

INSTITUTE OF CURRENT WORLD AFFAIRS

RFG - 21
Pare-Taveta Malaria Scheme

c/o Barclays Bank
Tanga, Tanganyika
March 24, 1956

Mr. Walter S. Rogers
Institute of Current World Affairs
522 Fifth Avenue
New York 36, N.Y.

Dear Mr. Rogers,

Not the least of my difficulties in writing newsletters has been in visualizing readers. In general I have tried to adhere to the principle, which you recommended to me in New York, of writing with a definite person in mind as a reader. This seems to help me to keep my feet on the ground.

In the present letter I have departed from that principle, for better or worse. I simply could not decide on any one person whose interests, if written for alone, would not seem to exclude other possible readers. As a compromise I wrote for two hypothetical readers, aiming half way between them and probably missing them both: (a) the layman with general and omnivorous interests in African affairs, and (b) the doctor who has forgotten most of the tropical medicine that he learned at medical school, but who retains an interest in medical problems outside of his own field.

More than any previous ones, this letter presented me with a problem in condensation. The people at Amani are orthodox scientists and refused to make generalizations about their work which were not fully substantiated by field or laboratory data. They took pains to explain the technical side of their research and presented me with a stack of printed material (which I dutifully waded through). But the generalizations which are necessary to make the report readable, even if premature, are mine. . . . In short, I have more than my usual qualms about this letter.

Sincerely,

Bob

Robert F. Gray

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Dear Mr. Rogers:

Malaria, which has a higher morbidity rate and is responsible for more deaths per year than any other transmissible disease in the world, has presented the medical departments of the East African territories with one of their most serious health problems from the first. Earlier hopes for the control of the disease, based on the successful eradication of certain mosquito vectors in Brazil and Egypt, diminished as it was realized that the special conditions in East Africa made mosquito control more difficult and complex. It was realized that basic knowledge about insect vectors in tropical Africa lagged behind similar knowledge in other regions.

These points were all discussed at the World Malaria Conference held at Kampala in November 1950. The director of the newly-established East African Malaria Unit, Dr. D. Bagster Wilson, attended the conference and argued for a conservative approach to the problem of malaria control pending the acquisition of more detailed knowledge about the transmission of the disease and its effect on the people living in endemic areas. The members of the conference concluded "that the outstanding undecided question for solution in tropical Africa is the effect of malaria in communities living in the most endemic areas, and that this question can only be solved by the application of mosquito prevention to such an area under controlled conditions."¹ The East African Malaria Unit, whose constitution and early activities are recorded in JBG - 51, has applied itself to the task of acquiring this knowledge through basic research and a large-scale experiment in malaria control. This research is in addition to its training program and its advisory functions to the East African governments.

Betty and I recently spent a long week end at Amani, which is the headquarters of the East African Institute of Malaria and Vector-Borne Diseases (hereafter to be referred to as the Institute), the new name for the old East African Malaria Unit. There I talked with Dr. Wilson (who was our host) and other members of the staff about their work, and inspected the laboratories and other installations. The project on which most of the research is centered at present is known as the Pare-Taveta Malaria Scheme. The object of this project is to solve the question that was defined at the

¹ East African Malaria Unit Annual Report, 1950.

Kampala conference concerning the effect of malaria in endemic areas. In 1953 a subsidiary organization, commonly called the Pare Scheme, was established and separately financed for the purpose of carrying out intensive field work on the project. In addition to the Institute and Pare Scheme, four other organizations have provided scientists and field officers who are working under the direction of Dr. Wilson. These are the Colonial Insecticide Research, World Health Organization, East African Medical Survey, and Tanganyika Medical Department. Assistance is also being given by the United Nations International Children's Emergency Fund (UNICEF) by gifts of insecticide and equipment. In the brief account of this research which follows I shall not always distinguish between the contributions of these different organizations.

