WORLD HEALTH ORGANIZATION
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ORGANISATION MONDIALE DE LA SANTE

WHO/Mal/317
18 October 1961

ORIGINAL: ENGLISH

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A LIST OF SUBJECTS FOR BASIC AND APPLIED RESEARCH RELATED TO THE AIM OF MALARIA ERADICATION[1]

INTRODUCTION

The research activities of WHO in the field of malaria could be broadly divided into three groups: (1) Incidental research, (2) Applied research, and (3) Basic research.

The first term is applied to the gathering, sifting and assessment of a number of facts and observations reported as a result of normal field activities in malaria eradication projects. The term "applied research" refers to a specific technical problem of general and immediate importance which has to be rapidly solved in order to overcome obstacles standing in the way of malaria eradication. The term "basic" or "fundamental research" refers to the pursuit of knowledge in a definite branch of science, without necessarily assessing the potential usefulness of the results obtained.

The general policy of the Organization in the matter of malaria research is to give the highest priority to problems that have a direct, almost immediate bearing on malaria eradication. Problems of basic research are undoubtedly important, but, being somewhat removed from the current world-wide malaria eradication programme, cannot receive the same degree of priority or financial support. Thus the greatest attention is generally given to applied research, but without losing sight of the fact that at times the solution of a practical problem may be found as a result of some fundamental discovery. Basic research of this type is stimulated, encouraged, guided and supported by the Organization, even though most of it is done independently by national scientific organizations.

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[1] Prepared by the Division of Malaria Eradication, World Health Organization, Geneva, Switzerland

On the other hand the areas of possible incidental research are usually connected with field activities aimed at malaria eradication. The amount of such research is considerable and the task of assessing and consolidating it is increasing every year. It should perhaps be stressed that the more spectacular and definite research activities represent only a small part of the contribution to the vast amount of information of potential importance to research, gathered from routine operational reports.

Every plan of malaria eradication must be based on a detailed pre-eradication survey of the conditions of the area involved, to determine the strategy of future action. This is necessary because the local features of malaria vary very greatly in relation to the parasite species, its mosquito vector and the physical, biological and also socio-economic environment.

Even more information is gathered when the malaria eradication programme is gathering momentum during the attack phase or when it comes to its crucial stage in the consolidation phase. Investigation on the persistence of transmission, once operational failures have been discounted, may require some modifications of, and additions to, the conventional technique for collection of parasitological and entomological data; more precise assessment of the volume and infectivity of the parasite reservoir; the outdoor and indoor behaviour of the anopheline population; and last, but not least, the improvement of the epidemiological follow-up during the surveillance activities in the terminal phase of malaria eradication.

The list of subjects of basic and applied research in malaria given below is far from complete and is presented mainly to outline the areas of scientific interest related to the aim of eradication of this disease. The subjects quoted below have a varying degree of importance, different degree of practicability and different angle of approach. Some could be solved only through a series of experiments, others need a sociological approach, and a few are of administrative nature.

Some of these research subjects, previously mentioned in the Report of the Scientific Group on Malaria Research (Geneva, November 1959), are now being actively investigated; others are still in abeyance because of their inherent difficulty.

The list of these subjects was submitted to the Third WHO Advisory Committee on Medical Research (Geneva, June 1961) and is now circulated in this series for information and stimulation of a creative response by those who are interested.

1. Parasitology and Immunology

1.1 Development of practical methods for cultivation of malaria parasites in vitro

Practical and relatively simple methods for cultivation of simian and human malaria parasites in vitro are needed. These methods would be of value for studying the metabolism of malaria parasites in relation to various haemoglobin types as also for basic studies on the biochemistry of malaria parasites and on their resistance to drugs. There is a special need of a method of tissue cultivation of mammalian exo-erythrocytic parasites.

1.2 Study of tissue stages of malaria parasites of rodents and of P. knowlesi of monkeys

This study would complete the knowledge of various patterns of exo-erythrocytic schizogony and assess the hypothesis that malaria parasites of rodents are a link between avian and mammalian parasites.

