ones, then an "old" drug is vested with new therapeutic value; if, as with progesterone, controlled delivery can allow practical use of a physiological agent, truly old agents can be vested with new therapeutic value. The second strategy is to determine important parameters of patient compliance in real life, recognizing the wide variety in custom and culture that will influence acceptance and utilization of pharmaceuticals. Such information is no less fundamental to design of widely beneficial products than are the pharmacologic characteristics of the active substances they convey.

It is impossible to over-emphasize the importance of this last point. Yet the problem of noncompliance is so widely ignored that it might, but for its universality, seem a conspiracy of silence among patients, doctors, industry, and government. Major programmatic research support should be provided for study of patient noncompliance -- the giant orphan of therapeutics.

Up to now, we have led ourselves to believe that the regimen required for effective use of an active substance was inherent in the substance itself. Conventional, first-order pharmacology has perpetuated that thought by teaching the distinction between short- and long-acting agents. Yet now we see that the therapeutic systems class of dosage forms has made obsolete that restrictive thinking; the practical ability to conceptualize drug action in terms of zero-order pharmacology provides a new basis for seeking and finding specificity of drug action. The new therapeutic systems class of dosage forms allows unprecedented latitude in tailoring therapeutic regimens to human needs.

Improving methods of drug administration, then, is a multifaceted research opportunity for improving "Pharmaceuticals for Developing Countries," for improving quality of drug utilization, and for improving outcomes of their utilization.

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# CLINICAL TRIALS IN DEVELOPING COUNTRIES

## A. METHODOLOGY OF CLINICAL TRIALS IN DEVELOPING COUNTRIES

Alvan R. Feinstein

In transplanting modern technology, a developing country must consider its own needs and aspirations, while carefully scrutinizing what the technology has to offer in both advantages and disadvantages. The purpose of the scrutiny is to help planners learn from mistakes of the past, so that advantages can be exploited while disadvantages are avoided. Like all other types of modern technology, controlled clinical trials require such a careful evaluation.

During the past 30 years, controlled clinical trials have been developed as a powerful method for evaluating agents used therapeutically either to prevent or to remedy disease. The power of the method comes from several major scientific advantages that help reduce or eliminate the bias with which treatments were formerly compared.

The way that these advantages occur can be demonstrated from a review of the basic scheme of a therapeutic comparison, as shown in Figure 1. Treatment A, the active agent under consideration, is contrasted against Treatment B, which is a "control." It can be an alternative active agent, a placebo, or no specific treatment. As shown in Figure 2, to compare the effects of the two forms of treatment, we contrast the outcomes noted in the eligible people, who have been divided into Group A (the people who receive Treatment A) and into Group B (the people who receive Treatment B). In many situations of the past, and sometimes even today, this comparison has been conducted nonconcurrently. When a new treatment has come along, its results have been contrasted against those noted at an earlier time period, using the treatment or treatments available previously.

Such nonconcurrent comparisons create the hazard of two potential biases. If Treatment B was used in an earlier era, Group B may have contained people assembled with the old diagnostic standards for eligibility, whereas Treatment A may have been tested in a later era, with improved diagnostic methods that allow Group A to include "earlier" or "milder" cases, who would have better outcomes than the Group B patients, even if the two treatments each accomplish nothing. A second source of bias in nonconcurrent comparisons of therapy is that the old

FIGURE 1. BASIC STRUCTURE OF A COMPARISON OF THERAPY

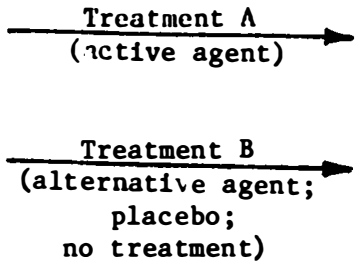
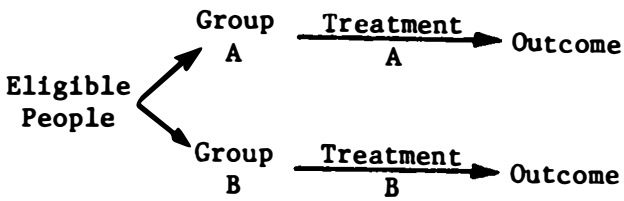



FIGURE 2. DIVISION AND FOLLOW-UP OF THERAPY

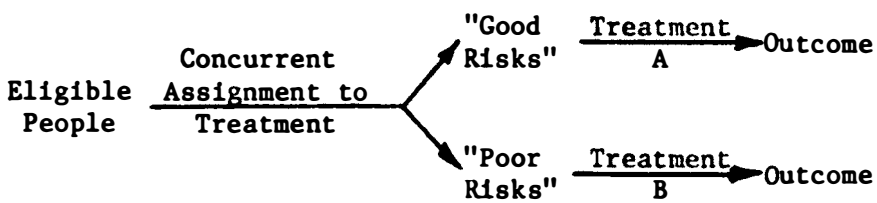



Treatment B may have been accompanied by ancillary treatment that was either primitive or absent, whereas by the time Treatment A comes along, the ancillary treatment may have been substantially improved. This improvement in ancillary treatment -- rather than intrinsic differences between A and B -- may then be responsible for differences noted in the results of the two treatments.

These two problems can be removed in the modern design of controlled clinical trials, because treatments are compared concurrently with presumably similar diagnostic standards and with similar kinds of ancillary therapy. Even with concurrent comparison, however, an important scientific hazard can be produced by the way in which the treatments

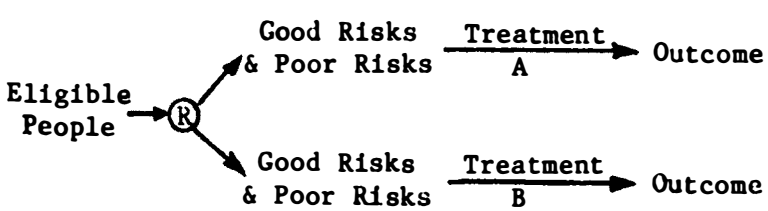
are assigned. If the therapeutic agents are prescribed according to the ad hoc judgement of a clinician and accepted according to the ad hoc judgement of the recipient, a major bias can arise, as shown in Figure 3. The "good risk" patients may be the predominant members of the group receiving Treatment A, whereas the "poor risk" patients are predominant in Treatment B. With this type of "allocation" bias, Treatment A should regularly achieve better results than Treatment B, even if both treatments are ineffectual.

FIGURE 3. ALLOCATION BIAS IN SELECTION OF THERAPEUTIC AGENTS, DESPITE CONCURRENT COMPARISON




The reduction or elimination of this problem is a second major advantage of modern clinical trials. They are designed as a planned experiment, as shown in Figure 4, using randomization as a mechanism for allocating treatment in an unbiased way that allows good risks and poor risks to be equally distributed within the limitations of the chance introduced by randomization.

FIGURE 4. USE OF RANDOMIZATION FOR "UNBIASED" ALLOCATION OF TREATMENT



Even with randomized assignment of treatment, however, a bias may still arise if observers of the post-therapeutic course, shown in Figure 5, are aware of the treatment received by each patient. Prejudices of the observers may then consciously or subconsciously affect the way outcome is noted and reported. Figure 6, which shows how this problem is avoided -- by use of "double blind" observers and/or a "hard endpoint," such as death -- is the third major scientific advantage of modern clinical trials, in addition to concurrent comparisons and randomized allocation of treatment.

FIGURE 5. SOURCE OF POTENTIAL BIAS IN OBSERVATION OF OUTCOME EVENT

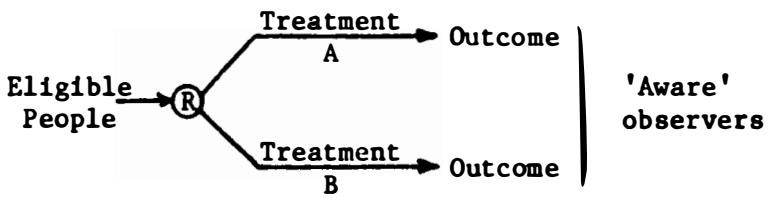
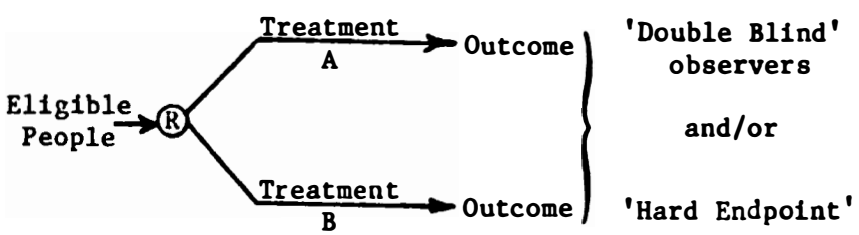
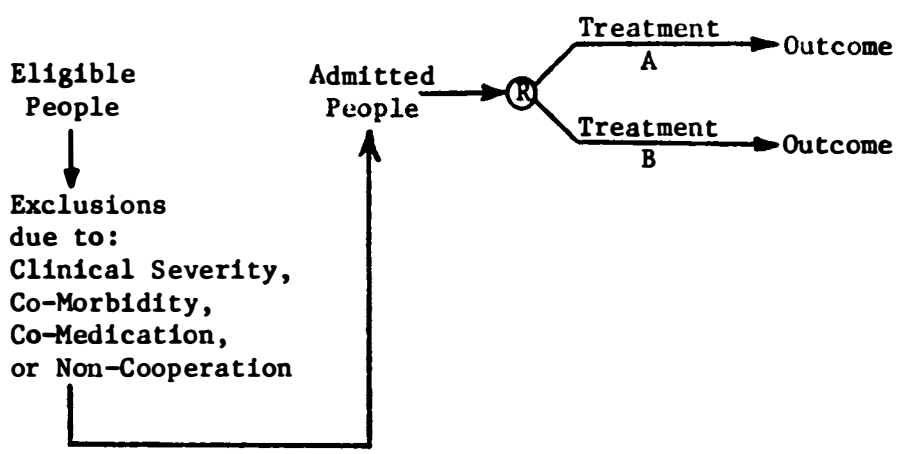



FIGURE 6. METHODS OF AVOIDING BIAS IN OBSERVATION OF OUTCOME EVENT



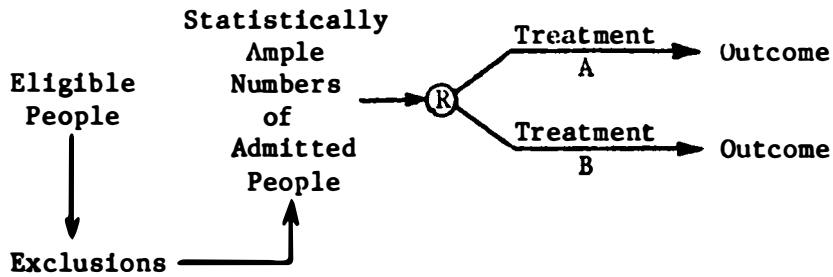
Yet another scientific effort made in modern clinical trials is to "purify" the groups who enter the trial. As shown in Figure 7, the clinical state of the eligible people is simplified by a series of exclusions that remove many of the complex, heterogeneous features of a human ailment. These exclusions may eliminate people who have particularly high or low degrees of clinical severity, or who have the co-morbidity of additional diseases beyond the one under study, or who are receiving other medication that may affect the action of the treatments under study, or who give the impression that they may be non-cooperative in complying with instructions for maintaining either the prescribed treatment or the schedule of follow-up visits. The eligible people who are not excluded for any of these reasons then form the group who are admitted to the trial and randomized for therapeutic comparison.

FIGURE 7. USE OF EXCLUSIONS TO "PURITY" THE PATIENTS ADMITTED TO THE TRIAL




The last main step, shown in Figure 8, is taken to ensure that results will be statistically impressive. Sample sizes are commonly calculated, either before or during the trial, to provide an ample number of people for admission and study. If the numbers cannot be obtained at a single institution or medical setting, several institutions may collaborate to use the same research protocol and to pool their results in a cooperative study.

FIGURE 8. DETERMINATION OF STATISTICALLY AMPLE NUMBERS OF PEOPLE




In science, as in politics and economics, there is no such thing as a "free lunch." We should therefore not be surprised to discover that each of these five major advantages is accompanied by some distinctive problems and disadvantages.

First, if we rely exclusively on concurrent comparisons of therapy, we reject whatever was learned in past clinical experience. The older data, which often may be quite valuable, are left unused and possibly wasted. Second, if we rely on randomized allocation of therapy to prevent any baseline imbalances in the treated groups, we leave ourselves susceptible to hazards of the luck of the draw. Working at a P level of .05, we take the chance that one out of every 20 randomizations will produce an imbalance of a statistically significant magnitude. Furthermore, the idea that randomization has equalized distribution of good risks and poor risks may make investigators fail to identify and analyze results separately for good risks and for poor risks. Consequently, we are left in a position analogous to that of having performed clinical trials in groups of mice, dogs, and elephants who are not otherwise identified and who are simply lumped together and called "animals." The person who reads the results might like to know what happened separately in mice, dogs, and elephants -- but the investigator reports only what happened in the randomized "animals."

The third issue -- objectivity in observation -- creates several problems. A reliance on hard endpoints as outcome events may lead to an inflation of sample sizes if those hard events do not have a high rate of occurence. Furthermore, if results are expressed mainly in such statements as death rates or remission rates, investigators may neglect the many important clinical phenomena expressed in such soft

data as relief of symptoms, ability to function, and other aspects of quality of life. Although double-blind observation is a splendid technique when feasible, it is not always feasible; and furthermore, the double-blind masks are often perforated so that investigators or patients become able to recognize the identity of treatments on the basis of such things as appearance, taste, or certain side effects, such as bradycardia. Besides, belief that the double-blind method will prevent biased observation will often make investigators too complacent to develop suitable methods of "hardening" soft data.

As the fourth point in design, "purity" is an excellent attribute for the clinical condition of admitted people, but results found in this "pure" group of patients may not be pertinent for realities of the impure complexity treated in clinical practice. As the fifth main feature of design, statistically significant numbers may be mathematically convincing, but may sometimes lead to an excessive focus on statistical rather than clinical issues in design of the research; and need for large numbers often creates major logistic complexity in acquiring, standardizing, and maintaining the data when multiple institutions must collaborate.

Beyond these difficulties, certain additional problems have arisen in the way that controlled clinical trials have been designed and supported by Federal agencies in English-speaking countries in the past two decades. The first problem arises from new methodologic issues involved in what might be called contratrophic therapy. As shown in Table 1, the classical trials conducted in the domain of epidemiology have been contrapathic, concerned with primary prevention of disease in healthy people. The classical studies conducted in clinical medicine

TABLE 1. DISTINCTIONS OF BASELINE STATES AND OUTCOME EVENTS IN DIFFERENT STUDIES

| Baseline State | Outcome Event | Type of Study |
|---|---|---|
| Healthy | Disease | Contrapathic (1 Prevention) |
| Clinical Manifestation | Removal of Relief | Remedial |
| Disease | Adverse Progression | Contratrophic (2 Prevention) |

have been remedial, concerned with removal or relief of a clinical manifestation such as pain, dyspnea, or infection. Contratrophic therapy, however, is concerned with secondary prevention. The aim is to thwart adverse progression of an established disease. Contratrophic goals are illustrated by the use of anticoagulants to prevent thromboembolism in patients with myocardial infarction; by the use of lipid-lowering or hypoglycemic agents to prevent vascular complications in people with hyperlipidemia or diabetes mellitus; or by the use of any kind of surgical, radiologic, or chemotherapy to prevent death in patients with cancer. Some of the major therapeutic controversies that rage today have come from difficulties in studying these issues, which make the clinician confront unfamiliar statistical problems in a different kind of preventive medicine, and which make the epidemiologist confront unfamiliar complexities in classifying a diseased baseline state. These problems create new challenges in clinical epidemiology -- an intellectual domain that is itself still underdeveloped.

A second additional problem arises from issues in "potency" of the treatments under investigation. For the sake of the statistical model used in trials, treatments may not be given or evaluated in a clinically suitable manner. For example, inadequate use of double-blind procedures may lead to fixed rather than flexible dosage for a drug that should be given in flexible dosage. In many situations where an intermediate target must be regulated -- such as level of blood sugar, blood pressure, or serum lipids -- results of treatment may not be reported according to success of the regulation. For example, in the celebrated controversy over the UGDP study of diabetes mellitus, one of the points at issue is that treatments were analyzed exclusively according to the therapeutic regimen, but not according to the good, fair, or poor degree with which blood sugar was regulated. Another difficulty has been an inadequate assessment of compliance with oral medication. Thus, when blood pressure has not been lowered by an antihypertensive agent, we cannot be sure whether the agent itself has failed to work or whether the patient has failed to take it. Finally, we have still not developed satisfactory methods for analyzing changes in treatment. If a patient stops taking an assigned treatment after two months, changes to another treatment, and dies four years later, it seems silly to assign his death to the first treatment -- and yet this type of analysis was used in the UGDP study of diabetes.