Three zones can be distinguished in East Africa as regards the pattern of transmission of malaria--epidemic, hyperendemic, and endemic zones. The epidemic zone includes the comparatively small highland areas where malaria is substantially absent for a year or more at a time. The population of this zone is lacking in immunity to malaria and the control of the disease is essentially therapeutic--treating the epidemics as they arise. The hyperendemic zone is a vast extent of country where year after year for much or all of the year transmission of malaria is maintained at a high level. As a result of frequent reinfections, which may occur as often as fifty times a year in unprotected people, communal immunity of the native population is found. The adults born in this zone do not usually suffer from evident attacks of malaria so long as the indigenous village immunity is not interfered with. Between the two extremes of little and intense malaria transmission lies the endemic zone where there is both an annual period of malaria transmission and a considerable intermission of freedom from malaria. The low rate of transmission is not enough to maintain a high level of immunity in the human population of this zone, and adults of these communities are liable to attacks of malaria, though often modified in severity.

The hyperendemic zone is of far greater importance than the others economically and medically, and the research now being carried out in East Africa is largely concerned with hyperendemic malaria. The three main constituents of the problem are the malaria parasites, the mosquitoes which transmit the parasites from person to person, and the human population which suffers from the disease and acts as a reservoir of infection. The protozoal parasite causing malaria belongs to the genus Plasmodium. Of the four species which are pathogenic for man, Plasmodium falciparum is far and away the most important in East Africa. This parasite causes the form of malaria variously known as estivo-autumnal, malignant, or subtertian malaria, and is responsible for the serious complications of malaria and most of the deaths. Mosquitoes which transmit malaria are females belonging to the genus Anopheles. Two species are of outstanding importance in East Africa--Anopheles gambiae and A. funestus.

Before going on to list some of the lines of investigation by which the Institute is tackling its problem, it may be useful to review the main events in the transmission of malaria from person to person. An infective mosquito is one that carries a form of the parasite in its salivary glands. When such a mosquito bites a person the parasites are injected into his

blood. These parasites soon disappear from the blood and penetrate into the liver cells where they undergo a period of multiplication and development. From one to two weeks after the mosquito bite the parasites again enter the blood stream and this time invade the red blood cells. Their presence may be detected at this time by routine microscopic examination of a blood slide, the usual method of diagnosis. The parasites then undergo a series of divisions which result in new generations of parasites capable of invading and destroying red blood cells. After ten days or so of this asexual cycle of reproduction in the patient's blood, the parasites develop sexual forms which become infective for mosquitoes a few days later. The female parasites, which are ingested by a mosquito while biting an infected person, are fertilized in the mosquito's stomach, and in the subsequent division the new generation of parasites migrate through the body cavity of the mosquito, some of them finding their way to the salivary glands. They are then capable of infecting a new person through the bite of the mosquito. The development within the body of the mosquito requires seven to ten days.

The most obvious way of breaking this cycle of transmission is to destroy the mosquito host, or at least to prevent it from biting people. On a small scale this is sometimes achieved, as in urban communities, where breeding places of mosquitoes are eliminated, or in individual homes, where screens and nets, spraying, and other antimosquito measures protect the inhabitants. Anopheline mosquitoes bite only at night, which simplifies the problem of individual protection against bites. These measures, which are expensive and require careful control, are not applicable to the scattered African population which inhabits the vast hyperendemic regions. A simpler method of mosquito control must be found which is feasible to apply on a very large scale.

The method which is being tested in the Pare-Taveta Scheme is to treat the interiors of human dwellings with residual insecticides which retain their mosquito-killing properties for several months after application. If this method is to be effective, all the dwellings in a comparatively isolated region must be treated. The test area must also be large enough to indicate whether the method is practicable for use on a broad scale. The Pare-Taveta region comes close to satisfying these requirements. The Pare Mountains of Tanganyika and the adjoining Taveta Hills of Kenya form a continuous block of hyperendemic country a hundred miles long and twenty to thirty miles broad. On the west, malaria transmission is partially blocked by the Kilimanjaro massif, which is nonmalarious. On the north and south the area is adjoined by uninhabited steppe. Only on the east is there considerable continuity, through two valleys, with another hyperendemic area-- the Usambara Mountains. These valleys will be guarded, as far as possible, to prevent reinfection of the test area from outside.