1.3 Study of the immediate fate of the sporozoite of primate malaria parasites

This investigation should elucidate the proportion of the sporozoites inoculated by the mosquito that reach the liver and by what routes. It should also answer the question why the the sporozoite invades the parenchymatous cell of the liver. More knowledge is needed on the physiological and biochemical aspects of exo-erythrocytic stages; this may provide data on the genetics of relapses and may open new possibilities for treatment. The use of radioactive tagging of sporozoites or of fluorescent antibody technique might be envisaged for this study.

1.4 Study of the quantitative relationship between the number of infecting sporozoites and the tissue stages of malaria parasites of primates

This investigation should assess whether the number of pre-erythrocytic schizonts in the liver corresponds with the number of sporozoites. In other words, there is need to determine if new exo-erythrocytic schizonts can develop from primary tissue merozoites.

1.5 Study of African strains of P. falciparum

There is evidence that some West African strains of P. falciparum differ in their morphology of blood and tissue stages from the "classical" P. falciparum. The duration of infection with these West African strains, the response to drugs, and the infectivity to Anopheles vectors should be studied in comparison with other strains of P. falciparum and particularly those of East Africa, the Far East and Southern Europe.

1.6 Asymptomatic malaria infections and their implications in malaria eradication

Detailed parasitological investigation should be carried out on the frequency, duration and comparative infectivity to malaria vectors of primary or secondary latent stages of infection with P. vivax and P. falciparum. Some aspects of this investigation should be followed up in the field, others in institutes where malaria therapy is still practised. Relationship of acquired immunity to malaria with asymptomatic parasitaemia should be clarified.

1.7 Study of simian malaria and its implications in malaria eradication

There is now some evidence that not only higher apes but also monkeys may harbour malaria parasites which can be transmitted to man by Anopheles vectors. Further information on the problem of relationship between simian and human malaria should be sought, particularly with regard to P. hylobati of Borneo, Indonesia, and the susceptibility of man to this species, P. knowlesi of Malaya (susceptibility of man to sporozoites and determination if man is infected in nature), P. simium of Brazil and P. schwetzi of West Africa (susceptibility of man to these species). A wide field for the investigation of simian malaria is open in Taiwan.

1.8 Duration of natural infection of man with the four species of human malaria parasites

A detailed study of the duration of P. falciparum, P. vivax, P. malariae and P. ovale infections is needed although much indirect information has already been collected on this subject in institutions where malaria therapy is practised. This indirect information has not been consolidated or published in spite of its obvious

importance. A thorough field epidemiological study carried out in a number of programmes in the consolidation phase might provide much valuable information. The study of the duration of infection with the four species of malaria parasites should be investigated in various genetic groups of populations living in areas with different degrees of malaria endemicity.

1.9 Relationship of haemoglobin types and thalassaemia to susceptibility to malaria infection

There is evidence that the presence of some "abnormal haemoglobins" such as S, C, E, foetal and others is related to the increased tolerance of malaria infection by the individuals and populations concerned. More information is needed on the presence and degree of such "protective effect" of balanced polymorphism in various populations and different age-groups. Laboratory and field investigations on the susceptibility to P. vivax infections in relation to various haemoglobin types are needed to explain the virtual absence of P. vivax in West Africa. Extended investigations on the comparative direct mortality due to malaria in African infants with and without the sickle cell trait are indicated. Little is known about the relationship of the high frequency of haemoglobin E in the Far East (Viet Nam, Cambodia) to the susceptibility of homozygous or heterozygous carriers of this gene to the infection with various species of malaria parasites and particular P. falciparum.

1.10 Improvement of the technique of detection of malaria parasites in the blood

There is great need of increasing the speed and reliability of detection of malaria parsites in the blood. Two methods are of potential promise: (a) development of an electronic scanning apparatus which would select only positive (or probably positive) slides for further checking; (b) development of a new simple and selective staining technique (such as fluorescent stain).