A third additional problem is deciding the exact role to be served by the "control" treatment. Is it being used to test efficacy, efficiency, or effectiveness? For efficacy, we want to know whether the active treatment works. Is it better than nothing? There are two distinctly different types of efficacy to be considered here. For one of them, which is purely pharmaceutical efficacy, the active treatment is compared against a placebo, so that the doctor can contribute his personal iatrotherapy in both active-treated and placebo groups. This type of comparison creates problems in the ethics of randomization and it is also disparate from clinical reality, because doctors do not

ordinarily prescribe placebos. The second kind of efficacy, which is purely clinical, would involve a comparison against no treatment. This type of trial is more closely allied to clinical reality, but it creates problems in the ethics of prescribing no treatment as well as in performance of the trial, since patients who are wholly untreated may not return for follow-up examinations. Furthermore, although results are clinically realistic, they may not be readily acceptable in the scientific community.

For efficiency, the main question is whether the tested treatment works better than an alternative active agent. If the two treatments are similar in efficacy, so that one is not clearly better than the other, we may need extremely large sample sizes to demonstrate a substantial difference between them or to be reassured that the difference doees not exist. Finally, the question of effectiveness relates to the agent's accomplishment in the community or in clinical practice. Thus, even though a particular anti-hypertensive agent is both efficacious and efficient, it may be ineffective in community usage because people do not continue to take it. The question of effectiveness can seldom be answered with controlled clinical trials, because the trials are usually not large enough or long enough to cover the huge spectrum of people who must be evaluated and followed for protracted periods of time. Consequently, answers to the question of effectiveness will often require not controlled trials, but observational surveys, such as the type of Phase-4 surveillance studies now being developed for new pharmaceutical agents.

A fourth additional problem occurs because randomization may be mistakenly regarded as a panacea for all difficulties in evaluating therapy. Despite the many overt and occasionally dramatic advantages of assigning treatment by means of randomization, we cannot rely on it as the major or exclusive method of evaluating all new therapeutic agents that will emerge in an age of proliferating technology. There are too many agents that will need to be appraised; and randomized trials will not be feasible for testing all those agents in all clinical situations in which evaluations may be needed.

The last additional problem I shall cite arises from the quest for hard data. In a multi-institutional trial, standardization of tests may be sought by sending specimens to a central laboratory -- a procedure that adds considerable complexity and expense. Furthermore, information collected in the central laboratory may not always be cogent for the study. What is needed is some intensive planning about what kind of information is necessary, and how it can best be collected. In some instances, an initial effort to standardize facilities or observers of collaborating institutions may be more successful than the apparently simpler, but ultimately less productive, tactic of using central laboratories.

The conclusion we can draw from these considerations are expressed

in the following eight points. Perhaps the most important point is to be sure that studies are designed to answer practical questions. The presumptive purpose of a therapeutic trial is to evaluate an agent that would be used therapeutically. To evaluate that agent in circumstances that differ from therapeutic usage may have certain scientific and statistical advantages, but clinically results may be meaningless. A second point is to be sure, when the basic protocol is implemented, that implementation of the design does not distort any fundamental goals of the project. For example, although diabetologists wanted to know whether regulation of blood sugar, rather than mere prescription of hypoglycemic therapy, was a worthwhile activity in patients with diabetes mellitus, the UGDP study was implemented in a way that did not address the basic issue of blood sugar regulation. A third point, which is a corollary of the second, is to choose designs that are suitable for the major goals of the study, even if those designs are associated with minor scientific imperfections. As several excellent statisticians have said, better a somewhat inexact answer to the right question than an exact answer to the wrong question. Fourth, because of the complexities of multi-institutional collaborations, they should be avoided if single studies can be performed successfully at individual institutions.

A fifth point is that remedial endpoints are easier to study than prophylactic ones, particularly if the target events to be prevented have low attack rates, so that very large sample sizes are required for the study. A sixth point is that soft-data endpoints are often more meaningful than hard-data endpoints, particularly if the necessary initial efforts are made to harden soft data. Thus, we might get more clinical value from studying relief of symptoms and restoration of functional capacity -- if we develop good ways of doing so -- than from studying changes in X-rays, changes in blood chemistry, or death. A seventh point is to recognize the potential value of data acquired in ordinary therapeutic situations. This is the information we may have to analyze in circumstances where controlled trials cannot be performed. A worthwhile type of research, therefore, is development of better methods for collecting and using this type of information. Finally, for many important situations, a carefully planned observational survey may be more productive than an experimental trial.

As developing countries grasp the opportunity to use the technology of controlled clinical trials, the primary considerations -- as in all other modern uses of technology -- are to concentrate on choosing worthwhile questions and arranging to get worthwhile answers. Technology is an important but a secondary contributor to those primary goals.

## B. FACILITATION OF CLINICAL TRIALS IN DEVELOPING COUNTRIES

Edmund de Maar and J. M. Kofi Ekue

The following is a summary of WHO experiences in Chingleput, India and Bamako, Mali in the evaluation of new treatment regimes for leprosy; in N'dola, Zambia, where a WHO clinical investigator and technicians have developed a research infrastructure while investigating anti-schistosomal drugs; in Tamale, Ghana, where international staff work in a local hospital testing drugs against onchocerciasis; and in Belem, Brazil where malaria chemotherapy trials are in preparation. From these experiences, broad guidelines are suggested which are not, however, intended as a rigid prescription.

Predictions on safety and efficacy under local conditions which derive from trials on affected populations in another region can not be accepted as reliable indicators of future performance. It is highly desirable that the study be carried out where the disease is endemic. A protocol outline stating objectives and procedures will help to determine whether such a study is feasible, taking account of the stage of development of the new agent.

Initially, research objectives should be restricted to answering a few simple but meaningful questions. The answers will help in future regional use of the agent for control, and will serve as feedback to the laboratory engaged in continuing research on improved agents. It may almost be mandatory to start with a trial run of the test procedure, using an established drug to detect potential problems concerning availability of scientific and technical expertise, equipment, or reagents.

It should be borne in mind that local capability will vary and that in some places it is continuously improving. Problems may exist only in certain neglected areas of clinical research. Reorientation of existing activities towards tropical diseases may be possible.

Specifics need to be considered for protocol, location, staff, patients, resources, and data.

## Protocol

A protocol should be developed through extensive consultation and coordination, particularly for cooperative clinical trials. It should be drawn up in the region where the disease is endemic, at a workshop attended by a planning group with the broadest possible representation. Its goal is to impart pertinent information, including:

- the aims of the trial;
- a detailed description of activities, especially of such procedures as laboratory tests, biopsies, etc.;
- report forms that can be made part of the patients' records;
- consent forms and warning notices for participating patients, written in the local language;
- the treatment allocation procedure and treatment charts, particularly when regimens are reallocated or changed;
- the labelling code and emergency code-breaking and referral procedures.

An independent measure of patient compliance must be agreed upon. This will avoid branding as ineffectual a compound that the patients have not actually taken, or having the design of the study blamed for results that are difficult to explain. Separate guidelines may be provided for management of adverse reactions, and work manuals for the pharmacist or drug supervisor have proven useful. The investigational drug data brochures should be annexed.

A subsequent standardization workshop contributes to the precision of clinical and laboratory results with respect both to the selection of patients and to assessment of response. Byproducts of the workshop are a great sense of fellowship in addition to training and motivation. In cooperative studies, a subsequent meeting of principal investigators to review progress is also highly desirable.

## Location(s)

Although the diseases are widespread, suitable trial sites may be difficult to identify. These should be carefully chosen to avoid conditions that might prevent application of suitable scientific standards. It will be necessary to check for the following:

- Prevalence and incidence of the target disorder and of other endemic diseases.

- Possibilities of reinfection during the trial or follow-up period. (Can the trial procedures discriminate between suppression with relapse and cure with reinfection?)

- Local variability in patient tolerance or parasite susceptibility. (Are they likely to affect efficacy and safety?)

- Capability of the medical infrastructure to support the projected research.

- Accessibility of reliable, adequate transportation and choice of season for study. (The problem of ready access to study areas, preferably throughout the year is not to be taken lightly. Rural roads described as not likely to be flooded may in practice turn out to be impassable for months because the health worker cannot afford to spend hours stuck in mud.)

- Attitudes regarding tendency to please, security (be wary of drug leakage for alternative uses of the drug), attitudes toward trials of new agents, investigational invasion of privacy, (e.g., blood tests, stool collection, and post mortems). Check absences for such occasions as religious holidays, harvests, sickness in the family, funerals.

When an appropriate site has been identified, it is appropriate to:

- Explore the will to investigate a disease problem of local importance and global consequences.

- Make a contract with national and local authorities, including national research councils, so that any agreement will extend throughout the administration from the Ministry of Health to the local authorities, and designate the project as national or local with no emphasis on internationality.

- Check the necessary clearances for investigating a new agent; both international and local permits may be needed in the country of origin of the drug or vaccine, from a review body, a manufacturer, or from an authority.

- Determine whether cooperative arrangements can be made; make full use of all locally available experiences in relevant medical research; and look for a twinning arrangement with a group with proven experience in clinical trials, particularly for clinical pharmacology, pharmacokinetics and training. -

- Obtain all possible cooperation, not only from participants in a trial, but also from all inhabitants of the area under study. When the community understands what is going on, work is likely to be facilitated. Neighbors may even see to it that patients turn up on days of study.

- Consult such local health dignitaries as the traditional medicine man and the dispenser or pharmacist; their cooperation and understanding of the clinical trial should be sought. Their displeasure may jeopardize the whole study.

## Staff

It is essential to find a competent, mature and enthusiastic principal investigator and to ascertain his (her) availability for the duration of the study. Recommended by senior health, hospital or faculty authorities, the principal investigator should ideally be a member of the local medical profession and, as such, acceptable to government health agencies. Dependable and, where possible, fully paid by the project, he (she) should be knowledgeable about clinical trials or willing to learn, and should have been a member of the protocol working group. The principal investigator(s) must be prepared to do most of the work, the volume of which should be planned with that condition in mind. One should be wary of too eager a delegation of supervision.

The trial group may include other medical and supporting personnel, such as physicians, nurses, secretaries, a pharmacist or drug supervisor, a financial or administrative officer, a statistician, and a clinical pathologist who are organized and prepared to substitute for each other in case of sudden unforeseen absences. Even the best motivated groups may experience the full range of causes of absences from accidents to unexpected departures for sabbatical leave. Clinical trials offer to young physicians training in planning and executing a time-limited project, and the opportunity to collaborate with senior scientists. Such an experience may well be the first step on the ladder to a research career.

A coordinator, familiar to the group and not alien to their culture, who adheres to high scientific standards and can appreciate local

problems is very useful for the necessary liaison with local groups in other locations, and with the sponsor of the trial. To promote self-reliance, national counterparts should be appointed for any non-local, temporary staff.

## Patients

There should be agreement on the population from which the sample will be drawn, and on the method of sampling of research subjects as regards the intensity of the disease, concurrent diseases, sex, age and ethnic origin. In addition to careful records of name, the household, tribe, domicile, and occupation, photographs may be useful to confirm identification when appropriate. A calendar for clinic visits should be agreed upon, and special clinic hours arranged for research patients. By reducing transportation time, satellite centers can promote recruitment of patients and encourage participation by all interested persons in the trial area. These centers should also offer medical care for conditions other than the disease of interest to the study.

Care should be taken during selection of a study population to avoid groups who have easy access to conventional medical treatment, for they might obtain treatment which could interfere with the clinical trial. In selection of school children for a clinical trial of a schistosomicide, for example, urban schools or rural schools located near a clinic are to be avoided, if possible.

The drop-out rate is usually minimal from a study which is well conceived, planned, and explained to the subject population. If a follow-up is needed of people in scattered villages one should try to assess mobility as nearly as possible before work is started. Mobility is usually underestimated, and many participants may therefore not be traceable.

## Ethical Clearance

Verbal or written informed and meaningful consent must be obtained from each patient. The methods for explaining safety issues must be predetermined. Handing out consent forms to people who may at best be semi-literate would not suffice. One may have to seek additional consent from the traditional "head" of the unit as well as from parents and from the head teacher if school children are to give specimens of blood or urine. The consent of a husband for participation of his wife should also be obtained in some areas. Withdrawal of subjects several weeks or months after a trial has been in progress is the penalty for neglect of these precautions.

Projects should be cleared by a locally approved, independent body practicing the highest standards of protection of the rights of the

individual. Such a body should be created if it does not exist. When presenting the study to that body, the information to be conveyed to potential subjects should be described in detail and should include:

- aims of the research project;
- expected duration of the study;
- alternative methods of treatment of the target disease;
- study procedures which are experimental;
- any known immediate or long-term risk or possible discomfort to which subjects are liable;
- benefits anticipated for subjects or others;
- the degree of freedom of each subject to withdraw from the study at any time;
- confidentiality of any information relating to patients should obtained during the course of the study.

Explanations should be included as to the manner (oral or written) in which this information will be conveyed, and names and status of staff members who transmit this information to potential subjects and who ascertain that it has been understood and that consent is freely given. The written consent form should be appended, if applicable.

Any special incentives or treatment services to be given to subjects in exchange for their participation should be indicated.

Resources

1. Drugs Test medications should never be smuggled into any country; a worthy scientific purpose is no excuse. Research drugs are new chemicals which cannot be classified by customs. A full formula should be placed on the tear-off label and the problem of unrealistic value assessments should be discussed with the manufacturer. The method for obtaining post-trial follow-up treatment supplies should be considered in advance.

2. Samples Responsibility must be assigned for carrying out each particular test of the laboratory work. If assays are to be run elsewhere, and methods of preservation are available, samples should be shipped on a regular schedule. A specimen identification form can be helpful. A laboratory report form links patients and laboratory data. The local laws on export of biological materials should be carefully checked. It is "medical colonialism" to take samples out of a

country, leaving no further trace of that export except a publication many years later from a laboratory in another part of the world.

3. Maintenance Availability of services for all laboratory equipment should be checked.

4. Time A realistic estimate of the duration of the study is needed with starting and completion dates. A flow diagram is useful. The rate of expected intake can be predicted by continuous (weekly/monthly) plotting of actual intake. Too rapid early intake, or too slow or unsteady intake can lead to incomplete data collection, missed visits and general disappointment of staff. Adding more field stations could increase output without disrupting a study. Consider the consequences of delays.

5. Funds The financial officer must determine the totals required and obtain the funds.

Data

Multi-center, short-term trials rapidly produce large amounts of data suitable for tabulation. For studies of longer duration, or for those involving many patients, it is useful to fix definite times for interim analysis, e.g., when 25 percent of the sample population has completed treatment. Continuous tabulation may be useful to detect trends signifying toxicity. Whether these results should be supplied to all investigators (at the risk of engendering biases on their part) should be carefully considered. Mechanized methods for data collection, storage, retrieval, and analysis are desirable to: -

- promote accuracy and thus ensure acceptability of the information to others;
- promote close surveillance of the project with quality checks as data are generated;
- keep up with the rate of data collection and thus ensure that the sponsor receives all data as they become available;
- obtain significant savings in time and effort.

Before beginning, there should be agreement on ownership and confidentiality of data, on who is to analyze interim and final results and where, and on publication policy (e.g. acknowledgements), including public announcements.

## Conclusion

If these specific guidelines are observed, clinical studies carried out in tropical countries on the diseases endemic in those countries can proceed as smoothly as trials carried out in more developed, temperate countries; the results obtained will be just as reliable.

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# OPPORTUNITIES FOR RESEARCH - AMERICAN INDUSTRY

Pedro Cuatrecasas

If industrialized nations are to contribute to the solution of the health plights of developing nations, they must apply the strengths and resources which they have most uniquely developed. Because for the pharmaceutical industry this resource is clearly that of drug discovery and innovation, the process by which this occurs must be clearly understood if one is to integrate new or additional challenges in a meaningful, productive way. As this essay will try to demonstrate, applications to specialized diseases must be an integral part of the discovery process in general if we are in fact to use industry's existing and proved assets and capabilities rather than to artificially create well-meaning programs that may turn out to be wasteful and unrewarding. Insofar as opportunities for research in American pharmaceutical laboratories cannot easily be segregated along therapeutic lines or disease states, opportunities and problems related to diseases of developing nations must be viewed and examined in the context of the entire research base and structure of this industry.1/ This essay will therefore address primarily the general features of research and development (R&D) which affect the industry's overall research opportunities.

In the past forty years, the ethical pharmaceutical industry has been extraordinarily successful in discovering new drugs through its primary emphasis on innovative research. The value of innovative research has been the basic, unique characteristic of the industry which is responsible for its existence and without which it cannot be expected to survive in the future. The contributions of new therapies to the control of diseases, and the impact on the health care systems of our societies, have been profound. Thus, the discovery of drugs and their expeditious evaluation is industry's most important resource.

