UNFINISHED BUSINESS*

CLAY G. HUFF

Department of Parasitology, Naval Medical Research Institute, Bethesda, Maryland

Through some quirk in the democratic process followed by this Society in the selection of its president I have been chosen to stand before you this evening presumably to spill forth words of wisdom. I am grateful to you for this honor. Our joint meetings with the American Society of Parasitologists are particularly happy and beneficial occasions. Being a charter member of that Society I am pleased to have the opportunity to present my views to you also. This is a particularly auspicious occasion for me by virtue of the fact that it occurs in a city where I spent about one-half of my professional life.

The concern of this Society is with the health of peoples in tropical countries. I shall be talking about parasitic diseases in tropical areas and, hence, my remarks are as appropriate before one Society as the other. Our national interests include more than improvement of the health of people in tropical areas of the world. We as a nation are concerned in advancing their economic growth, their educational development, and their political stability. Hence we in our concern for the improvement of the health of these peoples must be aware of their over-all betterment. The interdependence of these various endeavors is a well-established fact. A recent study of 75 countries has been made by Harbison and Myers on the relation between education and the gross national product per capita. Although their complete report is not yet published, Harbison[1] has presented the main findings from their study, illustrating them with descriptions of four countries, Nyasaland, Colombia, China, and Egypt, which represent different stages of development. Their study showed a strong correlation between educational development of a country and its economic productivity. The coefficient of correlation between educational level (based on enrollment in secondary schools and universities) and the gross national product per capita was +0.89. They warned against the assumption, however, that investment of a given sum of money in education might be expected to bring about a relative increase in economic production. For example, the training of more engineers in one country might lead to a high rate of unemployment of engineers, whereas in another country such an effort would fill a need for engineers. I believe that we may safely conclude that similar differences in underdeveloped countries may strongly affect the success of efforts to improve the health of the people and, therefore, the over-all state of their culture and economy.

Our government has a multiplicity of agencies attempting in one way or another to improve the lot of the people in these underdeveloped countries. Where is the over-all purview and control of these agencies which could prevent the kind of undesirable effects which may result from their independent operation?

To pass from generalities to a specific example, I should like to devote the major portion of my discussion to malaria, a disease with which I have been concerned for the whole of my professional life.

I want to make it clear, however, that I am not speaking for the Society, for the Naval Medical Research Institute, for the Navy or for the Department of Defense, but only as an individual. Like most of the individuals who are concerned with the struggle against this disease I do not know all aspects relating to it. It is, therefore, not surprising that there should be a wide disparity of opinions among malariologists on several questions relative to the problems yet to be solved and on the best methods for solving them. If the opinions expressed here are in the minority it will not be the first time this has happened to me, and if the future course of events proves me to be wrong in some of my opinions this will also not be the first time.

I feel sure that this audience is well aware of the great advances made during and since World War II in our basic knowledge of malarial para-

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sites and the interrelations between them and their hosts, and in the relative success that has been achieved in the practical prevention and care of malarial disease. It is a matter of common knowledge that many countries which were previously malarious have eradicated the disease within their boundaries, and that a world-wide, intensive effort is now being made to bring about its complete eradication as rapidly as possible. There is no doubt about the fact that the world has become a better place in which to live as the result of the sum total of all of the thinking, planning, financial support, labor, and devotion of all people who have participated in this effort.

I do not believe that it is as widely known, however, that the job is not finished, and that new and formidable problems have arisen to slow the progress of the campaign against malaria. I believe that this side of the picture should be presented not in the mood of pessimism, not in the spirit of discouragement but rather in an attempt to be realistic. Malaria is an enemy of man, and in any war it is axiomatic that the strength of the enemy should not be underestimated. Our ultimate aim is the complete eradication of malarial infection in man in all areas of the world. This will be attained only when our knowledge, technical ability, and financial support is commensurate with the task.

Reduction of malaria depends upon the destruction of the parasite or the transmitting mosquito or by breaking the chain of transmission from mosquito to man. Even before the aim for eradication became widely accepted, it had been repeatedly shown that mosquito reduction was more effective than chemotherapy in reducing the amount of malaria in a population. Mosquito control had been sought through the use of oils as larvicides as early as the end of the 18th century. In the early decades of the 20th century Paris green and powdered pyrethrum came into wide usage as larvicides. The spectacular eradication of *Anopheles gambiae* in Brazil in the early 1940's, mainly by the use of Paris green against the larvae and pyrethrum-spraying of the resting places of the adults, gave a great impetus to the idea of malaria eradication. A potent residual spray, DDT, was discovered and widely used against adult mosquitoes during World War II. In quick succession other chemical compounds were found to serve as potent residual insecticides. These compounds killed the mosquitoes either before or after becoming infected with malarial parasites in the houses of persons suffering from malaria, thus breaking the cycle. Therefore, it appeared that the most important element in an eradication program was at hand.