1.11 Investigations of cytology, cytochemistry and genetics of human malaria parasites

Study of finer points of the cytology and cytochemistry of sporogonic stages of four species of human malaria parasites. Study of the presence and function of chromosomal bodies in human Plasmodia. Possibility of hybridization of some species and strains of malaria parasites should be explored.

1.12 Study of transfusion malaria in man and its implications in malaria eradication. Extension of experimental studies on transfusion malaria in monkeys

From the point of view of malaria eradication the study of transfusion malaria in man is of importance whenever the newly infected case may become a source of a new focus of malaria. More information is needed on the infectivity to mosquitos of malaria transmitted by blood transfusion from donors with asymptomatic infections. Methods for prevention of such infection by suitable treatment of donors or of their stored blood need to be improved.

A study of experimental infections of monkeys with P. knowlesi, P. cynomolgi and P. inui with the view to determining the shortest time of storage of the blood at a given temperature after which it is no longer infectious. More information on the importance of transfusion malaria in the late phases of malaria eradication in different countries should be collected, evaluated and made available. Investigation of methods for prevention of malaria transmission through stored blood or through direct blood transfusion from infected donors.

1.13 Investigation of the degree, mechanism and strain specificity of immunity to malaria

Investigation of the degree of immunity to P. falciparum in the indigenous population of an endemic area of West Africa using: (a) the longitudinal follow-up of the presence and intensity of parasitaemia; (b) the challenge of reinfection; (c) the "respiratory test" of immunity based on the change of oxygen consumption of malaria parasites, immersed in homologous immune sera in the Warburg apparatus.

1.14 Development of techniques for quantitative measurement of immune response to experimental malaria infection

This research project will adapt to the study of malaria immunity a useful, sensitive and specific immunomanometric method of measurement of antibody response to trypanosome infection. There is evidence that the oxygen consumption of protozoa, measured in the Warburg apparatus, is decreased when the protozoa are suspended in an immune, strain-specific serum. This decrease of oxygen consumption is proportional to the antibody titre and so the degree of immune response can be quantitatively measured. The development of this method may lead eventually to assessment of the presence or absence of latent malaria infection.

1.15 Differentiation of strains of malaria parasites using fluorescent antibody method and other new serological techniques

Development of the fluorescent antibody method for the identification of various strains of human malaria parasites may constitute an important practical advance for distinguishing between a relapse and reinfection, if the reinfection is caused by a heterologous strain. The results should be compared with results obtainable using the gel diffusion technique for precipitating antibodies.

1.16 Relationship between plasmodial and viral infections in arthropod vectors

Study of the influence of some virus infections of mosquitos on the development of the simultaneous sporogonic cycle of malaria parasites. A field observation made in Uganda suggests that there may be interference with the development of human malaria parasites in Anopheles infected with the O'nyong-nyong virus.

1.17 Investigation of the presence, duration and degree of humoral immunity passively transmitted in primates

There is some evidence of the transmission of humoral immunity passively transmitted from the mammalian mother to her progeny transplacentally or through milk. There is some circumstantial evidence of the presence of transient humoral malarial immunity passively transmitted from the mother to the newborn in highly endemic areas of Tropical Africa. An experimental study of this problem in lower monkeys and anthropoid apes is needed.

2. Epidemiology

2.1 Study of epidemiological patterns of persistent malaria in areas of highly endemic malaria where pilot malaria eradication project failed to interrupt transmission

This study should assess in detail the distribution of persistent malaria infection in some malaria eradication programmes. The examination of the efficacy of evaluation procedures adopted should form a substantial portion of the study. More information is needed on the degree and epidemiological conditions of transmission occurring while the vector is at or apparently below the critical level of transmission potential. The entomological aspects of the results of the pilot project should be assessed. Particular attention should be given to the study of residual foci of malaria to assess the part played in the maintenance of transmission by the relationship between the man and the parasite.

