

LEAGUE OF NATIONS.

C.H./Malaria/209.

Geneva, September 20th, 1933.

HEALTH ORGANISATION.

MALARIA COMMISSION.

Note by the Medical Director.

The Medical Director has the honour to communicate herewith a report on the work of the Malaria Commission, drawn up by its Chairman.

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Report by the President of the  
Malaria Commission.

The programme of work which the Malaria Commission set itself for the year 1932-1933 has been carried out as follows:

1. Technical co-operation with malarial countries.

Such co-operation has been continued. Study tours have been undertaken by a number of malariologists attached to the anti-malarial services in China, British India, Indo-China, Italy and the Straits Settlements and they have been afforded opportunities of proceeding abroad in order to study the various aspects of malaria problems together with the methods applied in various countries for dealing with them.

In the course of their tours our colleagues have had an opportunity of studying local problems, exchanging opinions with European malariologists, acquainting themselves with anti-malaria organisation in the countries visited and of ascertaining the results obtained by the methods employed.

It is now no longer necessary to dwell upon the value of such study tours as a means of extending knowledge of malaria problems and improving methods of dealing with them through international technical co-operation. The co-operation of 93 public health authorities in the enquiries into the prevalence of malaria and its treatment (See C.H./Malaria 185) will be continued in accordance with the plan laid down in Document C.H./Malaria 207.

Co-operation with China: Professor Mühlens, from the Institute of Hamburg, who went for a study-tour in the Far East, has been requested by the Health Organisation to examine the results obtained by the Malaria Division of the Central Field Health Station at Nanking. During his stay there he was able to draw up a programme of research work to be undertaken with samples of Totaquina and other synthetic products. These experiments are being carried out at the "Central Hospital" at Nanking and in a few schools. Moreover the Central Field Health Station has set up mobile units for malaria control in centres where work of public utility is being carried out (Hankow, Kaipheng, Anking and Nanchang).

## 2. Malariology courses.

These courses, which were initiated under the auspices of the Health Organisation, have only been held this year in Paris and Rome as the number of English and German speaking applicants was insufficient.

The Health Section received fourteen applications for the course in Paris and one for the Rome course. Eight scholarships were granted for the courses and field work, one for the study of biological methods of testing anti-malaria medicaments, one for field work - which as in previous years was carried out either in Spain and Italy or in Yugoslavia and Italy - and one for field work in Italy. Seven of those who followed the courses did so at the expense of their respective Governments.

The participants were drawn from the following countries: Colombia, France, Italy, Persia, Portugal, Roumania, Spain, Turkey, Venezuela.

### The Singapore Courses.

In May 1933 the British Foreign Office informed us that it had conveyed to the Governor of the Straits Settlements its consent to the organisation of a malariology course in Singapore for young malariologists from the Far East.

The desirability and programme of this course gave rise to numerous discussions among the members of the Advisory Council of the Eastern Bureau which adopted the following resolution:

"The Advisory Council requests the Director of the Bureau to consider the progress of the proposed international malaria courses at Singapore in consultation with the authorities concerned or interested so that the experience gained from this first course might be used in considering for the future the furthering of the campaign against malaria in every country and international co-operation in this campaign.

The Health Organisation has requested the Colonial Ministries of the United Kingdom, France and the Netherlands to authorise practical field work in the malarial countries of the Far East where the variety of the problems and the highly developed organisation of the anti-malarial campaign would be of great value to those taking part in the course.

The Director of the Bureau has already informed the health authorities in the Far Eastern countries of the date and programme of these courses and has intimated to the Commission that four of these countries are prepared to take part in them. The first course will open on April 30th, 1934.

3. Co-ordinated research: Meeting of the Malaria Commission (Study Committee).

In deference to the wishes of the Health Committee (October session 1932) the Malaria Commission (Study Committee) met from April 25th to 27th, 1933, to consider the reports of the Reporting Committees on the various questions on the agenda (C.H./Malaria 206). The meeting was attended by the following members: Dr. A. Lutrario (Chairman), Professor G. Bastianelli, Professor J. Cantacuzène, Sir S.R. Christophers, Major A. Covell, Dr. L.W. Hackett, Colonel S.P. James, Professor A. Missiroli, Professor B. Nocht, Professor D. Ottolenghi, Professor G. Pittaluga, Professor Ed. Sergent, Dr A.I. Stanton, Professor N.H. Swellengrebel, Sir Malcolm Watson, Dr. C.M. Wenyon.