It is clear that there is still great need in all countries for new remedies for treatment and control of serious health maladies. Drugs and vaccines are the most cost-effective forms of medical therapy, and they constitute our major technology for further reduction of costs, as well as the further curtailment of disease. Public policy related to health care must therefore be formulated in the context of the potential contributions which can be derived from new drugs, and adequate

thought must be given to ways in which drug discovery can be encouraged, nurtured, and promoted.

If it is accepted as public policy that new drugs are desirable and needed, serious attention must be given to the nature of the drug discovery process. To deal with this issue properly, it is necessary to understand the extreme complexities, difficulties, and uncertainties involved in developing new drugs in the present era. The resources and requirements for discovering drugs for diseases of developing countries are, in my opinion, inseparable from those of drug discovery in general. It is naive, if not counterproductive, to believe that it is possible to establish special drug development programs successfully or to direct policies to particular disease states 2/ out of context or without addressing some fundamental problems of drug innovation in today's world. If American industry is to contribute, it must do so within the same framework of technical, regulatory, and economic constraints that restrict all its other, current innovative pursuits.

I firmly believe that, scientifically and technically, opportunities for discovering and developing new therapies for diseases in all countries are greater today than ever before. For the scientist, very exciting opportunities exist on the basis of the substantial progress of the past 20 years in fundamental biological and medical sciences.3/ The obvious deficiencies and needs of medical practice also provide strong challenges and incentives for delivery of health care. Despite this, current economic, political, and regulatory climates, and their impact on public opinion, are in my view seriously blunting drug innovation and threatening to deprive society of the benefit of potential new drugs. In my view, this is the extreme paradox of today: at a time when the potentials of science and technology are greatest, so also are the man-made restrictions, disincentives, frustrations, and discouragements. Because of the overwhelming significance of constraints that handicap all drug R&D, and because of my belief that much of this constraint results from a lack of understanding of the factors involved in drug research, I will address here some of these general principles rather than directing my comments to specific programs where there is research opportunity in a defined, limited class of disease states.

I will try to develop the theme that novel drug therapies will almost certainly arise primarily out of basic R&D programs of the pharmaceutical industry. Success can best be achieved through constructive, collaborative relationships with government and academic institutions. A mutual spirit of understanding and cooperation will be required in order to encourage drug discovery.

## Comparative Sources of New Drugs

In trying to anticipate the possible future sources of new drug

therapies, it is instructive to examine historical perspectives and trends, since this is the only available data on which objective, predictive judgments might be made with any degree of accuracy.

Recent studies indicate that during the past 35 years the overwhelming majority of significant new drug introductions, defined as New Chemical Entities (NCEs), were discovered and introduced by the pharmaceutical industry. For example, Schwartzman 4/ estimates that industry accounted for 91 percent of all such discoveries and introductions in the United States in the period 1960-1969 (Table 1). Furthermore, the trends since 1935 have been steadily shifting more and more to the source within industry,4,5/ as demonstrated by separate studies by Schnee, Seife, and Schwartzman (summarized in ref. 4).

TABLE 1. PERCENTAGE OF NEW CHEMICAL ENTITIES (NCE) DISCOVERED AND INTRODUCED IN THE U.S.A. BY THE PHARMACEUTICAL INDUSTRY 1/

| | Period in Which Drugs were Introduced | |
|---|---|---|
| Source | 1950-1959 | 1960-1969 |
| Total | 100% | 100% |
| Industry | 86% | 91% |
| Other | 14% | 9% |

It is important to note that these data refer to discovery as well as the development of new drugs,4,5,6/ since there are prevalent common public misconceptions that see industry R&D as merely seizing upon or developing (in a routine way) basic discoveries made in academic centers. The fact that in modern times industry has been society's main instrument of drug discovery must be recognized, not to exalt industry, but to understand better the forces and factors with which we must work if we are to maximize future discovery.7/

As will be discussed later, drug R&D has become increasingly complex, and it has unique features toward which industry has directed its attention. Academic and government laboratories, on the other hand,

have been relatively unproductive in this area (with the exception of vaccines) despite the increased allocations of resources for medical research that now far outweigh those of industry (Table 2). As government-sponsored research, through its research grant and contract system,

TABLE 2. NATIONAL SUPPORT FOR PERFORMANCE OF HEALTH-RELATED RESEARCH BY SOURCE OF FUNDS ($ Millions) 1/

| Institution | 1960 | 1965 | 1970 | 1972 |
|---|---|---|---|---|
| Total | 798 | 1,715 | 2,499 | 3,102 |
| Government | 471 | 1,229 | 1,740 | 2,223 |
| Private, academic | 121 | 158 | 193 | 211 |
| Industry | 206 | 328 | 566 | 668 |
| Industry % of total | (26%) | (19%) | (23%) | (22%) |

has proliferated and matured over the past forty years, the proportion of new drugs contributed by this sector has declined steadily. This is not meant to belittle or downgrade the enormous contributions of those institutions to advancement of fundamental knowledge, but to indicate that their fundamental orientation is such that it is unlikely that they will be major sources of applied research and of new drugs for the future. With some exceptions, academic research does not have the orientation, temperament or organization required to mount successful programs for drug discovery and development. In addition, non-industrial research is not equipped to deal with the complex regulatory processes which are in today's world intrinsic to and inseparable from the process of drug discovery itself. However, as will be described later, these institutions can contribute along with industry in important ways to specific programs of drug development. But, in my opinion, it is the American pharmaceutical industry which, because of its special interdisciplinary scientific and technical skills, organizational strengths and economies of size is best suited to carry the principal initiative in this area of innovation and development.

## Threats to the Drug Discovery Process

Several factors encourage the pharmaceutical industry to decrease its commitments to innovative research. Spiraling costs of R&D (estimated to amount to an overall average of $25 to $40 million per NCE), 10-12 years required to bring a new entity into the market, risks and uncertainties of the discovery process itself, proliferating and restraining regulatory machinery and governmental economic policies which do not favor profits by the innovator have all worked to seriously reduce the appeal of drug discovery and return on investment of research. It has been estimated 4/ that the return is now 3 percent on an industry average, which is not a sufficiently high level for prudent investments relative to other alternatives (e.g., about 10 to 12 percent for other industries). There is little question that drug companies are now being forced to turn away from competition in innovation (i.e., new drug discovery) to competition in pricing, alternate formulations and presentations, defensive R&D, etc. These reactions are being largely fostered by public policy, which has been adversely shaping public opinion, perhaps not deliberately but nevertheless with negative impact.

There is little doubt that spiraling costs of industrial drug R&D, bolstered by staggering costs of compliance with proliferating regulatory requirements, have markedly shifted distribution of resources away from substantive, creative activities toward less productive developmental efforts. Even with increasing R&D budgets, there has slowly emerged an important shift of attention toward relatively nonproductive, bureaucratic tasks which are required for survival. Costs of adapting to increasing regulatory requirements and standards, such as Good Manufacturing Practices (GMPs), Good Laboratory Practices (GLPs), and Clinical Practices, among others, have been immense. The net result has clearly been a substantial decrease in efforts devoted to basic research programs which on the surface may not be too visible because it represents a re-allocation of funds within large total R&D budgets.8/ In this context, laboratories have been forced to restrict themselves to more limited fields of research, and to abandon or avoid programs that from the outset do not offer attractive economic rewards, regardless of their scientific merit or appeal. This is one of the reasons why many laboratories have curtailed research in tropical diseases. It is notable that despite this, several research-based pharmaceutical companies have maintained large programs directed to diseases of the Third World, a situation that may be judged by some dispassionate observers as being economically foolhardy. The Wellcome Foundation, for example, is spending at least one million dollars a year in such research.9/

It is important to note that even if drug research by non-industrial laboratories need not be concerned with economic rewards or opportunities, it must nevertheless still conform to regulatory requirements if it is to seriously participate in drug discovery and development. This will involve enormous problems since in addition to bureaucratic

restrictions and standardization requirements, for which academia has a strong distaste, it will be necessary to divert funds away from innovative research. A large proportion of the requirements, even if based on a rational principle, stifle creativity. It is unlikely that academia can tolerate standardizations which in many areas are incompatible with originality.10/

The decreased allocation of efforts and resources to substantive research by industry, although understandable, is alarming. New drugs being introduced today are not today's drugs or discoveries, but those of ten years ago. Today's decreased efforts and discoveries will only be evident ten years from now, when it could be too late to do much about it. We see now a reluctance to tackle important but difficult research programs that have of necessity long-range objectives. Such programs are too large, expensive, and risky. The pressures are for shorter term, more certain but less revolutionary contributions. There are pressures that discourage bold programs and aggressive pursuit of tough problems, even though the fundamental scientific knowledge is available to point to a sound rationale and potential feasibility. The tendency is to be super-cautious, to avoid possible research failures or anticipated demands or denials by regulatory agencies. Potentially useful compounds, for example, are being dropped from further development because an in vitro test shows potential mutagenicity, or because of a suggestion of addictive potential.

To me, this is the drug lag of substance. It is an absolute rather than a relative lag. Many potentially useful drugs are not being examined (or discovered) at all, and society may ultimately be denied discoveries within our technological capacity to achieve. If this is the case even for important breakthrough drugs in our industrialized nation, where good potential for economic rewards exists, is it any wonder that few deliberate programs exist to pursue possibly non-profitable "orphan" drugs or those for disease of other nations where marketing factors are unpredictable?

## Need for a Proper Climate for Industrial Drug Innovation

It is widely recognized that over the past ten years we have seen a dwindling rate of significant new drug introductions,11/ which is especially severe if it is judged relative to the enormously increased research expenditures (by all sources) and basic scientific progress which have occurred during this same period of time. It must thus be recognized that it is not just tropical diseases or rare disorders that have apparently been "neglected" in terms of the supply of new, improved drugs. The reduced productivity is, instead, a reflection of an affliction which has affected drug discovery in general.

The challenge now in new drug discovery is how to overcome the obvious constraints and substantially increase efforts and resources

allocated to basic research programs in this industry. Industry must be encouraged to exploit in its research the vast wealth of fundamental scientific information which has been accumulating, and to better integrate its strengths with complementary talents in the academic community. To do this, the potential economic rewards for success must be assured; incentives and encouragement must be such that competition in drug discovery becomes the dominant force. A healthy, vigorous, and economically rewarding research community within the industry will result, I am sure, in substantive contributions in many therapeutic fields, including those of the developing nations.

Pharmaceutical research is highly unique, unpredictable in the direction of its results and characterized by serendipity. As a matter of principle, the best way to assure discoveries in some areas is to encourage excellent research in all areas. New therapies for parasitic diseases, for example, are as likely to result from a program initially directed to the discovery of an antimetabolite, an anti-bacterial, or even an anti-hypertensive as from a deliberate, rational program for a specific parasitic disease. History is replete with such examples, which despite their appearance of being totally accidental, in fact require scientists with intuition and insights based on experience, and broadly based and well-organized programs. In today's scientific arena this is even more likely to be the case than ever before because of the increasing interdependencies and overlapping nature of scientific disciplines. Certainly, specific programs in therapeutic classes must exist, but they must all be closely integrated.

Regulatory agencies, whose task it is to protect against hazards and the regulation of new products, should somehow be balanced in their judgment by public policy mandates which acknowledge the cost-effectiveness of this type of health care technology and the need and value of new therapies. This will encourage innovation. Drug development should proceed in a regulatory environment dominated by encouragement and optimism, not suspicion, adversarial postures or hostility.

The fundamental role of the pharmaceutical industry in drug discovery needs to be recognized. The need to recover enormous investments in R&D should be acknowledged and fostered. The nature of its research technology, which differs in important ways from that of other industries, must be better understood. The rate and nature of success must be examined for the industry as a whole, and not taken out of context to assess its value in selected areas. For example, most new drugs will have poor sales and low return,10/ which is tolerable if those commercially very successful drugs are accepted and allowed. It must be appreciated that it is those few, highly successful drugs that must recover the costs of R&D of all the failures (which never make it to the market) as well as those of low profit or for relatively rare diseases. If these few major successes are unfairly singled out for attack on the basis of cost (or pricing) or possible monopolistic practices without regard to the totality of R&D requirements and rate of

returns on investments, funds for investment in future risky ventures can be seriously compromised. These few highly successful and profitable drug products may make possible subsequent discovery of new drugs, some of which would undoubtedly be for rare but important diseases. This may in effect be the means by which the consumer can pay for supporting future drug discoveries without deliberately re-distributing resources through the government. Programs such as MAC and the policy of generic substitution, product liability and proliferating regulatory requirements further complicate the tenuous profitability structure for R&D investment. The focus of federal attention should shift away from excessive and narrow considerations of pricing (which, to possibly save consumers a few dollars today, may result in loss of new drugs which could result in truly substantial economic and health savings tomorrow) and of misguided interpretations of monopoly ascribed to a few novel, successful agents.4,5/ Instead, efforts should be re-directed to serious threats to future technical innovations. Influence should also be brought to bear on other countries, since many of these, even some highly industrialized countries without significant input in innovational R&D, apply unrealistic controls and disregard patent conventions. The American consumer may be unfairly asked to carry the burden of disproportionately supporting new technologies in the area of new drugs if widespread duplications and imitations are allowed.

## Characteristics of Industrial Drug R&D

In an era of enormous potential and great need for discovery, but also of abundant disincentives, it is particularly important that academia, government, and even industry be well-informed about the special skills and technical resources required for successful, innovative drug development.

It is sometimes said that basic research and discoveries should be left to academic and government research institutions, and that industry should concentrate on "applying" or "developing" those "discoveries" in the form of new drugs. Such views totally ignore the modern history and nature of drug discovery. Although it may be that basic discoveries and new principles in physics, for example, can be readily translated into applied processes or products, it simply does not work out that way in the biological and pharmaceutical research field. As noted earlier (Table 1), in recent times the vast majority of new drugs have been both discovered and developed in private laboratories. It is very likely that this will continue to be the case, perhaps even more so in the future, as discovery and development become more regulated, sophisticated, and complex. The fact is that drug development today is an extremely complex and convoluted process that requires many years of persistent collaboration between chemists, biologists, physicians, and other experts in a highly empiric fashion. It involves continual accumulation of ideas and information in small incremental steps by teamwork which bridges many different fields. A new concept in a

biological process, a new insight into the molecular events of a pathologic state, or even complete knowledge of the specific genetic basis of a disease, despite their scientific importance are not enough to "develop" a drug. These may provide the stimuli or theoretical basis for specific, concerted efforts to discover a particular type of drug, or they may allow establishment of improved biological models or testing systems, but there are such enormous gaps in our knowledge of theoretical biology and chemistry that the subsequent process of obtaining a useful drug is highly empiric, risky, and unpredictable. We have known, for example, the molecular basis of many genetic diseases and abnormalities of the hemoglobin structure (e.g., in sickle cell anemia) for some years, but these basic discoveries have not yet led to new drugs for the correction or treatment of many of these disease processes.

Even when a specific chemical lead is available, innumerable things remain to be done (e.g., synthesis of all reasonable analogs for comparative structure-activity studies in as many tests as possible) and many obstacles (e.g., numerous toxicology studies, metabolism, absorption, disposition, formulation, ease of synthesis, etc.) to be met even before testing for efficacy in man. The first introduction into humans may only serve to gain information which the clinician will convey back to the chemist and pharmacologist in order to improve the parameters of the drug under study. This discovery and development process must be continuous, intensive, and must be sustained over many years before the drug is "discovered." At many stages it must abide by complex regulatory requirements and obligations, even in the early discovery phases. Identification of candidate drugs and safety and efficacy evaluation involve an interplay which makes it difficult to identify a particular moment of discovery. It is very unlikely that in today's world such a drug would be "discovered" independently in an academic setting because the organization to do this does not exist there. In this setting it is exceedingly difficult and most often unproductive for an industrial laboratory to "take over" or assume a specific lead or discovery that has arisen elsewhere (unless it is far advanced in efficacy testing), regardless of whether this comes from an academic or another industrial laboratory.

Industrial laboratories involved seriously in drug discovery must have large groups of specialists in many different disciplines, and they must work together collectively and efficiently over protracted time periods. Even within disciplines a broad spectrum of specialists must be present to obtain optimal scientific cross-fertilization and to exploit various leads and ideas simultaneously in many systems. Close communication, scientific curiosity, motivation for achievement and excellence, astuteness of observation and cognitive and technical skills must all be present to seize on the unexpected. Often work in one area will lead to a "spin off" in another area. In our company, the extraordinary discoveries by Dr. George H. Hitchings in one particular basic scientific field (i.e., purine and pyrimidine biochemistry)

led to the discovery of drugs important in treatment of such diverse diseases as malaria, gout, bacterial infections and cancer, and for kidney transplantation, yet these were not diseases which were originally "targeted" for attack by the basic scientific work which was very broadly based in biochemistry. The principal "targeting" comes from being consumed in the drive to have one's basic work lead to the discovery of a new drug, in any field, and from having the organization, resources, and motivation to assure the realization of a final product.