2.2 Study of population movements in malaria eradication programmes

A study of the patterns of mobility of one or more nomadic groups with a particular emphasis on the extent and nature of their exposure to malaria and the impact of the infection. The study would include the investigation of methods which may be used to interrupt transmission in such circumstances.

2.3 Study of the value of the infant parasite rate in endemic areas as a guide to the assessment of the progress of malaria eradication

There is some evidence that the infant parasite rate in Tropical Africa may not be a very good guide for the assessment of the progress of malaria eradication because of the passively transmitted maternal immunity which lowers the infant parasite rate during the first six months of life so that it cannot be used as a fully reliable indicator of the probable interruption of transmission.

2.4 Development of standardized methods for evaluation of the progress of malaria eradication programmes

The methodology of assessing the progress of malaria eradication varies in relation to the initial endemicity of the area, to the phase of malaria eradication and to various local conditions. In spite of the fact that full standardization of methods of evaluation is not possible, attempts should be made to streamline the criteria employed as much as possible in order to enable an easy comparison of the speed of progress of malaria eradication programmes from the initial level of transmission to the complete interruption of it.

3. Chemotherapy

3.1 Development of a schizontocidal and sporontocidal drug with a prolonged action

In view of the difficulties of mass drug administration in many parts of the world there is a genuine need for a schizontocidal and sporontocidal drug or drug preparation with a prolonged action so that a single dose of it should maintain its activity for not less than three months and preferably longer.

3.2 Development of an anti-relapse drug radically curative at a single dose or at most after a three-day treatment

Since the generally adopted radical treatment of relapsing infections with P. vivax and P. malariae requires at present a repetitive administration of 8-aminoquinolines over two weeks or longer and under supervision, there is need for developing an anti-relapse drug free from side effects and radically curative at a single dose or at most after a three-day treatment.

3.3 Development of various combinations of existing drugs

Combinations of 4-aminoquinolines, 8-aminoquinolines and pyrimethamine should be studied to determine if there is a useful synergism of antimalarial properties of this combination without the corresponding increase in toxicity.

3.4 Investigation of the following technical and operational problems of mass drug administration through the use of medicated salt

(a) Development of a simple and reliable procedure for estimating the daily intake of common salt in various age-groups in communities among which the use of medicated salt is to be introduced.

(b) Investigation on the minimum concentration of pyrimethamine when administered in medicated salt (together with 4-aminoquinoline) to obtain a sporontocidal effect and to be excreted in milk of nursing mothers in sufficient levels to protect breast-fed infants.

(c) Study of the intestinal absorption of amodiaquine base or sparingly soluble salts of chloroquine when administered in medicated salt.

(d) Development of a fully satisfactory method for prevention of the "leaching out" effect of soluble chloroquine salts mixed with common salt, without interfering with the intestinal absorption of the antimalarial drug.

(e) Development of a suitable 8-aminoquinoline with adequate heat stability to withstand conditions encountered in the preparation of cooked food.

3.5 Investigation of the possibility of measuring the duration and level of activity of antimalarial drugs using the "respiratory test"

There is need for a new and sensitive method of measuring the activity of antimalarial drugs and it seems that the newly developed "respiratory test" used for immunological studies of trypanosomes may be adopted for this purpose. The test would consist of maintaining in the Warburg apparatus malaria parasites (freed from the red blood cells) in sera taken from treated subjects at various times after treatment and measuring the variation in oxygen consumption in comparison with oxygen consumption after the immersion in "pre-treatment" serum.

3.6 Investigation of comparative haemolytic properties of primaquine and quinocide in a population with high frequency of the glucose-6-phosphate dehydrogenase deficiency

A thorough comparative investigation of the haemolytic properties of primaquine and quinocide might be of particular interest in an area inhabited by a population with a high proportion of the G-6-P-D.deficiency. On the other hand the investigation of the frequency of this genetic trait might be of interest in areas where quinocide has been widely used with few if any side effects recorded.

