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MALÁRIA AT THE RIO CONGRESSES 1963

A review of papers on malaria presented at the Seventh International
Congresses on Tropical Medicine and Malaria, Rio de Janeiro,
September 1963

The Editor has received a further seven abstracts of papers on malaria
presented at the Rio Congresses which are now released in this Annex to
WHO/Mal/417-WHO/Vector Control/52. Any further abstracts received will be
released in a second and last Annex. It will be observed that the abstracts
in this Annex are numbered in accordance with the headings of the original
WHO/Mal/417.

1.21 Demonstration of pre-erythrocytic stages of *P. cynomolgi* by transplantation techniques

New title: The localization of infective pre-erythrocytic forms of *P. cynomolgi* - R. N. Rossan, K. F. Fisher, R. D. Greenland, C. S. Gunther & L. H. Schmidt (Cincinnati, Ohio and Davis, California, USA)

The investigation was aimed at localizing the site(s) of development of the pre-erythrocytic forms of *P. cynomolgi* by use of tissue implantation techniques. Twelve infant rhesus monkeys sacrificed four, five, six and seven days after having been inoculated with *P. cynomolgi* using massive numbers of sporozoites, served as donors of liver, spleen, lymph nodes, lung and bone marrow. Fragments of these organs were implanted into the abdominal cavities of 115 young monkeys of the same species.

Positive results (development of parasitaemia) were obtained with 26 of 61 liver implants carried out four to six days after sporozoite inoculation. The incidence of takes was largest at six days, at which time the peripheral blood was still negative. None of 44 implants of spleen, lymph node, lung or bone marrow induced infections.

These observations add strength to earlier morphological studies which have focused attention on the liver as the site of development of pre-erythrocytic forms of primate plasmodia. Because of technical problems not yet resolved, they should not be interpreted as excluding the possibility that such development occurs in other organs.

2.39 Susceptibility and resistance to residual insecticides of Anopheles vectors in Romania after 16 years of employment of DDT and BHC - M. Linea, G. Fupasco, M. Duport, M. Sandulesco, A. Cristesco, I. Cambiesco and I. Sandesco (Bucarest, Romania)*

The introduction of residual insecticides (DDT and BHC) in Romania on a large scale, dates since 1949 for malaria control campaigns and since 1955 for malaria eradication. These insecticides were used mainly as imagocides directed against the main local vectors: A. atroparvus, A. m. messeae, A. m. maculipennis and A. sacharovi characterized by their endophily and endophagy.

The results of observations and resistance tests carried out (by the method of Busvine & Nash and that of WHO) on adult Anopheles during the period 1956-1960 indicate: (a) normal susceptibility to DDT, BHC and dieldrin and (b) increase of tolerance particularly to BHC and dieldrin, during the pre-hibernation period.

Studies carried out during 1961-1962 showed the presence of resistance to dieldrin in eight out of 20 investigated localities and a certain degree of tolerance to DDT in seven of these localities. The Anopheles population was composed mainly of A. atroparvus (59.3% - 95.2%) associated with A. m. maculipennis and A. m. messeae. A. sacharovi identified in 1961 and present to the extent of 84.1% and 99.0% in two localities remained susceptible to the two insecticides.

The appearance of dieldrin resistance in 1961 was an important fact. Nevertheless, taking into account that the year 1961 was the seventh year of the national malaria eradication programme when over 2/3 of the endemic malarious area was in the consolidation phase, one could state with certainty that DDT was an active residual insecticide and that its further use is justified to complete the programme of malaria eradication in Romania according to the foreseen schedule.

* Asterisk indicates that a summary was either prepared or translated by the editor

2.41 Behaviour of the Anophelines of Mexico during the malaria eradication campaign - A. Martínez Palacios (Mexico, D.F., Mexico)*

Present malaria eradication policy presumes the existence of two basic properties in the vectors, which make possible the eradication by the application of residual insecticides against the adults. These properties are: (1) the domesticity of the vectors, and (2) their susceptibility to the insecticide to be applied.

The campaign in Mexico, carried out by the Comisión Nacional para la Erradicación del Paludismo, was planned following the above-mentioned principles in the light of the experience and technical knowledge available. The attack operations were conducted on the assumption that the two major vectors, A. pseudopunctipennis and A. albimanus had the above-mentioned properties. The information concerning domesticity in its accepted sense was based on observations carried out before the campaign while the determination of susceptibility was done in the preparatory phase in 1956. Although the attack phase throughout the country started in 1957, insecticide pressure on the vectors had been felt in several parts of the country since 1946 when chlorinated hydrocarbons were introduced in Mexico in malaria control campaigns. To this should be added that in certain parts of the country residual insecticides have also been used in agriculture.