Industrial laboratories of research-based companies must undertake substantive basic or exploratory research if they are to have things to "develop" in the future. The distinctions betwen basic and applied research in drug discovery are meaningless, for these merge ever so closely, and they go hand-in-hand. Some of the most important "drug discoveries," such as the contributions of Pasteur, Ehrlich, Fleming, and Domagk would today be classified as "applied" research. The contemporary "applied" research of industry is equally challenging and meritorious, and in addition it continues to contribute important fundamental knowledge to the general scientific base. Science in industry is not bureaucratic or rigid, as some might believe, but science there is the same as elsewhere except that collective, multidisciplinary efforts are the rule, and there is a compulsive drive for discovering new therapies. Academic labs, in contrast, are highly discipline-oriented, and the obsession with individual discovery, achievement, public recognition, and "advancement" further restrict interdisciplinary approaches, especially over long periods. The primary objective and underlying motivational forces are excellence in basic discovery, for its own sake, publication, and generation of research funds to keep the cycle going. In addition, mandates to teaching and training further underlie the differences in the nature of the objectives.

The process of drug discovery and development today is vastly different from that which existed prior to 30 to 40 years ago. Failing to recognize this, many today still look back naively to earlier eras to describe examples of how independent academic laboratories can contribute to drug discovery. The changes that have occurred during the last decades, however, have been truly pervasive. Biological and medical sciences have in themselves progressed dramatically, becoming highly sophisticated, complex, multidisciplinary, molecularly oriented, and expensive. Regulatory factors have become dominant in drug research, and industrial research laboratories have emerged as new and powerful technological centers. Importantly, the nature of academic research has also undergone significant evolution in form and objectives. The impact of NIH and the grant system has revolutionized approaches, duration (time-range), goals, and execution of projects. There now exists an intense grant-dependency ethic, and the scientific literature and conferences have proliferated almost beyond comprehension. Today, it is not uncommon for academic scientists in biological sciences to speak apologetically of "applied" aspects of their research, as if the purity

or excellence of their basic research were to be prostituted by practical objectives. Too frequently in biology is work which is directed to "useful gains" looked upon as being less good for that reason. Yet, scientists of earlier eras are today exalted without explicit appreciation of the fact that many of these were in fact involved in "applied" research in that they continuously sought therapeutically useful goals. Many "academic" drug discoveries of earlier eras would for many reasons today be virtually impossible to reproduce in our academic centers. Most pharmaceutical scientists (pharmacists) and medicinal chemists of earlier times are today concentrated mainly in industrial laboratories. These considerations are raised not for making adverse value judgments, but to acknowledge realities.

The notion that science in industry is second-rate or inferior to that of academia is misguided, and those who hold this philosophy retard potential collaboration and information transfer between these sectors. Scientists in industry can be and, on the whole, are as well motivated, creative, imaginative, and devoted to their work as those elsewhere. The view that they are super-technicians or uninspired is totally misplaced. Yet, a degree of elitism and arrogance persists which works to the detriment of the ultimate aims of all scientists in their quest for advancement of science for the benefit of society.

In addition to maintaining strong laboratory activities in basic scientific disciplines, industry has to develop highly sophisticated laboratories and groups for toxicology, metabolism, pharmaceutical formulation, scientific information, computing, regulatory affairs, quality control, medical specialties, etc. These activities, which today can consume upwards of 70 percent of the total costs of R&D, are required to bring a compound through the technical and regulatory maze to clinical use. All these activities must always be in close communication so that they function in concert.

## Suggestions for Promoting Drug Discoveries

There are, in my opinion, no single or simple formats for promoting or encouraging pharmaceutical discoveries in any disease process or therapeutic field. The entire system of innovation must be studied and considered. As there are multiple defects in our system, so must there be multiple solutions and actions that must be considered. I have listed some areas for discussion, and although considered separately, many are closely interrelated.

1. Need for a constructive public policy supported by sound public opinion Official policy should recognize need for drug discovery and integrate this in its objectives for improved medical health-care systems. The economics of drugs versus hospital, surgical or other labor-intensive modalities must be appreciated. The central role of industry in drug discovery should be acknowledged.

2. Changes in regulatory requirements and climate Excessive bureaucratic red tape and unnecessary, baseless, and unreasonable requirements for proof of safety and efficacy must be curtailed to accelerate and streamline the drug approval process. Changes in this area could go far to restoring incentives and decreasing the enormous frustrations associated with research. Demonstration of safety and efficacy need not be compromised, but they must be based on sound scientific judgments and simple principles of common sense. Rigid regulations and FDA administrative "guidelines" and "standards" (such as GMPs, GLPs, Clinical Practices) become petrified and inflexible over time. They not only require establishment of complex and costly systems to deal with them, but worse, they also in themselves discourage creativity and imagination. New tasks and challenges must be accommodated to preconceived "standards," and exploratory research (e.g., in toxicology) is discouraged because of fear of "inspections" that do not recognize this. There are intrinsic incompatibilities between originality and conformity with standard procedures cast in iron. In my opinion, development and approval processes could be substantially accelerated without compromising scientific principles or safety considerations.

Over the years, regulatory standards and requirements have become progessively entrenched and accepted, and it is more prudent and expedient for the regulated to adopt and adapt rather than fight losing battles that leave them behind and may incur the wrath of the holders of power. It is amazing but understandable how readily new proposals are accepted or even anticipated by the regulated, regardless of costs and logic involved. A system has consequently been deeply ingrained that will not only be difficult to change but even difficult to understand.

Clinical research in particular needs attention, for we are even now heading into ever more restrictive regulatory constraints that severely hamper investigation of new agents in man. Investigators are being literally scared away by, or are finding it professionally repugnant to deal with, the regulatory framework of clinical drug research. The increasing administrative red-tape, continuous monitoring (by drug firms and regulatory bodies), purposeless "standardization," scrutiny and caution of institutional review committees, patient consent requirement, responsibilities for future latent drug effects, etc. are becoming so overwhelmingly demanding on the academic clinical drug investigator that there is a serious risk that the creative, competent clinicians in this area will be driven away altogether.

Another complication is that we have entered an era where, for the sake of "objectivity" and scientific "control" of clinical data, detached principles of statistical theory sometimes virtually dominate performance of clinical studies and trials. This often leads to mad demands that defy simple logic, good medical practice, primary objectives, and even ethics.

Paradoxically, in our experience, the more novel the drug, the

more difficult and tortuous the process, presumably because of the FDA's lack of experience in that area (together with the spirit of extreme caution). The extraordinarily slow process of clinical research increases costs enormously, decreases the crucial feedback needed in the laboratories to introduce further improvements (thus, breaking an essential cycle), and dampens the morale and interest of scientists. We are currently studying some very interesting fundamental chemotherapeutic leads for leishmaniasis, trypanosomiasis, and malaria. These have arisen from tangential research efforts ("spin-offs"), not from directed, deliberate efforts targeted to these diseases. Given the difficulties and expenditures that we are encountering in clinical studies of new drugs intended for important diseases of the United States, we are frankly very discouraged with the potential problems that we would face should these other drugs for tropical diseases merit study in man.

For diseases of developing countries a very serious problem is that present law prohibits exporting a drug even for investigational purposes until an IND has been approved in this country. If the disease is very rare or does not exist in this country, it is extremely difficult if not virtually impossible to perform studies abroad under the rigid requirements of the FDA IND system. Certainly, this provision must be re-examined if United States scientists are to be encouraged to develop drugs for such diseases. Equally significant, the fact that our existing laws prohibit export for sale of any drug unless it is approved for sale in this country does not particularly encourage discovery and development of drugs intended for diseases which only exist in other countries -- and to which it is not possible to export.

3. Strengthening of patent systems Because patents and trademarks are among the few mechanisms by which R&D investments can be protected once a drug reaches the market, they are a crucial component of the viability of industrial innovation. Since the development period is now so long, more than half the patent life may have expired by the time an ordinary new drug reaches the market. This, together with the ease with which many pharmaceutical patents can be copied, challenged, bypassed or infringed without retribution, is causing increasing problems for the innovator even if the drug does reach the market. It must be more widely appreciated that, without the exclusivity that patents potentially provide, it is likely that industrial R&D and innovation would virtually cease since in this industry technology is too readily assessed and copied and thus trade secrets give virtually no protection.

Anything that can strengthen the patent system, or increase the useful life of drug patents, will add substantial vitality and effort into R&D investments. Insofar as many foreign nations do not honor or enforce patent or trademark laws, further discouragement arises. This becomes particularly serious for drugs intended for primary use in diseases of developing nations.

Many potentially useful agents may be known chemical compounds or may otherwise not be subject to strong compound patent coverage. For obvious reasons most pharmaceutical companies will be very reluctant to invest in development of such compounds since there is no protection from copiers. Developing an alternative patent or regulatory policy for such compounds would be encouraging to industry and could result in many new additional medicinal agents. Another change which would substantially help would be the strengthening of use patents by not requiring mandatory or compulsory licensing in such cases.

An interesting alternative possibility that could to a large extent mitigate the decreasing strength and value of current patent systems would be to assign to the innovator company, through regulatory statutes, a period of marketing exclusivity irrespective of any patent consideration. If this period were to be for 10 to 15 years, it is very likely we would see a very significant stimulus in many areas of drug discovery. It must be remembered that currently many laboratories understandably spend an inordinate amount of effort and time to find the compound which within an active series possesses greatest "patentability." If no compound patent protection can be obtained, for example, because of prior art citations, it is very possible that the entire series would not be pursued further.

The assigning of patent rights of discoveries made in universities with public funds to those universities and inventors, with their right to sublicense on an exclusive basis, would help in maximizing the ultimate public benefits of those funds. Industry will be understandably reluctant to invest heavily in costly development programs unless there are some assurances (e.g., through patents) that a reasonable return on that investment can be recovered should the product prove to be useful. A simple fact needs emphasizing: the best potential drug or discovery will not do any good to anyone unless it is developed and manufactured (by an industrial source), and the latter will not be done without some incentive which embraces economic protection.

4. Direct government support and involvement

a. Programs in basic research and academic-industrial joint efforts There are several forms of direct federal support that could promote new therapies (drugs and vaccines) for diseases of developing nations, but in my opinion these would be, in themselves, of limited (but definite) value unless truly massive resources (probably unwise) were to be devoted to this effort.

Basic research grants in tropical diseases to academic institutions, administered through NIH or other governmental agencies through established competitive channels, would certainly be of value. The principal impact would be to focus general attention and interest on these diseases by the American scientific community. This would provide visibility, acceptability, and excitement in this field. It would

encourage healthy research competition and general awareness. It would probably be wiser not to encourage "targeted" objectives of drug discovery or to fix unreasonable time requirements, but instead provide for long-range fundamental research which the academic community is better equipped to handle. Funds could probably be relatively modest since the realistic objective would be to kindle and ignite interest rather than solve all the problems. The value would be largely in the form of important intangibles. Workers in other fields, for example, would begin to think about the problems, and discoveries in apparently unrelated fields could eventually be most decisive for the long-term goals of discovering new therapies. An effect of this type of improvement of general awareness and credibility of this field of study would be to encourage industrial laboratories to initiate programs in tropical diseases, which would be integrated with their other research activities. It would be less wise and reasonable for industry to ignore activities in areas receiving such important national attention.

Such programs should also encourage collaboration with industrial institutions, and joint ventures should be actively promoted. In my opinion, the American research establishment has an enormous, untapped potential for meaningful academic-industrial joint research endeavors in all fields, including tropical diseases. Historically, there has been a void in communication which is most unfortunate because the resources, skills, and expertise are intrinsically complementary and mutually reinforcing. Maximal utilization of our national resources would require that potential collaborations between these sectors, including NIH, be fully developed.

What can be done, then, to foster the potential symbiosis of aca demic (university and research institutes) and industrial laboratories? Clearly, artificial barriers have existed that can be dismantled, if the reasons could be fully understood. In my opinion, several correctable factors have prevailed to separate these research communities. Traditionally, industry itself has avoided involvement with programs funded by federal monies since these generally have carried patent and ownership provisions which would conflict with potential proprietary rights, and thus restrict economic opportunities and returns on investment. Furthermore, in the past there has been a general philosophy that federal funds should not be expended in any way that could promote the "profitability" of institutions in the private sector, and that it would be inappropriate to utilize public funds to aid industrial programs or developments. Thus, it has generally been held that discoveries resulting from government-sponsored grants belong best in the "public domain." However, such policies virtually assure that no one will undertake the process of commercialization in order to deliver a product to the consumer! There has been an almost obsessive fear of "misuse" of public funds that may in many cases have actually worked to the detriment of both public and private objectives. Relaxation and enlightened patent policies in this area are in my opinion not only possible but necessary if all our resources are to be

used effectively. A deliberate policy to merge certain academic-industrial research activities could be easily promoted while protecting potential discoveries, patents, and commitments such as to ensure that the industrial establishment will have adequate incentives for continued development. An imaginative approach in this area, with incentives to both academia and industry, could prove very fruitful.

Another factor that has deterred collaborations has been the misunderstanding by many academic centers of the nature and quality of industrial research. The quality and creativity of science in industry are often underestimated, and sometimes their motives are suspect. This is most unfortunate since the level of scientific accomplishment, motivation, and dedication is very high indeed. Industrial scientists work quite independently and in the same overall framework and use the same tools, concepts, and theories of science as do all other scientists. Just as the objectives and type of research vary widely among various disciplines within the academic community, so are there similar differences between the orientations of some academic and industrial scientists. Scientists in basic pharmaceutical research laboratories are given considerable freedom and latitude for creative expression, a fact not generally well understood. For substantive, productive collaborations to materialize, it will be necessary for academic scientists to recognize and respect their counterparts in industry because collaborations must be based on equal terms and mutual respect and trust. Greater visibility and recognition of the scientific accomplishments by industrial scientists can be of help.

If consideration is to be given to funding and establishing special research centers here or abroad which are to be directed to the conduct of studies in tropical diseases, attention should be given to some of the concepts described in this essay that relate to drug research. Care must be taken not to simply create segregated "centers" of tropical disease research. The most productive and cost-effective research in restricted disease states is likely to be conducted under conditions and in an environment which is as broadly based in scientific and medical research as possible. It is likely that establishing relatively isolated "pockets" of strength in a particular tropical disease, although perhaps scientifically sound, are not as likely to yield new drugs. Likewise, it is naive to believe that setting up screening centers to which pharmaceutical companies will send all the compounds off their shelf will be a fruitful exercise. This is simply not the major way drugs are discovered or developed. Meaningful programs in tropical diseases must be closely integrated with other programs which are basic and broadly based in many disciplines. The key to success in this area will be to introduce testing systems and research programs as an integral component of the totality of research activities in a particular setting. This applies to academic and to industrial laboratories. Similarly, it is most likely that successful innovation in drug discovery for these diseases would arise from tackling these problems in the already sophisticated and advanced laboratories of the most

technologically advanced nations instead of setting up de novo centers or institutes in countries where the diseases are prevalent but technology is inadequate. The fastest and most economic approach is not to literally "transfer the technology" across oceans but to challenge those who already have the technology to transfer it internally by the incorporation of additional objectives and programs. In industrial laboratories, new programs and testing systems could be established and tied in with ongoing research relatively easily if the relevant incentives and promise for follow-up and economic rewards genuinely existed.

b. Federally sponsored clinical evaluation programs This most important area could very substantially stimulate and encourage new discoveries and facilitate development of others that may actually already exist but that linger for lack of proper testing capabilities in man. Although it may seem paradoxical, it is in this area (i.e., testing and evaluation in clinical settings), instead of in basic or applied research or discovery, that industry could use help. In addition to difficulties related to availability of proper patient populations for study, especially for diseases of developing nations, many other general problems exist in this area which industry R&D is not as well equipped to handle as are academic and government institutions. Clinical research is becoming increasingly difficult because of FDA, HEW, regulatory and ethical considerations and constraints, and the increasing sophistication of properly controlled clinical trials. Although fundamental knowledge of clinical research, study design, statistical analysis, etc. are well developed in industry, studies must nevertheless be conducted by institutions outside industry by clinical investigators with specialized experience with particular medical problems.