3.7 Development of a standard method for the assessment of the level of susceptibility of various species and strains of malaria parasites to drugs

The need for a standardized method for determing the baseline of the susceptibility of malaria parasites to drugs is great, since without it it is difficult to determine the degree and trend of a developing resistance. In view of the fact that the immunological relationship between the human host and the parasite complicates the establishment of any criterion of susceptibility, it is probable that a development of a satisfactory method of *in vitro* cultivation of several generations of human malaria parasites would be necessary prior to the attempt to assess the action of drugs or their metabolites on the growth of plasmodia. This investigation is linked with the projects 1.1 and 3.5.

3.8 Study of parasitological and immunological and other characters of a strain of human malaria parasites resistant to an antimalarial drug

Any reports on alleged drug resistance observed in the field should be carefully assessed with regard to the correctness of this information, and the degree and extent of any confirmed resistance.

Definite confirmation of resistance can best be provided through the transfer of the relevant parasite strain to a research centre for investigation of the drug resistance on non-immunes not exposed to reinfection and for the study of the response of the parasite strain to other drugs and its transmission through a mosquito vector.

3.9 Studies on the mechanism of drug resistance in malaria parasites

Study of the mechanism of development by malaria parasites of resistance to drugs should be carried out on avian malaria, on rodent malaria and particularly on simian malaria. The method of this study should be based on the follow-up of the effect of the drug on the clones of the parasites maintained by serial inoculations. The trend and degree of the induced resistance to the drug (or drugs) should be studied, as also the stability of the resistance after passage through a mosquito vector and the presence of cross resistance to related compounds. The investigation of the biochemical processes involved should be carried out on strains of parasites maintained in culture.

3.10 Development of a satisfactory liquid preparation of antimalarial drugs suitable for infants

The success of mass drug administration carried out in areas with insufficient public health service will often depend on the possibility of treatment on young age-groups, and the development of special, preferably liquid, preparations of anti-malarial drugs suitable for infants is of importance.

3.11 Research on chemotherapy of malaria in human volunteers

Chemotherapeutic research on the improvement of drugs for prevention and radical treatment of human malaria is severely handicapped by the difficulty in testing drugs on human subjects. The need for setting up an International Human Malaria Research Centre was fully expressed by the WHO Technical Meeting on Chemotherapy of Malaria (Geneva, November 1960), and the recommendation of this Meeting is quoted below:

> "Facilities for research into the chemotherapy of malaria and the full evaluation of existing drugs lag far behind the requirements and at almost every point in the group's discussion, more information was necessary for firm decision and such information was most often of the type which in the past has come from careful studies on experimental

human malaria. Most of the recent reliable information presented to the group came largely from the Human Malaria Research Units in USA and the group firmly believes that any future progress in the chemotherapy of malaria on which so much depends for malaria eradication must be based on experimental human malaria.

The group strongly recommends that WHO should explore as a matter of urgency the possibility of setting up some human malaria research centres, where research on chemotherapy of malaria could be carried out on volunteers."

4. Entomology and Insecticides[1]

4.1 Studies of resistant anophelines in colonies. Formal genetic studies on the inheritance of the resistance gene or of taxonomic relationship within a species complex

The establishment of laboratory colonies of both resistant and susceptible strains of those species of anophelines in which resistance has appeared in nature, together with studies of the spectrum of the resistance, its pattern of inheritance and biochemistry of its mechanism. A technique for securing pure individual crosses from anophelines which are difficult to colonize may be based on artificial insemination of female Anopheles by decapitated males.

4.2 Dynamics of resistance in the field. Investigations on the varying proportions of resistant and susceptible genes in anopheline populations under different degrees of selection-pressure

Comparative study of developing gene-frequency (a) under selection-pressure from different dosages of a given insecticide and (b) at different distances from the sites of selection.