The history of malariology has been filled with surprises. DDT, which had given us the added premium of reduction of houseflies in areas where it had been used as an anti-mosquito agent, began to fail to control the fly population. In quick succession, culicine, then anopheline mosquitoes were found to resist the effects of this compound and, as if this were not sufficiently disturbing, mosquitoes began to show resistance to residual insecticides of different chemical structure. In some instances the same species of mosquito developed resistance to two types of residual insecticide. This resistance proved to be hereditary in the mosquito and, if the use of the same insecticide was continued in an area, the resistant mosquitoes came to predominate over the ones which were killed by it. Here then had appeared a weakness in the most important weapon in eradication.

Although great strides have been made in reducing the amount of transmission of malaria, the mortality and morbidity of this disease is still among the four diseases of greatest importance in tropical areas. The story of the treatment of malaria is too well known to require detailed discussion. For nearly three centuries the alkaloids extracted from the Cinchona tree (quinine and cinchonine) were the chief drugs in use in treating malaria. The first syntheses of other antimalarial agents came after World War I, but at the outbreak of World War II quinine was still the most widely-used drug in malarial chemotherapy. The entrance of Japan into the War and the rapid severance of the Western world from the chief sources of quinine made necessary the initiation of a tremendous effort to synthesize and test new compounds for antimalarial drugs. Out of this program—which has been referred to as the greatest concentrated effort in medical history—came many new compounds which had therapeutic advantages over quinine and which could be synthesized in large amounts. The effectiveness of these compounds was well demonstrated in the war in Korea and in the low number of secondary cases which developed in troops who had undergone

attacks of malaria and returned to the United States. The percentage of secondary cases was slightly more than 0.3. The addition of these excellent drugs to our armamentarium against the disease gave a second weapon in an all-out attempt at eradication of malaria.

Unfortunately, the parasites—just as in the case of the mosquitoes—began to exhibit the ability to resist the action of these synthetic compounds. Reports then came—several of them confirmed by laboratory studies on human volunteers—of resistance of certain strains to one or more of the synthetic drugs in several areas of the world. These areas include Colombia, Malaya, Indonesia, Assam, New Guinea, Viet Nam, Kenya, Tanganyika, Nigeria, Ghana and Thailand. In some instances single strains of *Plasmodium falciparum* have resisted all of the synthetic antimalarials and it has been necessary to return to the use of quinine. The cause of resistance is not clearly understood, but there is evidence in some instances that it is found in areas where no chemotherapy has been practiced, hence the resistance cannot be blamed upon inadequate or improper use of a drug. Resistance is not confined to any one species of malaria but is found in all three of the principal species.

A new development in recent years is the discovery that two species of malarial parasites of monkeys may be transmitted to man by natural means and that such infections may be further transmitted to man or back to monkeys. The two incriminated species are *P. cynomolgi*[2,3] of rhesus monkeys, and *P. brasilianum* of South American monkeys.[4] It is as yet unknown (1) whether these parasites play any significant role in the epidemiology of human malaria, or (2) whether other species of animal malarias may infect man.

One of the most serious developments in malariology since World War II is the rapid decrease in interest and support of basic research in all phases of the subject and the dwindling efforts being put into training physicians, scientists, and technicians in the diagnosis, treatment, and control of malaria in our educational institutions and schools of technology. Excepting a few schools in which emphasis is placed on tropical diseases the instruction given to the medical, parasitological, entomological and control aspects of malaria has been reduced to a token amount.

When one looks for the causes of this sad state of affairs we find that they are multiple. In the first place many of the persons who contributed so much to the advancement of malariology entered this field because of the urgent need to reduce the part played by malaria against military operations during World War II. It was only natural that with the end of the war they would return to their original lines of work. Secondly, the great gains made against malaria during the war contributed to a feeling that malaria would soon cease to be a world problem. Finally, the decision to throw the most support behind quick eradication drew off funds that could have been used in support of research in malaria and the training of malariologists. It has always seemed to me that there should not have been a de-emphasis of basic research and training in all aspects of malariology including control but that, instead, the efforts toward an accelerated attempt at eradication should have been *added to* these efforts. The two goals need not have been mutually exclusive, for without doubt some eradication had already occurred through conventional control methods.