In order to plan this experiment intelligently, and to evaluate the data which will result from it, the existing knowledge of the habits of anopheline mosquitoes in East Africa had to be greatly expanded. Therefore entomology was given priority in the early work of the Institute, much of it being done by Dr. M.T. Gillies and his staff. More recently a second entomologist, Mr. M.G. Christie, was transferred from Tanganyika Medical Department to the Institute. Dr. A. Smith was employed as entomologist

when the Pare-Taveta Scheme was organized. Dr. Holstein of WHO has also given some help in entomological field work. The mosquito problem has been approached in a variety of ways. This research, which has been recorded in a dozen or more scientific papers, is still going on, and final conclusions have not yet been formulated. At this stage it is hard to predict which will be the most critical experiments, but I shall mention some of the problems and methods which seem to me to be significant.

What do mosquitoes do after birth, where do they spend their time, and how long do they live? In general it is known that anopheline mosquitoes feed during the night and rest during the day. The amount of night feeding can be directly estimated by trained observers who catch the mosquitoes lighting on their exposed legs. Information on this question can also be acquired by catching mosquitoes in the daytime and finding how many are filled with blood. The usual way of catching mosquitoes in houses is by spraying with pyrethrum and collecting the dead mosquitoes. The total numbers of mosquitoes found resting in houses during the day also gives an index of the amount of biting at night. In one experiment an entire village of 120 houses was sprayed; 27,000 mosquitoes were collected. From the classification and analysis of these mosquitoes it was concluded that in East Africa, particularly in the coastal regions, the rate of transmission of malaria was the highest of any place in the world previously reported.

The mere enumerating of the fed and unfed mosquitoes found resting in a house does not give much information about the life cycle and the daily activities of the mosquitoes. By field observations and experiments in the laboratory, methods have been worked out for determining the age of a mosquito in terms of its reproductive cycle. A fertilized mosquito normally seeks a blood meal before laying its eggs. Dr. Gillies discovered that a large proportion of newly emerged mosquitoes required two blood meals before laying their eggs, the proportion differing in A. gambiae and A. funestus. This finding has a bearing in calculating the number of potentially infective mosquitoes in a house. The first bite of a newly emerged mosquito, of course, is not infective, nor is it capable of infecting a person until the twelfth day of its life; but thereafter the chances that the mosquito will be infective increase with each biting and egg-laying cycle. The older a mosquito the more likely it is to be infective. Therefore a number of experiments have been done to determine the age composition of mosquito populations, the development of the ovaries and other characteristics being used as indexes of age. Thus a large population of mosquitoes composed mainly of young females would be less dangerous than a smaller population of old females. The longevity of mosquito populations and their mortality rates have also been calculated. Other experiments were done to determine the preferred resting sites in houses (the darker places) and the time of maximum biting rate (around midnight).

If all mosquitoes rested in houses when not actually laying eggs, the problem of controlling them would be much simpler. But a certain proportion rest outside, both before and after their meal of human blood, and it would be useful to know what the proportion is. Since the outside resting population is widely dispersed it is impossible to count them in their natural shelters. Instead, standardized artificial shelters are placed in various locations outside; the mosquitoes caught in the shelters

are taken as a sample of the outside resters. These mosquitoes are dissected and classified as to whether they are fed, unfed, or gravid, and whether or not they are infected with parasites. This information gives further insight into the habits of mosquitoes and will be of great value in planning control measures. The whole question of the preference for outside resting sites (exophily) was analyzed by Dr. Gillies in a paper which he presented last October at the WHO Conference on Malaria in Africa at Lagos, Nigeria. Research in East Africa, he stated, had revealed that exophily varied in different regions and in different environmental circumstances. He also refuted a theory which had been put forth by Dr. Holstein that exophilic races of A. gambiae existed and could be detected by a difference in maxillary index.