Federally-supported clinical research programs conducted through university hospitals or similar institutions would have the advantage for government of having readily identifiable parameters that could be publicly scrutinized and monitored. For example, contract programs to universities or other relevant facilities, administered through federal institutions, such as the NIH or the Armed Forces, could be established. Such programs could be justified to the public because benefits to society would be easier to assess at this stage. Programs in diseases in need of therapies, or rare, "orphan" diseases, including diseases of developing countries, could be specifically selected to spur and encourage interest and development in these areas. Industry would have little trouble accepting public support of this nature since admitting this kind (i.e., clinical) of data into the public arena would not compromise its patent or other ultimate rights to drugs. In fact, in my opinion industry would welcome help in this area, especially since the data would likely be of high quality and would have public and regulatory recognition because of having been generated in the public domain and of having been performed under auspices of independent third parties. Some such programs already exist under sponsorship of NIH, such as the extensive cancer testing programs of the National Cancer

Institute, the anticonvulsant testing of the Epilepsy Branch of the National Institute of Neurological Diseases and Blindness, and the antiviral testing of the National Institute of Allergy and Infectious Diseases. These and similar programs are already having an important impact in encouraging drug development. Perhaps from these we can learn something that could be applicable to tropical diseases, but some obvious involvement of WHO or other international organizations would be invaluable.

c. Improvement of drug and medical care delivery systems in developing nations Whatever can be done to improve general health standards and systems of health care will enchance the likelihood that new (and already available) drugs will reach those who need them. Improvements in these areas will undoubtedly encourage industry to devote greater emphasis to diseases prevalent in these countries.13/

Within the broad subject of prevention of diseases and nutrition-related health factors in developing countries, control of insect vectors of diseases by new insecticides, and control of parasitic diseases in food-producing animals deserve some mention. The veterinary research programs of major American pharmaceutical companies recognize the close interplay between drug development for both medical and veterinary indications. At this time, industrial research is providing one of the few effective bases for coordinated efforts to develop veterinary medicinals and insecticides.

d. Direct subsidies to industry by government In my opinion, such mechanisms of sponsoring drug research programs would be of little value and would not likely be acceptable to many in industry. Industry already has the potential expertise and organization for such research programs. The reason it may not be pursuing these areas as vigorously as it could is not so much lack of additional funds required for those specific programs, as the increasing disincentives to basic research programs in general and the perceived, economically unproductive nature of drugs in this particular area. Equally important, research activities in all therapeutic fields are so interrelated in industrial labs that it would not be possible to clearly distinguish exactly which activities had and which had not been supported by federal funds. Since this could challenge the propriety or ownership of unexpected discoveries and "spin-offs" in other areas, I suspect that most in industry would not use such funds unless they were in very well-defined areas (e.g., vaccines). Overall, this form of support would generally be short-sighted unless it were coupled to other major changes in attitudes and legislation affecting the industry.

It must be remembered that once a candidate drug has been "discovered" in the laboratory, the actual costs incurred in having made that discovery are very likely to be minuscule compared to subsequent costs of developing that drug for introduction to the market. However, the real costs of the research for that particular discovery are actually

the costs of maintaining the entire research programs of that company, including the many things that fail. There are many "discoveries" of chemicals with potentially useful properties which do not survive the rigorous safety and efficacy evaluations required before introduction into medical practice. Even considering only those drugs that are introduced for formal study in man (as IND), less than 10 percent are ultimately submitted (as NDA) for marketing approval.11/

e. Special tax incentives for industrial R&D expenditures Special incentives would certainly be achieved by allowing additional or special tax benefits, allowing for capitalization of such research investments to those pharmaceutical companies who invest a substantial proportion of their sales in R&D.

5. Identification of new lines research In my opinion, innumerable, exciting opportunities exist for applying our current body of fundamental knowledge and technology to diseases of developing countries. As we have already heard, advances in concepts and technology provide sound foundations for rational attacks on the basic causes of these diseases. The tools of molecular biology, protein chemistry, molecular modeling, and comparative biochemistry are now particularly powerful for understanding and possibly controlling diseases caused by parasitic, rickettsial or bacterial agents, or those mediated by insect vectors. Several parasites can now be cultivated in tissue culture under controlled conditions, providing new opportunities for biochemical studies and for characterization. Identifying specifics of what can be done, or particular strategies in specific disease states, is not the real problem since these are well known to specialists in the laboratories. The scientific details of programs will be forthcoming provided the overall climate is such that it will allow and encourage these scientific opportunities to express themselves through the best suited, natural, and economic channels.

## Summary

The optimal means for encouraging new drug discovery for diseases of developing nations are primarily to deliberately acknowledge the desirability of drug innovation in general. If trends which now discourage or prevent drug discovery in general can be reversed, I am confident that today's advanced state of science and technology will in the future provide society with new, innovative therapies for many diseases, including those occurring in developing nations. In order to begin to reverse the currently reduced degree of commitment to drug discovery, and the prospect of an ever dwindling rate of new drug introductions, it is essential to understand the complex forces, mechanisms, and sources involved in drug innovation and discovery. The pivotal role of the research-based pharmaceutical industry in this process must be clearly acknowledged and fostered.

## REFERENCES AND NOTES

1. In this essay "drug discovery" is used primarily to denote the process of identifying candidate drugs while the closely related process of "drug evaluation" involves several sequential stages of drug safety evaluation and clinical efficacy trials. As will be discussed, for important medical diseases which are virtually nonexistent in this country (e.g., Chagas' disease, filariasis, malaria), American industry has sound resources for "discovery" but will need cooperation with developing countries and government agencies for the phases of drug evaluation.

2. A notable exception may be found in the National Cancer Institute's cancer testing (and screening) program, which, however, has been extremely expensive and is directed not so much to a true drug discovery process as to testing of compounds synthesized by other sources.

3. This has occurred largely through funding by the government, which ironically has been inhibiting its use.

4. Schwartzman D: Innovation in the Pharmaceutical Industry. Baltimore, Johns Hopkins University Press, 1976

5. Regulation, Economics, and Pharmaceutical Innovation, Proceedings of the Second Seminar on Pharmaceutical Public Policy Issues. Edited by JD Cooper. Washington, DC, The American University, 1976

6. De Haen P: Compilation of New Drugs, 1940 through 1975. Pharmacy Times, 42:40-74, 1976

7. Participation of industry in development of drugs for tropical diseases is not a new or recent commitment. It is of historical interest that establishment in 1901 of the Wellcome Tropical Research Laboratories at the Medical College of Khartoum in the Egyptian-Sudan actually preceded that of the research center in London which was later named the Wellcome Laboratories of Tropical Medicine. There has been a continuing allocation of resources within the Wellcome Research Laboratories to research programs from which candidate drugs are identified for evaluation against parasitic, viral, and bacterial infections.

8. A just-released two-year study sponsored by the National Science Foundation 10/ has concluded that there has been a real and continual decrease in industrial basic research which should be of serious national concern. This trend was seen as "another

manifestation of the existing poor climate for private enterprise that is observable in the unwillingness of corporate management to commit resources to the future -- i.e., take risks." Among several factors responsible, the effect of the regulatory environment was described as "pernicious," and in this context "the problem is that these ruinous outcomes on fundamental research activity are never direct -- they impact on the way an organization sets R&D priorities." The study concludes that "many steps must be taken by the public sector to improve the climate for risk taking in the private sector."

9. The long history of efforts and contributions in tropical diseases by Burroughs Wellcome and the Wellcome Foundation has seen some notable accomplishments: successful development of yellow fever vaccine (1928); introduction of sulfones for treatment of leprosy (1938); discovery of pyrimethamine for malaria (1952); and use of methisazone as the first antiviral agent effective against smallpox (1963). A continuing effort in chemotherapy and on development of vaccines for parasitic diseases are part of the continuing research effort.

10. Support of Basic Research by Industry. Report prepared for the National Science Foundation by a grant to Industrial Research Institute Research Corp and Rensselaer Polytechnic Institute, 1978

11. Wardell WM, Hassar M, Anavekar SN, Lasagna L: The Rate of Development of New Drugs in the United States, 1963 through 1975, Clin Pharmacol Ther 24:133-145, 1978

12. For example, of the 79 NCEs introduced between 1962 and 1968, the majority achieved less than $2 million in sales in 1972, and 33 (42%) were under $1 million.14/ Only eight achieved a level of $16 million, a figure computed to be necessary 4/ to achieve a return on investment of 10 percent after taxes.

13. It is generally recognized that many developing nations cannot "afford" available drugs, and the solution to this problem has often been directed to the pharmaceutical industry. Industry is asked to make these drugs available free or at cost, for humanitarian reasons. This philosophy unfairly ignores the basic nature, objectives, and functioning of this industry. Furthermore, and more importantly, it apparently does not recognize that procurement and delivery of health care and drugs is basically the responsibility of the State, and that subsidization must therefore derive from public bodies and not from private firms.

14. De Haen P: New Product Survey and Nonproprietary Name Index; and U.S. Pharmaceutical Market, Drug Stores and Hospitals, IMS America, Ltd. (Note: new esters and salts are included in sales of the new single chemical entity.)

## DISCUSSION: THE SCIENTIFIC BASE: OPPORTUNITIES FOR RESEARCH

DR. LEDERBERG invited Dr. Lucas to comment on Dr. Cuatrecasas' advocacy of centering basic drug development research in places where the requisite expertise exists, instead of centering it in countries where the diseases occur.

DR. LUCAS, agreeing generally with Dr. Cuatrecasas, emphasized the necessity also to strengthen clinical research centers in developing countries, where clinical evaluation of new drug compounds must be performed. He acknowledged that the majority of new drugs would come from industrialized countries, where screening and testing of compounds in the initial stages can be done far more efficiently.

DR. CLUFF was interested in the imperative to find new avenues of communication between the scientific community and the industrial world. Referring to Dr. Cuatrecasas' pleas for improved relationships between the academic and industrial research communities, he requested the panel to address the question of how better communication can be fostered.

DR. JOHN URQUHART, drawing on his personal experience in both worlds, compared the narrower focus or perspective in the academic world, which digs deeper into the scientific base of problems, with the broader range and shallower depth in industry's search for practical applications of new discoveries.

DR. LEDERBERG deplored the fact that graduate students in the basic biological sciences have very little exposure to industrial perspectives, or understanding of the drug development process. He agreed that the overwhelming majority of practical new drug discoveries have come from industry, and sight should not be lost of the relative order of rule between academic and industrial contributions.

DR. de MAAR said that WHO had faced the same lack of communication between industry and academia in the early days of the Tropical Disease Research Program. A helpful solution was development of the Scientific Working Group concept, which brought together for continuing dialogue scientists from industry and from academia, and from developed and developing countries. This relationship between the industrial and academic communities has proved mutually advantageous and complementary.

DR. SEYMOUR COHEN remarked that the organization of this Conference is an indication of the deteriorating position of academia as compared with industry and government. He noted that the first two days of the

Conference were devoted to policy questions without considering the content of scientific issues that should have been examined first or as a basis for developing sound policy. Thus, there has been no overt recognition of the fact that progress in infectious diseases research generally will heighten the probability for also making useful discoveries or finding solutions to the problems of tropical diseases. One cannot consider tropical disease research separately from infectious diseases generally, since the scientific aspects of these two fields are intrinsically linked.

DR. ALVAN FEINSTEIN pointed out that the attitudes of his academic colleagues also serve to block communications with industry. He characterized the prevailing feeling among academics that they were "noble knights on horseback" holding the "evil dragons of industry" at bay. The profit-making motives that influence industrial decisions are analogous to the power and influence motives which pervade academic power struggles.

DR. LEDERBERG summarized by noting that: industrial and academic scientists belong to the same species, Homo sapiens.

# INTERNATIONAL HEALTH POLICY INITIATIVES

United States Senator Jacob K. Javits

I am especially pleased to be here today to address this prestigious gathering of American and foreign experts on international health. I would like to commend David Hamburg for his leadership in calling this Conference, Lee Cluff for his role as chairman of the Conference Steering Committee, and Harold Simon for his thorough staff work in preparation for the Conference. I am very grateful that the Surgeon General, Dr. Julius Richmond, is here, and other such distinguished New Yorkers as Joshua Lederberg and Jim Henry.

Most of you know of my long-standing commitment to alleviating the problems of disease and disability throughout the world. Few people know that my interest in international health first began in the 1930s when I was involved in establishing so-called sanitary organizations in Latin America.

Over the last three decades, I have been one of the major advocates of our foreign aid program and often its sponsor in the House and Senate. I have come to the conclusion that there is no single thing that has a greater benefit to every level of society and that pays off better than health care in developing countries. I might say also that this has been confirmed by the many authorities whom I've talked to and who have helped me to learn this. I want to mention, in particular, Kevin Cahill of New York who is now the medical and health advisor to Hugh Carey, our Governor. He has been instrumental in educating me and in encouraging my leadership in this area.

I have been the author of the last two comprehensive international health bills in the Senate. In 1971, and again last year, I introduced major legislation aimed at coordinating, strengthening, and renewing our federal programs to meet health needs of developing nations. My bill would revitalize international health programs in this country by establishing better coordination among the 22 different federal agencies which expend $600 million on international health, by strengthening our manpower development and training programs, and by upgrading the tropical medicine research programs at the National Institutes of Health and at the Center for Disease Control. The bill was based in

part upon the excellent report published by the Institute of Medicine last year on international health. I was honored that Senator Schweiker joined with me in sponsoring the bill of last session. Today, I announce my commitment to introduce a revision of my comprehensive bill in this area. I invite your comments and support as that legislation is considered in the Congress.

I will consult with the Institute of Medicine and with Jim Henry's Center for Public Resources, with the Surgeon General and with our aid authorities. Also, I have visited with leaders of the World Health Organization, seen some of its departmental heads and recognize the deep problems which they face in the monumental task of alleviating suffering from diseases of various kinds.

Your concerns at this Conference, however, are somewhat narrower in scope than the subject of my legislation. You are interested specifically in pharmaceuticals for developing countries. But the light you have shed at this Conference has served to illuminate a far graver problem. As the eminent British stateman, Benjamin Disraeli, said:

> The health of the people is really the foundation upon which all happiness, and all their powers as the State, depend.

I believe as Disraeli that the vitality of mankind can only be measured by the health of each man, woman, and child. The magnitude of this challenge is mindboggling.

I fear that the barrage of staggering statistics of death and disease in far-away places has had such a numbing effect on our sensitivities and awareness that they represent mere numbers rather than a chilling reflection of human tragedy on a global scale.

Every year 15.6 million children under the age of five die, almost all of them in the developing countries of the world, most of which are located in the tropics. This is nearly twice the population of New York City; it is five times the number of children born in the United States each year.

More than 700 million people still live in absolute poverty, defined as per capita income of $200 per year or less. This amounts to almost 40 percent of the developing world's total population.

How can we change this situation? -- a situation which is really an ongoing war against humanity. No army -- not even the most awesome military machine -- has caused more misery and destruction. The question that is placed before us, then, is how can we best fight this seemingly invincible enemy of disease and pestilence?

The topic of this Conference -- Pharmaceuticals for Developing

Countries -- is important. However, I strongly believe that we cannot restrict our concerns to this topic if we are really to address solutions for alleviating the pain and suffering of millions of individuals in the developing world.

Pharmaceuticals are tools which have therapeutic potential. But we must ask if pharmaceuticals are appropriate tools alone for eradicating the causes of poor health conditions in the developing world. Simply put, I believe that health conditions in this large part of the world cannot be viewed apart from the economic, environmental, cultural, and social conditions which exist in these countries. The core disease patterns, as I understand them, are due to infectious and parasitic agents. In order to effectively control these diseases, it is essential that water supplies be made safe, that there be sanitary waste disposal, that housing be adequate, that nutrition be drastically improved, and that environmental determinants of disease be controlled.

Our experience in the western nations has shown conclusively that dramatically improved health status is directly related to such public health measures which are in turn a function of rising overall economic development. The role of any single therapeutic agent has been of comparatively minor significance. What is accomplished by curing a man of a parasitic disease if he continues to live in the same environment and will become host to that parasite again within a short time? We accomplish our objective only if we cure the stricken and eradicate or control the parasitic source at the same time.

I am committed to a broad-based, multinational approach to solving these problems. Responsibility for this effort must be shared by nation-states, international, and national voluntary organizations, financial institutions, academia, and the private sector in partnership with one another.

For these reasons, we must involve ourselves in an unprecedented effort to attack health problems of developing nations.

I wish to discuss the public service responsibility of the industry for joining in this effort. Yes, the private industry. The United States has been responsible for two great concepts in private enterprise, which -- if freedom prevails -- will be the reason why it did. I deeply believe, and I feel most of my fellow countrymen also believe this, that unless you have the great preponderance of people of our society who wear two hats -- one in the private economy and one as a citizen, you cannot preserve freedom. Once the government requires the citizen to wear one hat, freedom is finished. So, the two lessons which we have taught the world are: one -- in business it is not necessary for A to lose so that B can gain. It is possible for both A and B to profit. This is the lesson vary well learned -- it is the whole gifted key to the American business system. The other lesson, which is now just being learned, especially by the larger companies of the

United States, is that when you are the head of the company, you are also a public official. A successful enterprise must make its fair economic as well as social contribution. The strengths, the disciplines, the devotion of resources, including research resources, must be applied to this public responsiblity.

We must convene as soon as possible an International Health Congress, under the auspices of the White House, to which nations, the voluntary organizations throughout the world, the financial and academic institutions, and the various interests in the private sector must send representatives to work out strategies and tactics that society must use to attack problems of debilitating health. I believe that in such a Congress the international pharmaceutial industry must play an essential role, a follow-up, if you will, to conferences such as this.