The insecticides used against the vectors in Mexico before and after the initiation of the eradication campaign have been DDT, usually at a dosage of 2 g per m² twice a year, and dieldrin, at a dosage of 0.6 g per m² once a year.

The entomological surveillance maintained during the eradication programme has demonstrated the existence of the following main developments in the two vectors: (1) physiological resistance of A. pseudopunctipennis and A. albimanus to dieldrin, and of A. albimanus to DDT; (2) avoidance of DDT by the two vectors.

Development of resistance of A. pseudopunctipennis to dieldrin took place in areas where this insecticide had been applied for indoor spraying. The resistance of A. albimanus to dieldrin and DDT is attributed to the spraying against cotton pests.

The insecticide avoidance is a more widespread phenomenon, and has probably a greater epidemiological impact than physiological resistance. The two vectors remain predominantly endophagous, but it has been noticed that the number biting man is not the same as the number getting in contact with the insecticide.

4.30 The pharmacology of pyrimethamine and related compounds - L. G. Goodwin
(London, UK)

Very large doses of 2,4-diaminopyrimidines given to mice, rats, cats, dogs, monkeys or man, cause salivation, excitement and periods of clonic convulsions alternating with quiet periods. The convulsions are controlled by barbiturates. Large doses given intravenously cause a persistent fall in blood pressure and decreased motility of the gastro-intestinal tract. Gastric function is also affected with a decrease in volume and acidity of gastric juice in experimental animals and man.

The action on the heart is a curious one: 2,4-diaminopyrimidines, and the related compound, proguanil, inhibit the beat of isolated rabbit auricles; the beat is restored by acetylcholine, very rapidly if the auricles are first exposed to adrenaline. Like quinidine, the 2,4-diaminopyrimidines restore normal rhythm to a fibrillating heart. All the active antimalarial schizontocides - the quinine alkaloids, pyrimidines and 4-aminoquinolines - appear to have this property. It has been shown that pyrimethamine arrests fibrillation because it decreases the permeability of cardiac muscle membranes to potassium ions.

It is possible that all the acute toxic actions of 2,4-diaminopyrimidines, including their central convulsant action, may result from changes in membrane permeability. The uptake of potassium ions by erythrocytes is also inhibited by these drugs and this may perhaps have some bearing on their antimalarial activity.

Diaminopyrimidines are well-absorbed after oral administration; injections of their soluble salts are irritant and give rise to lower blood concentrations. The use of injections of insoluble salts of this type of drug is quite another matter, and an exciting new field has now been opened.

Pyrimethamine persists in the body for long periods. Although we thought at first that it might be metabolized to an even more active substance, this is improbable. About 20 metabolites were detected from ¹⁴C-labelled pyrimethamine in laboratory animals, but none of the major metabolites were as active as the original compound when we tested them on P. gallinaceum in tissue culture.

The discrepancies originally observed between assays in serum by the dye-lake colorimetric procedure and a microbiological method are probably explained by the fact that the drug is very firmly bound to protein. The amount of the drug in serum samples was underestimated when the protein complex had had time to form. But investigators using a more suitable colorimetric method, considered that the time-activity curve of pyrimethamine could be satisfactorily explained without the invocation of a more active metabolite.

The therapeutic action of 2,4-diaminopyrimidines probably depends upon the inhibition of folic acid reductase. It is interesting that the best structural configuration for the anti-metabolite varies from parasite to parasite. The 5-p-chlorophenyl derivative, pyrimethamine, is the most effective of over 300 related compounds against experimental malaria infections.

Diaveridine (closely related to diaminopyrimidine), the best coccidiostat of the series, and trimethoprim, the best antibacterial, are 5-benzyl derivatives. The effect of small changes in chemical structure is also seen in drug-resistance studies. Experimental plasmodial infections which have been made resistant to pyrimethamine are fully sensitive to closely-related diaminopyrimidines.

Diaminopyrimidines are potentiated by sulfonamides through sequential blocking in the same metabolic pathway. Sulfaquinoxaline greatly enhances the activity of diaveridine in coccidiosis of poultry and sulfadiazine potentiates pyrimethamine in human toxoplasmosis and malaria. There is the interesting possibility that pyrimethamine-resistant human malaria might be sensitive to a combination of pyrimethamine and sulfonamide.

It is, of course possible that such a response could be explained if the sulfonamide increased the rate or extent of absorption of the pyrimethamine, or increased the antifolic action of the plasma. However, this was almost certainly not

the case, as shown by the results of experiments made many years ago on the antifolic activity in the serum of volunteers who took pyrimethamine, sulfadiazine, and the two drugs together. Sulfadiazine did not itself contribute in any way to the antifolic activity of the blood.