Man is not the only animal that anopheline mosquitoes attack in search of a blood meal. By means of the blood precipitin test the source of the blood found in fed mosquitoes can be determined. These tests are mostly done at the Amani laboratory by a WHO chemist, Dr. Press. It has been found that the choice of a host depends mainly on the proximity and availability to a mosquito population of humans and animals. In communities where cattle are not kept because of tsetse fly, and where suitable wild animal hosts are not present, all fed mosquitoes are found to contain human blood. But in areas where cattle are kept in village kraals, a large proportion of fed mosquitoes contain animal blood. Other experiments have been done to find out the rate of outside biting of humans.

Most of this entomological research has been done in the Pare-Taveta area or in the vicinity of the Muheza field station near the coast. A few experiments, though, have been carried out in other parts of East Africa. One of these projects was planned to explain the absence of Anopheles from certain papyrus swamps in Uganda. It was found that the oxygen tension of the water in these swamps was very low--probably below the minimum requirements of most mosquito larvae. This led to a series of experiments designed to gain further knowledge about the metabolism of mosquito larvae.

A certain amount of study has been given to the effect on mosquitoes when houses are treated with residual insecticides. However, much more work will be done on this question in the next year or two as the Pare-Taveta project reaches maturity, and it would be premature to attempt general conclusions at this time. An early experiment in residual insecticides was done on a sugar estate at Arusha Chini under the direction of Dr. Wilson. This was started before the establishment of the Malaria Unit, while Dr. Wilson was still employed by Tanganyika Medical Department. The 2,500 African workers on the estate were examined at intervals during a program of residual treatment of houses. Although the mosquito population was reduced, little effect on the human parasite indexes of malaria was observed. Dr. Wilson concluded that little benefit could be expected from applications of this kind if applied to limited areas.

The hypothesis on which the Pare-Taveta Scheme is based assumes that mosquitoes entering houses to bite the inhabitants will rest on a surface treated with insecticide before or after feeding, and thus be killed. If this invariably happened, and if all biting was done in houses, the chain of transmission would be broken, and malaria parasites would disappear from the area. A mosquito who bit an infected person would not

live to bite and infect another person, so that there would be no new infections in the human population. The parasites already present in the blood and tissues of infected persons would gradually be eliminated through the mechanism of immunity or, if necessary, by treatment. Actually the problem is not as simple as that, because there is known to be a certain amount of biting of people outside of houses. Even allowing for this loophole, the rate of transmission could theoretically be reduced to a very low level provided reinfection was not introduced into the area from outside. It is hoped that reinfection will be minimized by the geographical isolation of the area and the fact that its large size will reduce the need of the inhabitants to travel extensively in outside infected areas.

The first residual treatment of the Pare-Taveta area was completed last November, but from the reports now in it is not yet possible to estimate the effectiveness of the treatment. The plan is to treat all the houses in the area every six months. The insecticide used has been a 50 per cent dieldrin wettable powder applied with stirrup pumps. The spraying was done by eight teams of two men each, supervised by field officers. The sprayers wore protective clothing to minimize the personal danger of exposure to dieldrin. The optimum dosage is still under revision; the cost of the first treatment worked out at 8 shillings and 30 cents per house. A total of 13,280 houses, occupied by some 44,000 people were treated.

Supposing the program is successful in drastically reducing the rate of malaria transmission; then the population of an area which has long been hyperendemic will be virtually free of malaria. If the physical condition of the people were known before and after the change in transmission rate, it would be possible to evaluate the effect of malaria in a hyperendemic area. This is the ultimate aim of the Pare-Taveta Scheme, and the task of physical assessment of the population has already been started by Dr. Draper and his assistants. The plan calls for repeated examinations of a sample of the population at six month intervals. The sample consists of about 5,000 individuals of all ages, about one third living in areas where malaria transmission is seasonal, and about two thirds living where malaria is hyperendemic and transmission perennial though fluctuating. Two complete rounds of examinations were completed before malaria control reached the people.