In this Congress, representatives of the pharmaceutical industry should be prepared to discuss and to solve two distinct sets of problems with respect to health policy. The first set of problems arises in the situation where there is a safe and effective drug already available that is needed to treat patients in a developing country.

Should the drug industry provide these drugs at cost or at a loss? Should there be an international fund to pay for these health care needs based on some percentage contribution from receiving nations? What should the United States foreign aid program's policy be with regard to subsidization of such costs? And, importantly for this Conference, what is the involvement of the pharmaceutical industry in the development process?

The United States and other countries around the world have mounted developmental assistance programs through the years which have sought to assist developing nations in improving conditions there. United States aid efforts have adopted a basic human needs approach that focuses on the poorest people and their achievement of self-sufficiency to obtain the necessities of life and to bring them into the market economy. This approach recognizes that developing countries are characterized by dual economies and attempts to involve the poor in movement toward economic development.

Right now, the pharmaceutical industry is expanding in the markets of the newly industrialized countries, such as Brazil and Argentina, that have affluent and rapidly Westernizing strata. It is clear that the industry has benefited from newly industrialized countries that have undergone dramatic transformation in a relatively brief time period and have a strong appetite for developed countries' products and services.

It is the poorest countries and the poorest populations, however, that have the most desperate and fundamental need for our health and

pharmaceutical technology. While the poorest people and countries are not yet participating in market economies, the potential demand for health products and services is immense.

Only economic development can translate this desperate need into market demand. The responsibility for development has been delegated to official assistance programs and international aid institutions. However, I do not believe development will occur without the essential factor of private sector participation and involvement.

For humanitarian reasons I would like to see private industry play a larger role in the development process because of the tremendous benefit to millions of people through the improvements in living standards that would result. However, I believe the pharmaceutical industry has an extremely pragmatic interest in furthering economic development. Only when the developing countries "take off" will they provide new markets for pharmaceutical products and services.

The industry itself must decide what their role is and the extent of their involvement in the development process -- specifically public health. However, it is undeniable that, as developing countries progress toward economic realization, they will benefit the pharmaceutical industry. Therefore, I urge the industry to support international foreign assistance efforts. In the long-term, foreign aid and the economic development it fosters have tremendous implications for the industry represented here today.

I also believe that the challenge of improving international health must be undertaken by a partnership of government and business. This joint effort approach is the basis of a proposal put forward by the President that has important ramifications for the health industry. The proposed Institute for Scientific and Technological Cooperation (ISTC) is an institution that will identify critical problems of developing countries and apply technological expertise toward their solutions. An example of an ISTC project might be to finance studies on causes of vaccine and chemotherapy failure in tropical countries or to develop current satellite technology for use in mineral exploration and planning natural resource development.

An advisory council drawn from private industry, universities, foreign participants, and other institutions will develop priorities on which basis ISTC will make grants and contracts. This is the kind of imaginative and long-term thinking that I believe would be of immeasurable service to developing countries and to the United States pharmaceutical industry.

In addition to acquisition problems -- who pays -- there is the very serious problem of an appropriate delivery system. Many developing countries have attempted to model their health delivery systems on the Western style, with super-specialized, hospital-based care, which

may in fact use up 75 percent of that nation's health care expenditures and serve fewer than 25 percent of the people. In most developing countries, the greatest health needs are located in the often inaccessible rural areas. Such rural populations may have little access to drugs, let alone other health care and follow-up treatment.

These complex questions can only be tackled, and solutions found, in the context of an International Health Congress at which the entire universe of health needs and solutions can be discussed in full context.

I raise this issue to challenge you who are attending this specific Conference to wrestle with the full seriousness and complexity of the problems associated not only with the use of existing drugs to treat patients in developing countries, but also to recognize that the health needs of developing countries require much more than treatment which can be provided by drugs.

The second situation I wish to discuss is one in which a clearly needed safe and effective pharmaceutical has not yet been developed. This situation raises serious questions about the responsiblity of the drug industry to engage in needed types of drug research in the face of uncertain economic rewards. What incentives can be created to attract the industry's capital to these activities? Should United States companies be required to engage in this research? And if so, shouldn't non-United States companies be treated similarly so as to maintain equity among their contributions? If the private sector is unwilling to undertake this effort, should the government enter directly into drug research and development?

I realize that this Conference is designed to address these issues. However, I believe that research and development in a wider range of health areas is needed to address the immediate problems in achieving improved health status in the developing world. I do not believe that activities in drug research alone will achieve that objective.

I believe that we can address the need for a wider range of health care solutions in an International Health Congress. Such a Congress would remind us all of the complexity of the problems of the developing world, many of which are reflected in the health status of their people. An International Health Congress would emphasize the need to address health-related problems by a coordinated, multifaceted, and multidisciplinary approach that is directed not only at the symptoms of disease but also and most importantly at the causes of disease.

In addressing international health we cannot forget that there can be no economic development in a community if the people are ill and dying. And there can be no real solution to the health condition of a people without some economic development. What is needed is a coordinated plan for dealing with these interrelated conditions.

An International Health Congress could provide the umbrella organization to begin dealing with the complex issues that translate into the deaths, disfigurement, and debilitation of men, women, and children the world over.

The United States and other countries around the world have mounted developmental assistance programs through the years which have sought to assist developing nations in improving conditions there. Unfortunately, as a proportion of gross national product, United States aid has fallen from half of one percent in 1965 to one-fourth of one percent in 1976. The role of the United States in these efforts must be increased but in such a way as to involve more nations, as well as involving private industry and the voluntary sector.

Some have said that there are insuperable obstacles to substantially improving the health of millions of people. Some argue that there are political, economic, and cultural barriers which can never be overcome, and therefore we must simply make what limited effort we can to extend the benefits of Western technology and achievement to those classes in the Third World who are able to utilize and afford our level of health care. The human imperative dictates our course. We must not rest until we can overcome this tragedy in all of its complexity and in all of its breadth.

# STRENGTHENING INCENTIVES AND OVERCOMING DISINCENTIVES

# PANEL PRESENTATIONS

Introducing the panel discussion on policy implications of encouraging new efforts for development of pharmaceuticals, MR. JAMES L. HENRY advised the Steering Committee to focus not only on government relations with transnational organizations, but also on private initiatives that can be undertaken by the pharmaceutical industry. MR. HENRY underscored Dr. Hamburg's comments at the opening of the Conference about the pluralistic system existing in the United States, and the recognition that the government's resources and flexibility of action are limited. He emphasized the need to think creatively and as entrepreneurs in terms of how to bring market forces to bear on critical health needs of people in developing countries.

To mobilize the forces necessary for such developments, several tasks must be undertaken simultaneously:

1. Government must turn its attention to developing real market incentives for new drug research, or establish surrogates. These might include tax or other financial incentives, industrial revenue bonds, or specialized insurance.

2. Disincentives, such as the anti-trust laws that impede collaboration between companies, must be removed.

3. Simultaneous pursuit of public and private strategies must be fostered to create the conditions necessary for an academic and business partnership.

4. The policy and strategies necessary to stimulate and protect new technology must be developed.

In shaping these strategies, some basic realities must be appreciated. These include the limited resources available for improvement of health conditions in developing countries, and the lack of markets in developing countries for new drugs active against their endemic diseases. Such countries usually lack adequate health care delivery systems. There is also a serious time lag between the development of new pharmaceutical products and their readiness for application in

large populations.

Several recent developments are encouraging, and ought to be listed on the positive side of equation. Thus, Dr. Omenn spoke of the President's interest in fostering private initiatives to overcome problems in the developing world. The health arena probably offers greater resources of leadership and talent than almost any other field of human endeavor, thus leading to greater hope for scientific breakthroughs. The World Bank and other international organizations have had increasing interest in health investment in developing countries, with a concomitant recognition of the potential benefits.

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DR. IVAN BENNETT addressed the need to coordinate international health policy, given the many similar activities pursued simultaneously by various branches of the United States government. Much of DHEW activity in international health is barely within the bounds of its established legislative authority. Certainly, the applicable statutes might be changed. A.I.D. is the only agency specifically authorized to promote health in other nations for their benefit. The Agency has not been able to enlist the best talents in health to focus their attention on the needs of developing countries, nor has it developed the capacity to manage research programs. In countries where it has invested in health services, it has been unable to raise government health budgets to reflect a higher priority accorded such activities. Considering this record in AID over the last 15 years, perhaps the proposed Institute for Scientific and Technological Cooperation (ISTC) could become the new research arm of the United States assistance effort. It might be able to promote better career opportunities in international health and thus attract better talent.

DR. BENNETT suggested several tactics to pursue in reorienting the present government regulation of the pharmaceutical industry to promote efforts to develop drugs for use in developing countries. The inability of companies to form consortia should be reexamined and attempts to revise legislation should be made. In addition, it would be useful to revise the tax laws and remove the disincentives for such drug developments. Dr. BENNETT observed that the American pharmaceutical industry was certainly able to accomplish miracles during wartime. If a national leader declared that health problems in developing countries were the "moral equivalent of war", it might be possible to mobilize government, industry, and academia into action in desired directions. Developing country governments have found it possible to invest heavily in maintaining good health care for their armies. In fact, political considerations often result in the best medical care available for the exclusive use of the army. DR. BENNETT concluded by saying that he was nevertheless pessimistic about the possibility of developing a real

international health policy in the United States, because this country has not yet developed even a domestic health policy.

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From the perspective of the research manager, DR. BARRY BLOOM proposed to suggest actions or policy initiatives that might encourage resource allocation decisions toward increasing the level of commitment of the pharmaceutical industry to research seeking new drugs for the treatment of tropical diseases.

First, it is important to adopt a realistic perspective of what drug discovery research can accomplish. Previous speakers at this Conference have reminded of the great complexity of the challenge of upgrading health in the tropics -- of the root causes of disease, such as the gross undernutrition brought about by grinding poverty; of the critical need for hygiene education to bring about behavioral change; of the vital need for improved water and waste sanitation; and of the need for vector control. Because the ultimate usefulness of pharmaceuticals in bringing endemic tropical diseases under control will be largely, if not entirely, determined by our ability to cope with these basic needs, those who propose and fund laboratory research need to be careful not to promise more from our research than can realistically be delivered as effective health care.

Without doubt, important challenges must be met where we are limited by available technology and where investment of research and development resources by the private sector toward development of needed pharmaceuticals would be desirable. What restraints need to be removed? What incentives provided? The common wisdom holds that the major bar to more research is the necessity of the sponsoring company to earn a satisfactory return on its research investment. The implication is that previous experience with the marketing of drugs for tropical diseases has been largely unrewarding.

But it would be wrong to assume that these economic considerations alone dictate what research will or will not be done by pharmaceutical companies. Decision-making under conditions of uncertainty is never that simple. Indeed, the substantial investment in tropical disease research already being made by major firms in the United States and Western Europe could hardly be justified on the basis of projected return alone.

A more accurate perception of the decision-making process would place tropical disease research among the high-risk projects that are part of the research project portfolio of every innovative firm. Investment in this kind of high-risk research can best be encouraged in two ways: by improving the climate for therapeutic innovation in

this country; and, on the incentive side, by showing, as we have yet to do, that we can muster the will, the discipline and the insight necessary to overcome the formidable challenges, many of them not technical, that stand in the way of delivering improved health care in meaningful quantity to areas where tropical diseases are endemic; and, more specificially, to deliver health care in which chemotherapy can play a significant role.

To elaborate: Concern about the climate for innovation has become an important item on the agenda of this country. The present Administration is committed to improving that climate and has already undertaken a study entitled, "The Domestic Policy Review of Industrial Innovation," preparatory to initiating appropriate action.

The national climate within which the pharmaceutical industry seeks to innovate has deteriorated strikingly during the last fifteen years, as layer after layer of regulatory constraints has been imposed on drug research. Several bills introduced in the last Congress would effectively rewrite our drug laws. The Administration Bill clearly recognized the need to facilitate therapeutic innovation and set that as one of its goals. Unfortunately, in the view of many, the provisions contained in that bill had little chance of accomplishing that goal. Drug research experts from the pharmaceutical industry and from academia, in testimony before both Houses of Congress, offered specific suggestions as to how the necessary objectives of regulation could be met, without requiring drug research to bear such an onerous burden of regulation. The last Congress adjourned without taking definitive action on a drug bill.

Now, everyone expects that bills of similar intent will be introduced in the present Congress. Our drug laws unquestionably need to be rationalized, but it is imperative that in doing so we pay due heed to the importance of fostering innovation. The direct relevance of the issue to tropical diseases research is that unless innovation is encouraged, the research managers of the pharmaceutical industry will continue to be confronted by -- indeed preoccupied with -- the prospect of a continuing, steep decline in return on research investment. Since the research manager's overriding concern has to be a satisfactory return on the investment he manages, he can hardly be expected, under prevailing circumstances, to increase the allocation of resources to high-risk projects. In his present frame of mind, confronted by a difficult productivity challenge, he has to remain dubious about the wisdom of increasing his commitment to tropical diseases research, despite his inclination to do so for other reasons.

As regards incentive, there would be a powerful, favorable impact on research decision-makers if they were better able to see existing drug technology being applied effectively to bring endemic tropical disease under control on a substantial scale. Understandably, they harbor some very real doubts about the likelihood of that happening.

Do we have the necessary social will? Will the coalition of forces now developing to confront this enormous challenge identify and produce a focus of leadership to plan and carry out substantial health delivery programs? Will technical advisers provide crisp advice to those who must shoulder the burden of the political decision to proceed? Obviously, it can hardly be justified on either economic or humanitarian grounds to fund research, if indeed the fruits of that research have no foreseeable chance of improving health.

DR. BLOOM is convinced that this form of incentive is important because he has seen at first hand, in his own company, the dramatic impact it can have.

DR. BLOOM then referred to the massive program currently underway in Brazil to control schistosomiasis in the vast endemic areas of that country. The Brazilian program is far larger than any previous effort to control schistosomiasis through chemotherapy, comprises elements of vector control, health education, water and waste sanitation, and drug treatment. What made this massive undertaking feasible was the discovery and development by Pfizer scientists, in collaboration with experts in Brazil and elswhere, of the drug oxamniquine, which is highly effective against American S. mansoni in a single oral dose, and sufficiently well tolerated to be safely administered by paramedical personnel under the primitive conditions that prevail in areas where this disease is prevalent. In this truly ambitious program, more than 1.25 million Brazilians have been treated to date, and about 100,000 subjects are receiving chemotherapy every month. Indeed, the ambitious scope of the program appears to be causing problems, because the other components of the program are now said to be lagging badly behind drug treatments. Nevertheless, the fact that a nation has shown the collective will to mount a strong attack on endemic tropical disease, using modern drug technology, must be viewed as a strong sign of encouragement for the future. It has also been encouraging to hear the emphasis previous speakers in this symposium have placed upon the critical importance of developing the necessary field systems to deliver the useful technology we already have. As these efforts progress, and as other mass control programs are successfully mounted, the private sector will no doubt be stimulated to commit a larger portion of its resources to research on tropical diseases.

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DR. WILLIAM HUBBARD proposed several actions to be pursued promptly by government, industry, and the academic world in contributing to the development of new drugs for use in underdeveloped countries. He described four major strategies that must be initiated simultaneously, but which would come to fruition after varying time intervals.

The first strategy would be to improve availability and distribution of existing medicinals in developing countries over the next five years. It would provide short-term market surrogates where economically effective demand does not presently exist. Such market surrogates have been developed for distribution of food supplies and military equipment for developing countries. Some communist-bloc governments have already made the political decision to absorb the cost of supplying essential drugs at low prices to underdeveloped countries. The United States should encourage industry participation in carefully planned demonstration projects to assess the economic benefits to developing countries that can be achieved by expanded health investments. Finally, this immediate program should include efforts to improve appropriate utilization of pharmaceutical agents.

A second strategy, which must be begun immediately and pursued to fruition over the next 5 to 20 years, is to assist developing countries to attain self-sufficiency in manufacture of basic drugs. Regionalization of such efforts will be the likely key to their success, especially in fine chemical and pharmaceutical chemical production. We should examine the model of development assistance in agriculture for applicable lessons, because analogous kinds of capital assistance and training would be required.

The third strategy is a greater investment in research and development needed to promote the discovery, development, and distribution of improved medicinals for the tropics. This research should be undertaken in the United States by industry, academia, and government, and within the developing countries. It could include cooperation with other countries. More than 90 percent of discoveries will fail and, from discovery to distribution, ten years or more will have to elapse. Here, the government is challenged to provide better economic incentives or market surrogates for new pharmaceuticals coming from this strategy in order to make industry-funded research feasible.

The fourth and the most important of these strategies is long-term commitment to institution building in developing countries. It is this effort which will allow the creation of truly cooperative linkages between industry and academia in developed and developing countries, between industry and academia, and between government and the other two communities. This strategy will require decades of consistent support in order to succeed.

All these efforts require multi-year commitments, imply hard political decisions, but must be undertaken now.