There is still a hope that associations of antimalarials may help to prevent the emergence of resistant strains. In tuberculosis such associations have been eminently successful but we do not yet know how they behave with protozoan infections. Combinations of pyrimethamine and chloroquine have been used in prophylactic campaigns and for presumptive treatment of fevers in cleared areas. Chloroquine or amodiaquine in association with primaquine is now being used for prophylaxis in P. vivax areas. Combinations of pyrimethamine and primaquine have not yet been properly assessed.

A great deal remains to be done in the assessment of drug associations and their effect on the emergence of resistant strains. It is likely that the diamino-pyrimidines with their elegant mode of action will play a part in such associations, either with sulfonamides and sulfones which potentiate them, or with drugs of different chemical structure which complement their action.

5.12 Epidemiology of persisting transmission - N. N. Dukhanina (Moscow, USSR)*

Cases of persistent transmission of malaria were quite frequent in various landscape-geographical zones of temperate and sub-tropical climate, until the introduction of residual insecticides. This was due to the fact that the methodology of malaria eradication was not perfect. With the large-scale use of residual spraying with DDT the effectiveness of such measures became so great that malaria eradication could be achieved within a few years, if there was no DDT resistance in the vector. In some separate localities the transmission of malaria might have been maintained without an introduction of the source of infection from the outside, and in spite of antimalarial measures. Usually the degree of such transmission was low. Any changes of one or more of the epidemiological factors (increase of density of the vector, changes in the temperature and humidity, increased contact of man with mosquitos) caused the growth of incidence of malaria.

The reasons for such a maintenance of foci of malaria were not always clear. There were even hypotheses referring to some particular aspects of epidemiology interfering with malaria eradication. Another point of view was that, in such foci, there were no particular aspects of malaria epidemiology, and that their presence was due to the insufficient quality of malaria eradication activities. An analysis of slowly reducible or remaining foci of malaria in various zones of the Soviet Union and other countries of temperate and sub-tropical climates showed that, in every case, the main factors responsible for maintaining transmission were due to defective malaria eradication activities. The maintenance of transmission, in spite of malaria eradication activities, was seen usually in foci with vivax malaria with short incubation in the south and - exceptionally - with vivax malaria with long incubation in the north. In the sub-tropical area the maintenance of malaria transmission in a few foci took place under the following conditions, related to the epidemiology of malaria or to the defective carrying out of antimalarial measures:

(1) Epidemiological aspects of malaria

(a) High remaining density of malaria vectors; (b) presence of exophilic species of vectors; (c) rapid completion of the sporogonic cycle; (d) presence of separate foci of malaria in a given administrative territory, even though they were far apart; (e) continuous mobility of the population.

(2) Difficulties in carrying out antimalarial measures

(a) Lack of total coverage with residual spraying or inadequate timing of it, particularly in areas where the silkworm industry is prevalent; the same effect follows premature cessation of spraying which allows the mosquitos to live until the epidemiologically dangerous age; (b) delayed detection of malaria cases; (c) (c) inadequate administration of radical treatment by quinocide which is responsible for the maintenance of the source of infection; (d) inaccurate or otherwise imperfect epidemiological follow-up of malaria cases so that the origin of infection could not be traced.

The study of the characteristics of epidemiology of malaria in residual foci, and the rational build-up of the system of antimalarial measures will lead to full and permanent malaria eradication in these foci.

6.27 Factors conducive to resumption of transmission in areas where malaria has been eradicated - N. N. Dukhanina (Moscow, USSR)*

In most of the localities where malaria eradication has been completed, the cessation of the epidemiological process is related to the absence of the vector. In other areas the vector is present and the climatic conditions are such that an eventual sporogony can be completed, if there is an adequate degree of contact between the human population and the mosquito. Whenever the source of the infection is brought either from residual foci of the same country or from outside the country, the transmission of malaria could be resumed. In some cases the resumption of transmission of quartan malaria can take place from blood donors, or through recipients who were infected with malaria after blood transfusion. The larger the territory where malaria has been eradicated, the greater the certainty that the introduction of the infection from residual foci is difficult, if not impossible. The degree of danger of conversion of former malaria foci into active foci depends on a number of factors which could be placed in two relative groups:

(1) natural factors related to the vector and the development of an infective agent in it, and

(2) factors which pertain to the degree of contact between man and Anopheles.