Dr. S. de Buen, Professor Brumpt, Dr. I.J. Kligler, Professor E. Marchoux, Professor F. Mühlens, Professor W. Schüffner and Lt. Colonel J.A. Sinton were unfortunately unable to be present.

The Committee's task was greatly facilitated by the meetings of the three reporting Committees which took place immediately before the plenary session to consider the reports on "The Therapeutics of Malaria", "Housing and Malaria" and on "Malaria of the Deltas", and to agree upon their details.

The Therapeutics of Malaria.

The report drawn up by the Rapporteurs\* together with the amendments introduced in the course of its examination by the Study Committee brings out the development of the latter's work on this problem and the progress made in regard to the treatment of malaria during the past ten years, while at the same time analysing the data already collected which are based upon experimental laboratory research in clinics and in the field.\*\* The report particularly deals with the treatment of the disease and the various standpoints from which prophylaxis must be considered (causal clinical prevention of relapses, gametocyte therapy) and also contains a survey of the efficacy of the most widely used anti-malarial products. To make comparison possible of the results obtained by investigators in different countries where conditions vary according to the types and geographical strains of parasites, endemicity, the degree of acquired immunization, etc., etc., the report devotes a chapter to the methods to be used in therapeutical research with anti-malarial products, due account being taken of biological tests both in regard to avian and to human malaria (natural or induced infection).

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\*Colonel James, Professors de Langen, Nocht, Pittaluga and Sergent. Professor Mühlens, who is also a member of this Committee, was only able to be present at one meeting in January.

\*\* Quarterly Bulletin of the League of Nations Health Organisation, Vol.II, No.2.

The conclusions bring out the progress made in regard to the biology of malaria and of its treatment and emphasises the importance of the discovery of synthetic products. At the same time they express the view that the latter are still in the experimental stage and that the time is not yet ripe for recommending the actual use of any of these preparations either as a substitute for quinine or other febrifuges derived from cinchona bark or in preference to such products.

The Committee was careful to point out that, from the medical point of view, the question of competition between natural and synthetic medicaments does not arise; it also demonstrated the efficacy of anti-malarial remedies, both for the prevention of infection and in the treatment of the various phases of the disease.

The new research work set out by the Committee in its programme of studies shows how far one still is from the solution of this problem.

The report, together with the various amendments, was adopted, the Committee passing the following resolution:

"The Study Committee of the Malaria Commission expresses its gratitude to the members of the Reporting Committee, to all the experts who have been good enough to undertake research work, as well as to the members who have supplied the full documentation which has served for the editing of the report on the Therapeutics of Malaria.

"It adopts the report and expresses the hope that the researches will be continued on the same lines and with the same methods as those described in the report."

#### Housing and Malaria:

This problem, the study of which was suggested by the Malaria Commission in 1928, has given rise to extensive research work undertaken both under the auspices of the League of Nations and independently. The Reporting Committee's report and the work of the experts constitute an extensive study of present knowledge on the biology of anopheles in relation to the conditions of environment and housing and to the transmission of malaria in malarial countries of different climates. In these works the study of the factors capable of bringing about profound changes in the relations between anophelism and the occupants of houses is not overlooked. The study of local problems in countries where there is only one important carrier confirms the existence of numerous factors which might be responsible for "malarial houses"; several of these factors have still to be determined.

While recognising the value of the material already collected and dealt with in the report, the Commission considered it indispensable to carry out further research in order to elucidate the points raised in the course of the discussions; it therefore adopted the following resolution:

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\* Sir S.R. Christophers and Professor A. Missiroli.

"The Study Committee greatly appreciates the Report on Housing and Malaria submitted to it and expresses its thanks to the Rapporteurs\* and wishes to state that further studies should be included in the programme of work in order to make clear and define the various points raised by the members of the Committee.