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[1] It should be mentioned here that an international collaborative programme of applied research in the field of new insecticides is now being successfully carried out by WHO, under the aegis of the Division of Environmental Sanitation. This programme provides for a standardized evaluation of new insecticidal compounds produced by the chemical industry. The evaluation is carried out in five successive stages as follows: I - Initial evaluation; II - Preliminary laboratory evaluation; III - Advanced laboratory and preliminary field evaluation; IV - Advanced field evaluation; V - Final field evaluation.

4.3 Study of the range of dispersion of infected Anopheles of some species

There is some unconfirmed probability of the appearance of foci of malaria originating from long-range dispersal of infected A. pharoensis. Studies on the maximum and average range of flight of this and some other sturdy species are indicated in various climatic and meteorological conditions. Much information could be obtained by labelling the investigated species of Anopheles with radioactive isotopes.

4.4 Development of suitable field techniques for the study of longevity in populations of malaria vectors

The investigation concerns the application to tropical malaria vectors of techniques for assessing the proportions of females old enough to be infective. The reliability of calculations based on the proportion parous, and those based on the number of ovipositions by each parous specimen, will be assessed in the light of the relevant sporozoite rates, together with the practicability of the alternative techniques in the field. The use of radioactive isotopes for the assessment of longevity of labelled mosquitos shows much promise and should be stimulated and assisted.

4.5 Assessment of the infectivity and the age composition of malaria vectors in different seasons, and under the impact of residual insecticide

A study continued through wet and dry seasons will trace in each vector the proportion of females old enough to be infective, in relation to its sporozoite rate on the one hand and its proportion of parous females on the other. Changes in the patterns of longevity after the spraying of residual insecticide will then be investigated.

4.6 Assessment of the significance of exophily of vectors in malaria eradication programmes

A comparative study will be made of the degrees of vector control obtained by residual insecticide in a highly endophilic or endophagic malaria vector, and in a second vector which is partially exophilic and exophagic. The methods of assessment will include trap-hut densities, room-kills, proportions of females parous and sporozoite rates.

4.7 Identification of feeding preferences of malaria vectors. Study of resting habits of Anopheles

Feeding preferences of Anopheles can be studied by means of precipitin tests carried out on the ingested blood. Serological investigation of the origin of the blood meal will be carried out by a specialized service using a number of animal antisera and employing a highly reliable and sensitive technique.

Changes of feeding preferences of some malaria vectors from areas under insecticidal spraying should be investigated.

4.8 The relationship between DDT-susceptibility and room-kill, and that between DDT-irritability and room-kill

The object is to show how much operational importance attaches to interspecific variations in the natural DDT-susceptibility and DDT-irritability of vectors, WHO tests will be performed to determine where only one of these factors varies as between two species. In the localities thus selected, standard trap-huts will be sprayed with DDT and the subsequent room-kills will be assessed against repeated measurements of susceptibility and irritability.

4.9 Development of entomological indices foreshadowing the resumption of transmission in a malarious area in the first year of total coverage with residual insecticide

Investigation of the connexion between degrees of vector control and the absence or resumption of malaria transmission through one or two years of total coverage of a holo-endemic area. The indices to be investigated are the "room-kill", the "man-biting rate" of the vector and the infant-parasite rate. An attempt will be made to assess the value of an "index of entomological effectiveness" (man-biting rate x 1 "room-kill"), or, alternatively, the number of blood-fed female vectors which survive 24 hours after removal of the window-trap. Other practical indices may be developed during this study.

4.10 Methods of assessing the man-biting rates of malaria vectors

Methods of determining the average number of bites per person per night by an anopheline population will be compared, and their weaknesses or drawbacks will be critically examined. The methods to be studied include all-night (or intermittent)

capture on human bait, capture in bed-traps, capture in window-traps, and spray-capture in bedrooms. The value of each method in an area sprayed with residual insecticide should be assessed also.