The first information to be obtained concerned the spleen rate (the percentage of enlarged spleens) and the parasite rate (the percentage of positive blood slides). These malarimetric data provided a direct index of the amount of recent and present malaria in the population sample. It also brought out differences in rates among the subareas and seasonal variations. These figures when collated with entomological data will give a clearer picture of the mosquito-parasite-man relationship which comprises the malaria problem.

An attempt is being made to collect vital statistics, which are so valuable in assessing the physical effects of disease--records of births, deaths, and other events in the lives of the people--but the difficulties are formidable. Africans do not often know their own ages, and are unable to date births and other events. Many women can not remember accurately how many children they have borne. During the course of the experiment

vital statistics will be kept as carefully as possible, but any changes observed in vital statistics will probably be of limited significance because of the short pre-control period of observation.

As a general indication of physical condition, anthropometric data are obtained from the subjects--height, weight, skin thickness, circumference of chest, and the like. It will be most interesting to see what effect malaria control has on general size and body build. Another important test is hemoglobin estimation, which is being done on every individual in the assessment group. Plasma cholinesterase estimation has recently been introduced as an additional examination, although the significance of this is not fully evaluated. It is at least known to be an index of liver function. Stool and urine examinations have been done in approximately 1,800 cases. These show the varying incidence of schistosomiasis and other helminthic infestations. The East African Medical Survey has carried out dietary surveys, but the analysis of their figures is not yet complete.

All individuals in the assessment groups receive a general clinical examination with a record of blood pressure, resting pulse rate and temperature. The Harvard step test was attempted in the beginning, but it was abandoned because of poor cooperation from the Africans. The most significant clinical finding to date has been a high incidence of hepatomegaly or enlarged liver. Blood pressures are uniformly low when compared with European standards, as found elsewhere in Africa, while some degree of tachycardia is common. The temperature recordings indicate that the natural temperature of the African is very labile. It was considered that only temperatures of 100° F. and over are truly pathologic.

Although mosquito destruction is considered to be the most thorough method of malaria control, another method is to eliminate parasites from an endemic community by administering antimalarial drugs to the people. This method is being avoided in the Pare-Taveta Scheme because it would only obscure the effects of mosquito control. However, the malaria section of the Tanganyika Medical Department, under the direction of Dr. D.F. Clyde, has been carrying out experiments in suppressive treatment of malaria in the Muheza area. This organization has its headquarters at Amani and works in close cooperation with the Malaria Institute. The special problem that Dr. Clyde and his laboratory technician, Mr. G.T. Shute, are working on is the resistance of Plasmodium falciparum to the drug daraprim (pyrimethamine). It has been known for some time that certain strains of P. falciparum in Malaya were resistant to paludrine (proguanil), and there was evidence that these strains possessed cross resistance to daraprim. It has also been suggested from work on non-human plasmodia that resistance might be developed directly against daraprim by the use of that drug itself. Dr. Clyde planned his experiments to discover whether resistance to daraprim appeared in P. falciparum following the use of the drug on controlled groups of Africans.

The investigations were carried out in a hyperendemic lowland village where the inhabitants were considered to be immune. The drug was given once a month to a sample of the population which included different age groups. Each time daraprim was administered--personally by Dr. Clyde or

Mr. Shute--a blood slide was taken from the subject. In this way the original parasite rates were obtained and the rates one month after each treatment. It was found in general that for the first two or three months there was a sharp drop in parasite rates; then the rates gradually climbed again until in some groups (the younger ages) the original rate was regained. This indicated that the parasites had become resistant to daraprim given at that dose and interval. The nature of this resistance is not clear and several theories are being investigated. On the one hand it may represent an acquired resistance in the strain of parasite which was exposed to daraprim--a resistance which becomes, at least temporarily inherited. An alternative explanation assumes that a minority strain of the parasite, which is naturally resistant to daraprim, profits from the reduction of susceptible strains and increases during the course of treatment until it becomes the majority strain in the village. After cessation of the drug, the resistant strain, whatever the nature of its resistance, appears to become again submerged in susceptible strains. This research has been criticized by the manufacturers of daraprim on the grounds that the intervals between treatments were too long. The experiments are now being repeated, administering the drug at shorter intervals. The practical import of these experiments are considerable, for daraprim is widely used by individuals in East Africa as a suppressive for malaria. If the dose or frequency of taking the drug are insufficient, resistant strains of parasites may be created which might then render the drug ineffective as a suppressive.