In various landscape-geographical zones, the danger of spread of malaria will be greater as the process of sporogony in the mosquito is faster and the "turnover" of the malaria parasite during the transmission season more frequent. The probability of resumption of transmission in malarious foci is greater in relation to the density of vector, to the distance between the inhabited localities and the Anopheles breeding places. On the other hand, it is in inverse relation to the zoophily of the vector.

Among the factors of the second group, the most important is the duration of the infectivity of the human case of malaria or an asymptomatic carrier of infection. The late detection or the imperfect treatment of such cases is mainly responsible for

resumption of transmission. The time of appearance of local cases depends on the species of malaria parasite and on its strain imported from the outside. It also depends on the immunological structure of the population. If the immunity to malaria is lost after its eradication one could expect that the course of the disease in the local population would be severe. On the other hand, if there is any degree of residual immunity in the population, then malaria will be of a mild character and often in the form of more or less apparent carriers of the infection. In order to prepare a rational system of epidemiological follow-up for various localities with varying degrees of the possibility of return of the infection, a proper classification of former malaria foci and adequate planning of the epidemiological follow-up for each type of such foci is necessary.

6.29 Malaria eradication in Latin America and its problems -- P. H. Owens
(Cali, Colombia)

The problems of malaria eradication in Latin America, and possibly elsewhere, may, like all Gaul, be divided into three parts. The parasite, having been cultivated so assiduously for so long at leading educational institutions and research centres, seems to have taken a few courses in organic chemistry in the process, to the present confusion of its curators. The mosquito, courted in similar fashion, has developed a disparaging opinion of benzene rings, and its comfortable proximity to the anthropological courses given by the Social Sciences Department in the next building has given it an insight into human vagaries which proves singularly frustrating. The people, who are supposed to benefit from the programme, are at times equally intractable; it is the author's belief that they have sometimes been sadly neglected at the expense of Plasmodium and Anopheles.

The author leaves the detailed discussion of the first two questions to experts in the respective fields. However, as a duty-paying member of the human race, he feels fairly competent to discuss the third dilemma in a general way.

Evidence is brought forward to suggest a disparity in the amount of attention given to a study of the intermediate host, and the plea is made that it merits at least a fraction of that devoted to the parasite and the definitive host. It is contended that almost all effort devoted toward the intermediate host will eventually prove rewarding.

A secondary facet of the "people problem" is explored, i.e., that relating to the people running the malaria eradication campaign. The author yields to no one in his admiration for those individuals, most of whom are woefully overtaxed. But as a one-time worker in the vineyard, and a quondam student of the problems involved, he suggests that the administrations might not be doing enough in the right directions.

6.30 The changing needs for personnel and their training in malaria eradication -
S. P. Ramakrishnan (Delhi, India)*

The special needs of personnel and their training with reference to the lessons learned in the course of the malaria eradication programmes comprise: progressive simultaneous increase in the demand for trained personnel for medical and health work in fields other than malaria resulting in a large turnover of personnel; limitations in the availability of personnel in adequate numbers and quality - this varies from country to country; the changing functional objectives from phase to phase of the programme; new qualities and responsibilities required of eradication personnel in organization and supervision; the need for continuous evaluation of procedures and data; the need for continuity of training after the primary intensive teaching course; the need for integrating the experience gained by the personnel at different levels for use in other public health programmes when the time comes and, finally, the need for new types of investigation in the course of the programme.

In general, the categories of personnel required to operate in an eradication programme can be considered under seven broad categories, namely: (1) high-grade (medical) professionals with administrative ability; (2) high-grade professional specialists (medical or non-medical depending on the specialization); (3) professionals with organizational and supervisory abilities; (4) sub-professionals (skilled specialists); (5) sub-professionals (trained in man-management); (6) non-professionals (skilled), and (7) non-professionals (non-skilled).

From the above it is clear that it is essential to establish schools at different levels in the country to take care of the training needs. Such a development of training facilities has not taken place in many countries on a planned basis. The national-level and state-level schools must provide for refresher training periodically, preferably by seminars, and design for continuity of training at all levels by field visits and/or postal tuition methods.

The national- and state-level schools which may have to train professionals of different academic disciplines will have to undertake the training of each category separately. In special situations it might be possible to design a course, a part of which is common to all trainees, the rest of it being for specialized groups.

At international levels the existing schools and any projected new ones should train future teachers for the national and state levels. In any country with an eradication programme there are ample facilities for field training. Trainees sponsored by international organizations are directly attached to country programmes for an observation tour. Generally this happens at different times of the same year, and frequently. This disorganizes the work of individuals involved in the host country's programme and it is not always true to say that the visitors get the best of the observation tour. It might be preferable that these fellowships should operate at specific period(s) of the year.

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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