"In particular they wish that the study of the subject should be extended to include a more complete account of the relation between anophelism and the families and their dependents who, together with their domestic animals, occupy the houses, out-houses and their immediate environment (the whole site which in English is comprised in the term "home") where it is considered that most cases of malaria are contracted".

The Committee was of the opinion that the report should be accepted on the responsibility of its authors, whose signatures it should bear.

#### Malaria in Deltas:

This question, the investigation of which was undertaken in 1925, has been dealt with in highly valuable reports on the Danube, Ebro, Po and Rhine deltas. The material contained in these documents, together with the observations carried out in the deltas of the Ganges, Nile, etc., bring out the various aspects of the problem of malaria in deltas.

The memorandum submitted by the Reporting Committee\*\* confirms one general epidemiological fact, namely, the absence of malaria in deltas in which natural conditions have not undergone modification. Changes occurring in geography, waterway conservancy and economic and social conditions (particularly immigration) have determined in each delta local epidemiological features. Malaria in deltas is the result of the settlement of human beings in such areas, and its development is proportionate to the density of the population. The conditions which promote its spread are determined in the first place by the works necessitated either in the interests of agriculture or of the protection of works of general concern, and in the second place of the new immigrants required for such undertakings.

What may be called the experimental demonstration of the importance of such factors has been carried out in the Rhine Delta, where the malarial areas correspond to the brackish water breeding-places of A. atroparvus.

The areas reclaimed by the draining of the Zuyder Zee have already benefited from the results of this research work, and an attempt is being made to eliminate the dangers of such brackish water breeding-places by special methods, including the construction of an artificial fresh-water lake from which the irrigation canals will in future be fed.

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\* Sir S.R. Christophers and Professor A. Missiroli.

\*\*Professors J. Cantacuzène, D. Ottolenghi, G. Pittaluga and N.H. Swellengrebel.

The following resolution was adopted:

"The Study Committee congratulates the members of the Reporting Committee on their researches, which are of great scientific value, and considers that similar researches should be continued on the basis of the results already achieved."

Darling Prize:

In accordance with the rules of the Foundation, the names of candidates were submitted by certain members of the Health Committee and Malaria Commission and also by certain Public Health authorities.

The Foundation's first prize is to be awarded on January 1st, 1934, to the author of an original work published in the course of the last five years or communicated to the Health Organisation in manuscript.

The Committee set up a Sub-Committee to examine the proposals received, and at the latter's suggestion the following resolution was adopted:

"The Study Committee, having considered the suggestions made for the award of the Darling Prize and having examined the work and claims of the candidates, recommends to the Darling Prize Committee in the first place Colonel James, and secondly Sir S. Rickard Christophers, Dr. D. Falleroni, Dr. L.W. Hackett, Professor W. Kikuth and Professor A. Missiroli ex aequo."

The Committee of the Darling Foundation, which met in Paris on April 29th, 1933, endorsed the above resolution and decided to award the prize to Colonel S.P. James.

This decision has been given a certain degree of publicity in medical journals and in the Quarterly Bulletin of the Health Organisation.

Enquiry into the quinine requirements of Malarial countries and the World prevalence of Malaria.

As long ago as 1924 investigations were set on foot with a view to carrying out the Health Committee's recommendation regarding the summoning of an international Quinine Conference.

During its study tours the Malaria Commission had observed that the consumption of quinine was not<sup>as</sup> high as might be expected in comparison with the malaria prevalence and the world production of quinine. The ascertainment of this fact led to the enquiry the results of which were published at the end of 1932 in document C.H. Malaria 185.

At its session in October 1932 the Malaria Commission proposed that the scope of the future conference should be extended so as to include not only quinine but also the new synthetic preparations.

At its session in December 1932, the Health Committee adopted the Commission's resolution and invited the Bureau to consider the date and general organisation of the proposed conference.