I am not alone in doubting the wisdom of the decision to use the goal of quick eradication as a means for obtaining support from various governments and funding agencies. However, to voice such doubts has become tantamount to being the Devil's advocate or to being against virtue. The few voices which have been raised questioning the advisability of using this mass effort as a quick and final solution have not been heard in the din of shouting about initial successes. The goal was correct. However, I feel that the promise to rid the world of malaria quickly if enough money were available was somewhat like Russian roulette. The gamble was great; the possibility of failure was underestimated. The possible backfire from the gun called "eradication" was underestimated. For who is willing to respond as wholeheartedly to an appeal for additional support if the results originally promised are not delivered on schedule?

As indicated earlier, the seeds of failure were sown when the nature of the eradication took the form it did. It assumed that we knew enough to abandon basic research and the training of personnel along lines which had proved to be efficacious even though more slowly than the promised quick eradication. In the midst of a

mighty war it is the foolish nation which abandons research. I believe we cannot deny that the eradication program greatly depleted the sources of support for a continuation of research and training in a highly complicated group of disciplines involved in the reduction of malaria. My report on the serious problems facing us in dealing with malaria today reveals a situation about which we cannot be very optimistic.

We are in a state of unpreparedness in respect to dealing with malaria in several regions of the world where the endemic disease is in the pre-eradication stage, or in military operations in areas where resistance exists in the mosquitoes to residual insecticides, or where resistance resides in strains of parasites to our best antimalarial drugs. A necessary military operation in such an area could be as disastrous as that in the Guadalcanal Campaign during World War II. Our vulnerability is heightened by the great lack of trained personnel already mentioned. Comparatively few persons in our armed forces are skilled in the diagnosis and treatment of malaria. This is reflected in the fact that deaths from malaria have occurred in recent years in military personnel because of failure of proper diagnosis.

In time of peace, people in general wish to forget about war. We can hardly refer to the present as a time of peace. However, few people are doing anything about preparedness for defense against such old enemies as malaria. This heavy responsibility rests upon our Department of Defense and the Public Health Service. They cannot afford to assume that malaria eradication is imminent. Yet their recruits—both officers and enlisted men—are coming into the services poorly prepared by our universities, colleges, and medical schools for action against not only malaria but all tropical diseases. I submit that the Department of Defense cannot assume the complete burden of responsibility for training of personnel in the many varied disciplines necessary to meet the challenges presented by (1) the necessity of limited warfare in tropical countries, (2) the need for protection of troops which may need to be moved into areas where tropical diseases are epidemic or endemic, and (3) the dangers of spread of diseases by rapid international travel.

Moreover, if we as a Society want to see steady progress toward a balanced program of the over-all betterment of people in tropical countries it seems to me that we bear heavy responsibility for attempting to obtain a greater degree of integration of effort among all agencies concerned with this problem.

I have on a previous occasion spoken on the challenges offered by parasitism as a scientific discipline[5] and, more recently,[6] upon the advantages which malariology offers toward a science of intracellular parasitism. Some of you may also remember a report of an *ad hoc* Panel on Parasitism Courses, Committee on Educational Policies, National Academy of Sciences-National Research Council,[7] of which I served as chairman, in which a plea was made for infusing the idea of studying *principles of parasitism* into the teaching of parasitology. I cannot help thinking that some of the big questions we now face in malariology would now either not exist or would be more easily solved if our generation of teachers had been able to realize some of the goals set forth in those earlier pleas.

The phenomenon of resistance in mosquitoes to residual insecticides should offer a tremendous challenge to insect physiologists, biochemists, and geneticists, and this research can be done whether one is interested in malaria or not. The unique physiology involved in intracellular parasitism offers challenges to the best of our physiologists and cell biologists. Again these problems are not uniquely pertinent to malariology. Good chemists and pharmacologists have continued their search for better antimalarial drugs. Many new chemicals of widely different structure have been synthesized and shown to be promising against the malarial parasites of laboratory animals. The real bottleneck is in the scarcity of personnel and facilities for carrying the tests of these drugs into human subjects. So far as I know, we have only two places in the world where testing on human volunteers can be carried out under optimum conditions. Our greatest need in the chemotherapy of malaria today is for a greater potential in the testing of antimalarial drugs in man.

In concluding my discussion I hope that by using malaria as an example I have not indicated that all is well in other fields of tropical medicine. Many of you know better than I how greatly these fields are in need of greater emphasis on research and training of personnel. I hope, however, that I may have accomplished one

thing, namely to emphasize that on our agenda there are many items of *unfinished business.*

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