4.11 Entomological evaluation of the reliability of field trials of dosages or cycles of residual insecticide

The subject of study is the degree of importance and means of solving certain problems which affect the reliability of field trials using the WHO "Tentative operational method for assessing the entomological effects of different dosages of DDT in the field". The problems include the hypothetical reduction of numbers of anophelines which enter a room or a trap-hut when it is fitted with masked entry-louvres and outlet-traps, the delay which may occur while they seek a way out of the room, any resulting increase in the room-kill, the proportion which may escape without being trapped, and the proportion of dead mosquitos in a sprayed room which are taken by ants or other predators before dawn.

4.12 Investigation of the value of mixed insecticides for prevention of the development of high resistance in colonized and wild populations of Anopheles species having a low frequency of an inherent resistance gene to the insecticide

Our knowledge of the combined action of two or more insecticides in anopheline populations with an inherent gene of resistance is limited. There is need for further experimental work not only to establish the processes by which different toxicants may interact but also to determine on a practical basis which insecticides may be expected to be mutually compatible for control of malaria vectors.

4.13 Assessment of the practical value of some new "residual fumigants" such as DDVP in malaria eradication

There is good evidence that DDVP - an organophosphorus compound with a high volatility - exerts a potent prolonged and rapid toxic action on various insects including malaria vectors at doses so small that they present little risk to humans. Intensive studies of this compound and of the means of using it are now in progress. These studies should be extended to various geographical areas and local conditions. The method for assessing the possibilities of "residual fumigants" for malaria eradication and particularly their long-term toxicity to man should be given much attention.

4.14 Development of a practical method for measuring the effects of the facultative exposure of mosquitos to an insecticide with an irritant action

There is need for a simple and reliable method of measuring the irritant effect of some insecticides on malaria vectors. Some devices have been proposed for a standard method but the design of the apparatus needs improvement. The best way of using it in unsprayed and sprayed areas and on colonized mosquito populations with a varying degree of susceptibility to insecticides, should be determined in further tests on colonized mosquitos and in the field.

4.15 Assessment of possibilities of biological control of malaria vectors

Detailed study in the laboratory and a small-scale trial in the field of the results of introducing some species of parasitic fungi (Microsporodia and Coelomomyces). The field trial should be preceded by a detailed study of the virulence, mode of infection, host-parasite relationship and ecological features relevant to such a control.

A variant of biological control of malaria vectors is that based on the introduction into an anopheline population of large numbers of males sterilized by means of gamma radiation. The value of this method is now being assessed in a field trial but more field trials, particularly in tropical conditions, are desirable.

4.16 Studies on cytogenetics of some malaria vectors to elucidate the systematics of Anopheles forming a species-complex

Many problems of taxonomy of such species-complexes as the "Gambiae group", "Punctulatus group", "Minimus group" and others remain unsolved. Present advances in cytogenetics may assist considerably in the investigation of the systematic position of separate members of such species-complexes.

4.17 Co-ordination of several large-scale investigations on the phenology of main malaria vectors

Co-ordinated studies on the recording and study of interrelations of periodic (seasonal) biotic events in populations of main malaria vectors have been carried out only in the Soviet Union with most interesting results. Such studies should be stimulated and assisted by the Organization in other parts of the world.

The purpose of the WHO/Mal series of documents is threefold:

(a) to acquaint WHO staff, national institutes and individual research or public health workers with the changing trends of malaria research and the progress of malaria eradication by means of summaries of some relevant problems;

(b) to distribute to the groups mentioned above those field reports and other communications which are of particular interest but which would not normally be printed in any WHO publications;

(c) to make available to interested readers some papers which will eventually appear in print but which, on account of their immediate interest or importance, deserve to be known without undue delay.

The issue of a paper in this series does not therefore constitute formal publication and a paper so issued may, with the agreement of the author and WHO, be published in a WHO periodical or elsewhere.

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