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DR. JAMES LEE presented the changing policy and activities of the World Bank with regard to the health sector. He indicated that similar trends were being seen in other development finance institutions, both bilateral and multilateral. Before 1971, the World Bank was largely concerned with the transfer of resources from developed to developing countries, principally emphasizing the provision of physical infrastructure, such as for power, transportation, or communications. Beginning in 1971, the Bank began to systematically address the concern being voiced in many quarters, that economic development schemes often introduce or exacerbate health problems, such as the spread of schistosomiasis by the construction of irrigation works and hydropower projects in countries where the disease is endemic.

It was this concern that first propelled the Bank into assessing the health implications of the development activities it was financing, and to providing appropriate measures for the prevention or control of disease problems attributable to a project's presence and/or operation. Since 1971, for example, approximately U.S. $63 million has been provided for the control of schistosomiasis -- the lives of 14 million people have been touched and over 35 million hectares of land treated to control the snail vector. Similarly, it has participated along with WHO in the control of the blackfly vector of onchocerciasis in the Volta River watershed of West Africa.

After long and careful study, the Bank issued a health sector policy in 1974, which stipulated that development projects could also offer opportunities for including specific health care components designed to improve the health status of the people affected by the project. Such components have been financed in 44 countries to date. In the past three years, the Bank has provided nearly U.S. $3.9 billion in health-related projects such as water supply and sanitation, nutrition, fertility reduction, and others. With WHO, the Bank has co-sponsored a Special Program for Research and Training in Tropical Diseases, a global endeavor to find improved tools for controlling six tropical diseases. In addition, it is co-sponsoring with WHO an International Program for the Control of Diarrheal Disease, an intensive research and development undertaking to develop vaccines and improved chemotherapy.

At present, development finance institutions are emphasizing the provision of basic health care to reach the rural and urban poor, rather than physician-centered, hospital-based activities, as they did a decade ago. While the World Bank has become an increasingly major source of financing for health-related development, other regional banks are likewise considering increasing their efforts. It is apparent that in the provision of equitable and affordable health care to the impoverished peoples of the world, the role of the pharmaceutical sector will become increasingly important.

DR. LEE concluded by expressing his hope and expectation that the results of the recent international conference on primary health care held in Alma Ata, USSR, will be translated into positive action by the developing countries, and that development finance institutions can be instrumental in furthering the provision of health care.

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MR. MAX TIEFENBACHER began by stating that the transnational pharmaceutical industry is central to any discussion of provision of drugs to the Third World. In the supply of existing drugs, and even more so in discovery of new drugs, industry must play a leading role. Conversely, the industry's absence would leave a gap that could be bridged only at great cost and with long delay.

The multinational pharmaceutical industry has an important presence and a long tradition of achievement in the developing world. It stands ready to explore new approaches for meeting health needs of developing countries. Multinational companies have the scientific talents and managerial resources to greatly increase their contribution to the well-being of the Third World. Only one essential factor is lacking -- the incentive to do so.

To explain, MR. TIEFENBACHER stated that the research-based pharmaceutical industry is both science-oriented and market-directed. Over the past century, it has become highly adept at inventing or discovering new therapeutic tools, translating laboratory events into economically affordable products, and distributing the products to those who find them useful. The pharmaceutical firm is the agency that links scientific capability with economic demand. In short, it marries science to the market. The pressures and incentives that govern this process are competition and profit -- the latter coming chiefly from product innovation, but also through process innovations that reduce costs and thus expand the potential market and utilization.

Thus, the existence of an adequate market and economic viability are the inescapable conditions, the essential prerequisites of a deepened industry participation in resolving Third World health needs. But if industry involvement is to do more than scratch the surface of this intractable problem, fundamental economic and political decisions must be made to improve the health care environments of the developing countries.

A foremost need will be to restructure and expand the health delivery systems in the public sectors. These are now in deplorable disarray -- poorly organized, understaffed, totally inadequate to the task. Only as progress is made in building an adequate health care infrastructure -- especially in rural and poverty-stricken urban areas,

can drugs developed by the pharmaceutical industry be properly distributed, prescribed, dispensed, and administered to patients.

Poverty is a major obstacle to the launching and success of a program which strives to fulfill the credo that health is a basic human right. But poverty is not the only reason that prevents developing nations from allocating more than a pittance for health services. It is also a matter of priorities. Health expenditures as a percent of GNP in the poorest nations are often no more than a fifth or a tenth of what more advanced nations spend.

The WHO has repeatedly observed that adequate financing can result only from political actions on two levels. Health care and its supporting services must be accorded higher priorities in the allocation of resources in the budgets of the respective countries. Further, affluent countries and international aid and development agencies should direct a greater share of financial and technical assistance to the critical health needs of developing countries. Health needs should be elevated from the lowest rung on the priority scale to a level approaching the status of urgency and importance now accorded exclusively to food aid and economic assistance. WHO Director General Halfdan Mahler has noted that improved health is a powerful engine of economic development. Only with commitment of such additional financial resources can developing nations create and/or extend medical welfare schemes to provide basic care at little or no cost to the citizens who are simply too poor to pay for them. Only with such social security systems will markets for drugs -- specifically those to treat tropical diseases -- evolve.

Health authorities are the only large scale purchasers of drugs to treat tropical diseases. They must allow innovators to recoup the massive expenditures of money and effort required to develop and test these compounds. This means that prices must be set at reasonable levels.

With drug procurement on a competitive tender basis, and with patent protection being the exception rather than the rule in developing nations, the award of a contract will go to the lowest bidder. Most likely, this will be a company that has duplicated the research achievement of an innovative firm without paying compensation, and without sharing in the formidable costs of development. Thus, procurement policies of international agencies and governments must provide for price levels affording innovative manufacturers a reasonable return on research investment. The absence of such policies, by contrast, will inhibit and perhaps lead to a drying up of all incentive for research into drugs for tropical diseases.

MR. TIEFENBACHER emphasizes this cautionary statement because no other adequate mode of supporting such research has yet been -- or is likely to be -- devised. One alternative, much debated in recent years,

is public funding of tropical disease research programs. The WHO has offered to cooperate with industry in providing funds for screening of compounds and large-scale clinical testing of promising agents. Some governments of industrialized nations are also prepared to finance research in this area. This mode of funding can be, at best, only a method of last resort. It provides scant incentive to an industry whose energies and talents are directed to the discovery and marketing of patentable drugs at appropriate prices. Contract research will not summon the same energies or talents as a competitive search for new, wholly-owned products. Moreover, contract research will engender problems of the sharing of industrial property rights. Research into tropical disease will flourish only in a favorable economic climate.

The time required to develop a pharmaceutical is now so long that nobody would even notice if all innovative research stopped today; the products now in the pipeline would still be coming to the profession for the next 10-12 years. Today's new medicines were started that long ago, and this time-lag disguises a slowing of innovative research in general, and of tropical disease research in particular -- a source of false reassurance.

The WHO insists that the most valuable form of external support to the health needs of the world's poorest countries is to provide additional basic drugs, and that the situation requires extremely urgent international action. WHO has appealed to the pharmaceutical industry to cooperate by providing a limited number of basic medicaments to governments of the MSAC (Most Seriously Affected Countries). These drugs would be made available at low prices -- hardly above cost -- and be specially packaged and labeled for primary health care in the public sector. These drugs would be selected because they could be safely and effectively used by health workers with minimal formal training. Several major companies have responded positively to this appeal, and discussions with WHO are under way, but two preconditions to fulfillment of this appeal must be met.

First, health authorities of the home countries of these firms must recognize the extraordinary character of this project in regard to price. The low cost at which these essential drugs will be supplied to poor countries cannot be used as a yardstick for the appropriateness of drug prices within home markets.

Second, it is doubtful whether the conventional method of procurement practiced by some developing nations and advocated by international agencies will be in the best interests of the recipient country. This seemingly very simple system consists of centralized purchasing of drugs under their generic names from multiple sources of supply and on a competitive tender basis. The superficial rationality of this method cloaks its crucial defects.

This is stated not only in the context of supplying the most basic drugs to the poorest elements of the population, but also because developing nations are being urged to adopt this method of drug procurement on the widest possible basis. Under such a procurement system, responsible manufacturers will very likely regard the provision of essential drugs as a "hit and run" operation. They will dip into this market when excess capacity or inventories appear, making decisions to participate on a week-by-week basis. Participation will be narrowly confined, however. Unchecked, this sytem would erode and ultimately degrade basic drugs to ordinary commodities.

As stated earlier, research-oriented manufacturers compete on the basis of innovation, quality, service, and price. Making price the dominant parameter of competition would reduce drug distribution to the lowest common denominator and destroy the ability of manufacturers to provide the closely integrated and interdependent complex of functions that elevate pharmaceuticals to their highest level of value to society. As with the computer industry, the pharmaceutical companies can only function to society's maximum benefit if they are allowed to deploy the full package of hardware -- the drug itself, and software -- innovation, documentation, information, and similar services.

A tender system of procurement would also endanger the product integrity of even the most basic grouping of drugs. For products that find their markets mainly in the tender business -- some antibiotics and vaccines, for example -- forces of supply and demand cause prices to fluctuate sharply as manufacturers move in and out of tender agreements, moth-balling production capacities or putting them back to work, as the supply position swings from glut to shortage and back to surplus. An orderly supply of drugs to the public sector could not be based on such an economic see-saw, particularly if volume were to reach the anticipated dimensions. Quality would also suffer, because it would be a mistake to assume that the manufacturer's self-interest to supply consistently the highest possible quality product could be replaced by quality control performed by government agencies.

Thus, a paramount condition for drug manufacturers to collaborate in supplying the very basic drugs and vaccines to MSACs is that tender policies be reviewed. They must be administered on a long-term basis, taking due regard of the innovative character of the industry, of the quality aspects, and the services the manufacturer is able to provide.

The question now is whether the drug industry can tailor its service functions more fully to specific needs of the public sector, especially to those of the Most Seriously Affected Countries. If the afore-mentioned conditions are fulfilled, private industry may have an incentive to cooperate with national governments in several areas. For example:

- Quality assurance: Building up effective quality control systems within the Least Developed Countries;

- Manpower development: Training in technical skills, such as quality control and good manufacturing practices; training in the management and logistics of drug supply including storage and distribution;

- Development of national resources: By cooperating with developing nations in evaluating the usefulness of medicinal plants, in developing standards for their identity, purity, and strength, and in developing scientific criteria and methods for proof of safety and efficacy of medicinal plant products.

- Local production: Contributing to the self-reliance of developing nations by erecting plants, or assisting in the erection of plants for production of basic medicaments and vaccines destined for the public sector, supplying basic technology, training local personnel, supervising construction and start-up of production.

Drug manufacturers may also be able to provide other services. Previous speakers provided examples of what companies have done in past years, for example, in the training of paramedics, and in conducting large-scale eradication programs. Drug companies taking additional initiatives in these directions could provide valuable complements to development programs.

These are only a few examples of how industry could cooperate with international agencies to provide basic drugs and vaccines with concomitant services. They must still be analyzed and assembled to form a comprehensive and coherent program. It is clear, however, that in implementing a thrust in this direction, private industry, governments of both recipient and donor countries, and international agencies such as WHO must work closely together. There will have to be a pooling of talents and resources of all parties to provide the package of goods, services, and know-how. A platform and the ground-rules must be created for dealing with the issues. But first of all, a workable concept must be designed.

Consortia of companies may prove to be the only vehicles adequate to the challenge. The reason is that the commercial link between the product and the services provided by a single company would be severed. The company would find itself engaged in public service activities, financed partly or totally with public funds. Exemption from anti-trust liabilities would become an essential prerequisite.

The foregoing remarks apply principally to the public sector of the market. MR. TIEFENBACHER then addressed himself to the private sector, which to this day still constitutes the major market; it serves the growing social strata of the middle income population. It is to

this segment that the main thrust of the multinational drug industry's activities has been directed.

The problems and constraints under which the pharmaceutical industry operates in this market sector were described in MR. TIEFENBACHER's earlier paper. The interventionist policies and overextension of regulatory control as advocated by political groupings, and assertive national policies may lead to the end of private enterprise in supplying pharmaceuticals to developing countries. The foundation needed by the transnational pharmaceutical companies to fulfill their role in the public interest, as described above, will thus be destroyed.

In this climate of suspicion and mistrust, it is imperative that in the private sector the needs of private enterprise must also be reconciled with the political trends towards more central state planning. A balance must be found between the competitive system of a free market and the spheres of manifest public concern.

John Maynard Keynes once remarked that one cannot push on a string. He was referring to the illogic of exhorting businessmen to invest more in the face of sagging demand. But his remark is just as valid today in the context of this Conference. The pharmaceutical industry does not view the developing world with eager expectancy. Indeed, the business conditions in large parts of the developing world have deteriorated so alarmingly that these countries have sunk to marginal importance in the world view of the multinational pharmaceutical industry.

The pharmaceutical industry has a vital role to play in resolving the formidable task of reaching acceptable standards of health care for all. It stands ready to work for this goal with new visions and new initiatives, but only if it is permitted to serve the private market responsibly and progressively. Controls that would destroy the private market will lead inevitably to a strategic withdrawal from the Third World.

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DR. KENNETH WARREN suggests that it might seem that academe has three specific things to offer to the pharmaceutical industry: research involving discovery of possible new drugs and vaccines, drug and vaccine testing, and training of personnel. The situation, however, is far more complex and interesting. Basic research in the universities, medical schools, and institutes of academe provides the underpinning for the organic chemistry, biochemistry, genetics, etc. of the drug industry. At more applied levels, however, academe is examining every aspect of human disease. It can therefore provide new understandings of disease problems which will drastically alter treatment systems. Academic scientists will do clinical drug testing, be involved

in the planning and execution of more treatment campaigns, develop and utilize statistical techniques for evaluating results, examine the genetics of host and parasite responses, and even work at the top governmental levels to provide advice on developing rational cost-effective pharmacopoeias. Antagonism and lack of understanding existing between industry and academe can cause much unnecessary harm by raising the specters of toxicity and carcinogenesis where the problems are not significant, by advising governmemts in an unrealistic manner, etc.

Because this is a Conference on "Pharmaceuticals for Developing Countries," DR. WARREN selected examples of these problems from one of the major tropical diseases, schistosomiasis. Thus, only recently has understanding of the unique host parasite relationship between schistosomes and their mammalian hosts been emphasized; to wit, that schistosomes do not multiply, that disease is related to intensity of infection, and that a high proportion of infected individuals have low worm burdens and negligible morbidity. Furthermore, the highest intensity of infection occurs in children. Thus, it is not necessary to treat everyone and, just as important, the objective of drug therapy can be shifted from cure to drastic reduction of worm burden. This means that low doses can be used. Drug toxicity and side effects can therefore be drastically reduced, and the cost of mass treatment campaigns significantly lowered. Academe is engaged in field projects which are now demonstrating that mass chemotherapy is the most cost-effective way of controlling schistosomiasis. Academe is also developing new, rapid, inexpensive parasitological and immunological means for diagnosis.

Recently, it has been shown that S. mansoni in Africa is much more resistant to treatment with an excellent new drug than S. mansoni in South America. The cause of this phenomenon is being studied, as is the whole question of the development of resistance following mass treatment. Again, knowledge of the unique host-parasite relation will drastically affect our conceptions in this area. Recently, the development of disease in schistosomiasis has been shown to be related to the HLA histocompatability response system. An organized research group is now planning to study hepatic drug metabolism in patients with hepatosplenic disease. A derivative of an important antischistosomal drug with similar efficacy but decreased toxicity has been developed in academe. Furthermore, a major "spin-off" has been the finding of a unique and powerful immunosuppressive agent as a metabolite of another antischistosome drug.

The relationship and communication between academe and industry is of great importance. On the basis of inadequate evidence, a major antischistosomal drug has been branded mutagenic, carcinogenic, hepatotoxic, and a rapid inducer of drug resistance. This information, which now appears largely untrue and irrelevant, has been strongly presented to both scientific and political forums to the marked detriment of the utilization of an excellent drug.

In another recent development, academe is being consulted by a country where schistosomiasis is endemic to aid in the establishment of a nationwide control system. Judgments about the the role of chemotherapy and the choice of drugs will be involved.

Another area of great interest to the pharmaceutical industry is the intense focus by academic researchers on the immunology of resistance to schistosomiasis, and on its pathogenesis. The mechanisms of these systems are being worked out, specific vaccines are being sought, and nonspecific means of preventing them are being pursued. A vaccine involving frozen schistosomula is being tested in animals.

DR. WARREN closed with a plea for greater understanding between industry and academe. Academe is a source of particularly strong scientific capability. Probably most of the best young scientists would opt for academe at the crucial formative and most productive stages of their careers. This source of talent should be available to industry. This involves a mutual sensitivity to the problems of patent protection. Enlightened means whereby industry provides more support to academe could be worked out so that academic scientists would cooperate to help solve industry's problems, and industry would give scientists the freedom they need and expedite the handling of information to minimize publication delays.