There has been some criticism of the Institute by sisal planters and some of the other Europeans of the area. "Why don't they get on with the job of controlling malaria, instead of all this experimentation and mosquito catching?" they ask. Dr. Wilson answers that it is not yet certain that an all-out effort to eradicate malaria is the most desirable course at this stage. The detrimental effects of malaria on the health and economy of the country have not yet been evaluated. The cost of a wide-scale program of malaria control might prove to be disproportionate to the benefits which would result. If success were certain, the expense might be a less important consideration; but it is by no means certain that effective control of malaria can be maintained over wide areas with the methods now available.

The main reason for caution, however, is that control methods which are only partially successful may do great harm by taking away the immunity which the inhabitants of hyperendemic areas now possess and leaving them susceptible to serious attacks of malaria if transmission rates return to higher levels. Partial immunity to malaria is normally acquired in these communities in early childhood, and by adulthood acquired immunity provides considerable protection against clinical attacks of malaria. This immunity is acquired through repeated infections. If these infections were prevented through malaria control measures, a generation would grow up lacking in immunity. Then if malaria transmission returned to the area because of the failure of control measures--as might happen, for example, if the mosquitoes developed resistance to insecticides--the danger of serious epidemics would exist. A similar danger is attached to the wide-scale use of suppressive drugs, which might produce resistant strains of parasites. In any case, once a control program is started it must be kept up indefinitely, unless complete eradication of parasites or mosquitoes is achieved--which seems unlikely in the near future, according to our present understanding.

The community might be committed to an endless round of malaria control, which it could support only by sacrificing its welfare in other forms.

Even in hyperendemic areas malaria causes a considerable amount of morbidity and death during the first year or two of life. No reliable figures on this question exist at present, but Dr. Wilson concedes that deaths from malaria probably account for ten per cent of the total infant mortality rate. However, malaria control measures for the whole area, depriving the people of immunity, would not be necessary to prevent these deaths, which could be effectively treated at improved dispensaries or other treatment centers.

Dr. Wilson's insistence on basic research and his conservative approach to control programs—"let's know where we are going before we start"—seems to be shared by the other scientists now working at Amani, but at one time his views were considered unorthodox and reactionary. Malaria is only one of many factors which impair the health and working efficiency of the natives of East Africa, he explains. Such factors as nutrition, schistosomiasis, or hookworm may turn out to be of greater economic and medical importance than malaria. Moreover, if the health of the people is improved in other ways, their resistance to malaria may be greatly increased. It may even disappear by itself from the country. He cites the example of the United States where malaria has virtually died out, as far as he can see, without any deliberately planned control measures. (I leave it to American malariologists to judge the truth of this statement.)

This has been an interim report of research which is only well started, and for that reason not very satisfying. The final conclusions are not yet in sight. But when the Pare-Taveta Scheme has run its course it should make a fascinating story.

Sincerely,

Robert F. Gray
Robert F. Gray.

(Received New York 4/3/56)

Bibliography

I list below the writings which I used in working up this report. The list does not include all the papers which have been published by the Institute and Pare Scheme members. Some of these have not been available to me.

Annual Reports. Five of these have been published, the first four (1950-53) by the East African Malaria Unit; the last one (Jan. 1954-June 1955) by the East African Institute of Malaria and Vector-Borne Diseases. These give concise accounts of Institute activities over the period of each report.

Bulletins of the Institute. Four undated Bulletins have been published on practical aspects of malaria control and therapy. These are circulated for the guidance of East African medical officers.

Progress Reports--Pare Malaria Scheme. Starting with June 1954, four of these Reports have been published at six month intervals. They describe in some detail the research in progress.

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