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DR. W. CLARKE WESCOE stated that he believed the so-called schism between the academic world and the industrial world, which had been mentioned, was not as large today as it seemed to be in the 1950s. He suggested that we often use it today as a "straw-person," or as an excuse for inaction. In fact, relations are quite good between industry and academia, as illustrated by the continuous exchange of personnel between them -- and meetings like this one. A possible threat to ever-improving relations lies in the federal "conflict of interest" legislation not yet implemented. It is a fact that the pharmaceutical industry, unlike any other, must turn to the academic community for the final stages of all its testing of medicines. The ultimate clinical research is conducted by professors who act as consultants.

He suggested continuing the dialogue between members of government, the academic and industrial communities, and the foundation world in order to develop an initiative for continued cooperation so that technical assistance and pharmaceutical products may be supplied to developing countries. The initiative would address the following points:

- To ascertain where and how the academic and industrial communities can work together.

- To develop procedures to supply technical assistance such as training and education to developing countries.

- To work with government leaders in order better to remove those constraints and frustrations which continue to act as barriers to cooperation.

- To define strategies to increase pharmaceutical industry involvement in developing countries.

In conclusion, Dr. WESCOE stated that it was imperative that all parties at the Conference continue the relationship that has been forged to serve as the basis of action programs. In the past, such a coalescence of interests was represented in the Pharmaceutical Manufacturers Association Foundation, which utilized committees with both academic and industrial membership. Still in existence, the Foundation this year granted over $1 million to universities for the support of scientists.

Each party must participate in defining its special contribution, in developing complementary strategies, and in enabling their implementation. The World Bank should also be involved in any such deliberations. DR. WESCOE challenged the diverse interest groups represented at the Conference to create and develop an appropriate initiative.

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## GENERAL DISCUSSION: STRENGTHENING INCENTIVES AND OVERCOMING DISINCENTIVES: A CALL TO ACTION

DR. FRANKLIN NEVA (National Institutes of Health) asked whether the schistosomiasis control programs in Brazil, in which the Pfizer Company is collaborating, was truly a good example (1) of effective cooperation between the academic and industrial communities and the government, and (2) of a successful schistosomiasis control program. A few months ago, some Brazilian scientists expressed their disappointment that there had been very little opportunity for Brazilian academicians to cooperate in this program. They also indicated that it would be difficult to evaluate the effectiveness of the treatment program, since inadequate baseline data had been obtained. However, DR. NEVA noted that these criticisms were based on opinions of the people with whom he had spoken, and not on first hand observations.

DR. JOSEPH PISANI (The Proprietory Association), representing nonprescription pharmaceutical products, presented his views on the importance of recognizing that appropriate use of self-medication, properly labelled and packaged, could play a significant role in containing costs of pharmaceutical programs.

DR. ALEJANDRO ZAFFARONI (ALZA Corporation) presented his perspective on the incentives and disincentives faced by private industry in developing pharmaceutical products for the public sector. He illustrated his remarks by referring to experiences of ALZA with WHO and NIH in a cooperative program for the development of injectable contraceptives. In this development process, the acceptance of injectables by Latin Americans acted as a significant incentive to continuing research and development efforts. The many years of research and development invested in improving contraceptive technology represent an important example of knowledge broadened even at the expense of a low level of profit.

An opportunity for collaboration might be development of a contractual relationship between one or more pharmaceutical companies and WHO in a specific program area for public sector drug development. In this case, the major obstacles might be encountered at the transition from research to development. Misunderstandings between members of the university community and the industrial world are common at this juncture, since results in the developmental stages are often slower to come about than those in the research stages. A long-term investment would be required.

DR. ZAFFARONI emphasized the need for greater representation by industry in the joint consultative group of WHO and NIH -- to increase the number of people who understand the frustrations of product development. WHO could easily work out a contractual relationship with pharmaceutical companies for specific research and development programs.

The size of the World Bank investment in health, and the commitment of WHO to supporting research in tropical diseases, are impressive. He hoped that a recommendation might be made to increase the amounts of World Bank resources available for tropical disease research, and that some of them could be applied to programs involving participation by pharmaceutical companies.

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# UNITED STATES INTERNATIONAL HEALTH POLICY: ROOM FOR PUBLIC AND PRIVATE INITIATIVE

United States Senator Richard S. Schweiker

This Conference has served a valuable function by bringing together representatives of private industry, academic experts, and government health policy officials to outline the political, scientific, and economic issues that surround development and use of pharmaceutical products in the developing world. The discussions are almost at an end, and now we must begin to chart a course for the future. In doing so we must consider the problem of pharmaceuticals in the broader context of international health.

As the ranking Republican on both the Senate Health and Scientific Research Subcommittee and the Labor-HEW Appropriations Subcommittee, I am well acquainted with the needs of our own country. I know many of my colleagues look askance at programs to help foreign countries while so many of our own health problems are far from solved. This is especially true now, at a time when government and the private sector are beginnning to realize that our resources are limited, and the Carter Administration is proposing to cut the budget for some of our efforts to improve health care in this country. The timing could hardly be less auspicious. Why should we undertake expanded international health obligations now?

I support our nation's role in international health, quite frankly, both because I believe it is a moral and humanitarian obligation and because I see our contribution as a measure of enlightened self-interest. As President Kennedy said almost 18 years ago, "The health of a nation is the key to its future, to its economic vitality, to the morale and efficiency of its citizens, to its success in achieving its goals." By promoting and improving health in developing countries, we will be helping them to build stronger, more stable societies, which in the long-run can only be to the advantage of our nation and our national goals of world peace and stability.

The international health problems we face are immense. More than half the world's population lives in developing countries, and more than half lives in absolute poverty. Rapid population growth exacerbates existing problems of malnutrition and unsanitary environments.

For example, it is estimated that in Central America the population is increasing at a rate of about 3.4 percent a year. If this rate continues, it means the population will double in 20 years, creating tremendous pressure on resources.

Lacking proper diet, clean water, and waste disposal systems, the people of these countries are, in overwhelming numbers, susceptible to a whole host of infectious diseases. Infant mortality is high, and more than 15 million children under the age of five die each year. More than 7 million of these childhood deaths are caused by diseases that are amenable to prevention -- pneumonia and diarrhea, which strike children who suffer from protein and calorie-deficient diets. Preventable infectious diseases also account for a great number of deaths, as evidenced by an Agency for International Development study of an African village which found that more than a quarter of all deaths were due to measles, tuberculosis, smallpox, and whooping cough. The health status of adults is poor, making them vulnerable to parasitic and infectious diseases. These problems are not readily correctable since because less than 20 percent of the people in these countries have access to any kind of modern health services.

In the face of these tremendous needs, the World Health Organization has set an ambitious goal: health for all by the year 2000. The resources that poor countries themselves are able to devote to attaining that goal are extremely limited. At the present time, governments of developing countries spend only 1 to 2 percent of GNP on health. In the United States, it is predicted that health will soon account for 9.2 percent of our much larger GNP. In absolute terms, developing nations are spending between fifty cents and $2.50 per person on health, and that amount is not evenly distributed according to need. Clearly, outside help is required if the WHO goal of health for all is to be reached, and it will be a long-term effort.

I would like to emphasize two basic considerations for United States involvement in world health issues. First, we must accept the simple fact that allocation of resources in any country is essentially a political decision that must be made by that country's leaders. Developing countries themselves must make the initial political decision that they want to improve the health and quality of life of their citizens. These are continuing goals in democratic societies, but we all realize that some developing countries are governed by elites who are not always sensitive to human needs and may not place a high priority on improving the health of their people. In that situation our role, and the role of the international community, will be limited.

Secondly, in deciding what we in the United States can do to help those countries that <u>have</u> made a commitment to improving the health of their people, we must carefully assess our strengths and weaknesses. We must share our expertise, and not export our mistakes.

There are some areas where our ability to help is limited. For example, it is obvious that when a developing country decides to develop or revamp its health care system, thorough health planning should come first. If the recent history of health planning in this country is any guide, we should admit that we have not yet been successful in the field of health planning and do not have an excess of health planners in government. Similarly, many of the population and nutrition problems facing less developed countries require a deep understanding of social customs and lifestyle factors, and the ability to change attitudes and behaviors. I believe it would be fair to conclude that a nation that has traded the health problems of infectious diseases for those of environmental degradation and such unhealthy behavior patterns as overeating, over-drinking, and stress, may not be in the best position to offer solutions to complex social and environmental problems in other countries. We have not been able to master these problems in our own society. Developing countries must take care to avoid making the same mistakes that affluent nations have. By the same token, a health care delivery system that serves a highly developed, industrialized society may not be at all appropriate for developing countries.

There is no question, however, that we have a great deal to offer in terms of health technology and scientific expertise. Our research establishment, both academic and commercial, is second to none and has led to development of a wide variety of methods and products to improve health and prevent illness. This is an area where we have much to share both now and in terms of future benefits we can expect from research. The private sector, the academic community, and government must all be involved.

Many of the tools needed to control diseases affecting developing countries already exist, developed by our scientists and marketed by our private companies. What makes some of the tragic statistics I cited earlier so shocking is the fact that we know the problems are preventable. We have a responsibility to try to see that vital drugs and vaccines get to those in need, through bilateral aid programs, private voluntary efforts, and international assistance programs. This is why I authored legislation during the last Congress to provide for treatment of yaws, a debilitating and disfiguring illness prevalent in certain African countries, and for expanded childhood immunization activities through a joint effort by the Agency for International Development and the Center for Disease Control. I hope this type of technology transfer will continue in bilateral and multilateral aid efforts.

Private industry can help by lending its expertise in marketing new ideas and educating the public on health matters. There can be no doubt that the private sector can effectively promote good health practices and significantly aid in the education process. Anyone who doubts this needs only to look at margarine commercials on United

States television and then note the decline in butter consumption over the last several years.

Industrialized countries, and the United States in particular, also have a great deal to offer in terms of research expertise and training. Here again, public and private sectors both have a role to play. Unfortunately, far from encouraging academic and commercial contributions, some of our government's policies have actually worked against achievement of international health goals, particularly in areas of new drug development. I would like to outline some of the ways I believe this situation can be remedied, so that government, universities, and private companies together can apply our strengths to the problems of developing countries.

I believe the academic community has neglected the international health field. I plan to sponsor a bill that will call for development of international health expertise in United States academic health science centers. To be successful, these programs must be based both in the United States and abroad. Much of the training of health care personnel can and should be done in foreign settings to be truly effective. I envision development of a multidisciplinary cadre of health professionals who will become international health specialists, trained in health sciences and health services appropriate for the problems of developing countries. This international health service would then provide research, teaching, and health policy advice to aid developing nations in building the needed health infrastructure and in training their own health care providers.

The United States government also must improve its efforts to provide assistance to developing nations who seek to improve health status and health care for their citizens. Currently, international health problems are addressed by more than 20 agencies of the federal government. Frequently, agencies with technical expertise are unable to work effectively with the agencies responsible for dealing with the problem. Hopefully, creation of an Office of International Health within HEW will bring order to that department's efforts, and Congress may be able to provide HEW with an expanded mandate to engage in international health activities.

Continuing and effective participation in joint efforts, like those sponsored by WHO, and sharing information through internnational organizations should be a priority.

Another important initiative that we in Congress can take to encourage development of new pharmaceutical therapies and stimulate research involves amending our drug laws, which now prohibit export of any drug not approved by FDA for use in the United States. AID regulations ban purchase of such unapproved drugs for use in our assistance programs.

The risk-benefit equation in the United States may be very different from the equation for a developing country. Delivery systems vary widely, and some diseases, as you well know, plague developing nations almost exclusively. There is no incentive for companies to develop and secure approval for drugs to treat these diseases, because the risk inherent in any drug could never outweigh a "benefit" which consists of treatment for a nonexistent disease. Obstacles to conducting the clinical tests necessary for FDA approval would be insurmountable. So, when drug companies consider whether or not to develop new drugs for these diseases, they must weigh the heavy financial burden involved in establishing overseas facilities -- all the while keeping in mind that even if the research is successful, the inability of poor nations to pay for the drug makes a fair return on investment unlikely. Pharmaceutical manufacturers are responsible to their stockholders, and must keep their business on a sound financial basis. Last session, my Health Subcommittee worked on legislation to relax the law and allow export of unapproved drugs. We found both FDA and the drug companies concerned about this issue, and I fully expect to deal with this issue during the present Congress.

Many of the government-oriented proposals I have detailed are designed to bring resources of the private sector to bear on problems of developing countries. But there clearly are some things which the private sector can do on its own. I have in mind privately-sponsored exchanges of information and training personnel. Also, there are promising opportunities for research aimed at adapting existing therapies, such as drugs and vaccines requiring refrigeration, to conditions prevailing in developing countries. The effort of one United States company (Smith Kline and French) to produce measles vaccine with less demanding storage requirements is an example of private initiative in this area. I am pleased by the quantity and quality of participation by representatives of private industry in this Conference, as testimony to the industry's interest and commitment to providing needed therapies to less developed countries. I hope your efforts will continue and expand.

In summary, I would note that while this Conference has focused on problems in the development and use of pharmaceuticals, we must always keep the bigger picture in mind. We are all aware of the criticisms that have been leveled at the developed world, and the pharmaceutical industry in particular.

All of us would agree with the need for more research, but the facts require us to acknowledge that drug research and development alone will not solve the health problems of the developing world. Data presented at this Conference make it clear that there exist a number of excellent therapies appropriate for treatment and prevention of disease in developing countries. However, these treatments are often not used for two major reasons.

1. Much of the developing world lacks even a rudimentary health care infrastructure. Control of disease requires not only the ability to delivery therapeutic agents but also the ability to upgrade sanitation and living conditions, develop vector controls, and educate people about disease prevention.

2. The underlying problem of malnutrition constitutes a major impediment to improvement in health status, and accounts for many deaths among the very young. Infectious diseases are an important health problem in developing nations; but it is clear that malnutrition is a far more serious problem and leads in turn to susceptibility to disease.

I suggest that a major effort of government and of concerned individuals and groups gathered here should be directed at finding ways to improve or develop health infrastructures in developing countries and more effectively address the problem of malnutrition.

We realize that health for all will not be easy to achieve. Our health officials will no doubt continue to give the health problems of our own people first priority, as is appropriate. Our private firms will continue to concentrate on domestic markets and research opportunities. It would be unrealistic to expect anything else. It would also be unrealistic to expect a major new influx of federal funds while inflation and controlling federal spending is our number one domestic goal.

But if you as leaders of the scientific community and pharmaceutical industry will join with us in government both here and abroad, we have a powerful coalition. Together, we appear to have eliminated smallpox throughout the world, and we may now be on the threshold of controlling measles. Important progress can be made along the lines explored at this Conference, and if we can learn to work more effectively together, I am confident that it will be made.

# CLOSING REMARKS

Leighton E. Cluff, Chairman

DR. CLUFF described the Conference as a remarkable achievement, a landmark in the struggle to improve the health of developing nations. The Conference represents an unusual gathering with participation from foreign countries, foundations, international agencies, the United States government, and the pharmaceutical industry. The major issues that will have to be addressed by the Steering Committee in preparing the final policy statement include the following:

- The underdeveloped countries are not all alike in their health problems: They differ economically, politically, and geographically. However, some problems do remain constant and are characteristic of impoverished conditions, such as diarrheas and the pneumonia complex in young children. These countries also differ in the development of their health infrastructure, and in their ability to deliver health care. Effective agents exist against many diseases. The impact would be enormous if there were means to deliver those agents to the people in need.

- In some cases, no effective interventions are available. But the evidence presented during the Conference by research scientists actively working on such problems does suggest that there is a fundamental research base for planning the research and development of active pharmaceutical agents.

- There is a tremendous need for manpower and strengthened institutions for training in developing countries. The World Health Organization, industry, and private foundations are assisting in the task of building these resources.

- We have recognized, but not yet effectively addressed the need to assist developing countries to develop their own health care delivery systems. This need is just as crucial as the need to develop more effective pharmaceuticals against diseases endemic to tropical countries.

- Developing countries have limited resources to purchase pharmaceutical products, both those currently available, and those not yet discovered. This limitation will be a major consideration in future development of products for the public sector in those countries.

- Constraints and disincentives act upon the pharmaceutical industry to slow the development of new products for developing countries, and there also are limitations on the academic community for conducting basic research.

- The capabilities and interests of the World Health Organization are evolving in an exciting way. Any future effort to develop new pharmaceuticals ought to involve the cooperation and coordination of the World Health Organization.

In summarizing the task ahead, the health problems of developing countries are of concern to all peoples, to scientists, to industry, and to governments. The world might well declare the moral equivalent of war in mounting cooperative efforts to control diseases in developing countries. These efforts can be achieved with clear and well-defined objectives. The Steering Committee now faces the task of examining the issues brought out at the Conference and formulating policy directions for future actions.

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