At its session in April 1933, the Committee came to the conclusion that it would be desirable to supplement the material which had already been collected and which might ultimately serve to secure more adequate supplies, and more efficient distribution of anti-malarial products. Having regard moreover to the new research work now in progress on these various remedies, it considered that the proposed conference should be adjourned. In this connection it adopted the following resolution:

"The Study Committee, in view of the fact that new researches on the different anti-malarial remedies are at present taking place, considers that the proposed conference on this subject should be adjourned to a future date.

"It expresses the hope that the enquiry will be kept up to date and that the health administrations of malarial countries and the corresponding members of the Malaria Commission will continue to collaborate."

This resolution was endorsed by the Bureau of the Health Organisation at its session in May 1933.

With a view to keeping the material on the prevalence and treatment of malaria up to date, a questionnaire was drawn up by the Study Committee (C.H. Malaria 207) and forwarded to malarial countries at the same time as the report on The Therapeutics of Malaria.

#### New Research:

In 1928 the Malaria Commission drew up a list of subjects to be brought to the notice of malariologists for their personal information.

In regard to certain of them, valuable communications have already appeared in medical publications.

After further discussion the Study Committee decided that it was desirable that the attention of investigators should again be drawn to the proposed studies enumerated in the 1928 programme, (C.H. Malaria 121) and recommended that further research be undertaken in regard to the following questions:

I. Treatment - clinical and therapeutical research work:

- Determination in hyperendemic and endemic regions of the age groups most seriously affected by the disease and consequently requiring most attention in the matter of treatment. Investigations should cover in the first place the indigenous population and then be extended to immigrants.

- Determination of the minimum dose of quinine sufficient for the treatment of the disease in hyperendemic and endemic areas where the natives have attained a certain degree of immunity.

- Ascertainment of the dosage (by age groups) of plasmoquine sufficient to prevent the gametocytes from infecting the anophelēs and the intervals (per week) at which it should be administered.

- Determination of the extent, if any, to which the therapeutical action of quinine is increased by the administration of plasmoquine (combined medication).

A beginning should be made with laboratory research on cases of induced infection before proceeding to apply this method in the field.

- Continuation of clinical tests with both types of "totaquina" in accordance with the method laid down in the report.

- Experiments in malaria-control by means of medicaments alone without the application of anti-anophelene measures.

- Blackwater fever; investigation of the relations between quinine and blackwater fever by means of experiments on animals (malaria in monkeys).

Housing and Malaria:

- Biology and geographical distribution of the different varieties of Anopheles maculipennis.

- Study of the following species of tropical anopheles from the point of view of a possible differentiation of races:

a) A. hyrcanus and its several varieties (though widely disseminated, this strain is not as a rule very dangerous though it may become so in certain countries, and especially Sumatra.)

b) A. bifurcatus (unimportant in Europe but dangerous in Palestine).

c) A. ludlowi var. sundaicus (dangerous everywhere, though there is a great difference between its breeding places on the coast of Java and in the interior of Sumatra.)

d) A. gambiae (dangerous everywhere, though its breeding places differ in the Union of South Africa and in Tropical Africa.

- Causes of the very great variations met with in the distribution of malaria in certain tropical regions, - such as the phenomenon of immune areas in the immediate vicinity of hyperendemic areas - and in particular the possibility of a relation existing between this phenomenon and the deviation of the anopheles.

- Investigation of the factors which make certain rice-growing areas highly subject to malaria while others remain immune.

Study of African anopheles and the connection between the various species of anopheles and malaria in Africa.

#### Malaria in Deltas.

- Initiation or pursuit of research on the varieties of A. maculipennis found in European deltas in connection with malarial foci (Danube, Ebro, Rhine, Rhone, Po).

The Sub-Committee suggested that Indian, Siamese and Indo-Chinese malariologists be requested to conduct similar investigations with regard to the races of malaria carrying anopheles in the deltas of their respective countries.

- Investigation of the influence of agriculture on the domesticity of anopheles and on malarial endemicity.

- Study of live stock in connection with local anophelism and the disease.

- Historical study with special reference to malaria of variations in the topographical and demographical characteristics of deltas.

- Investigation of the degree of susceptibility to malarial infection of inhabitants of deltaic areas.

INTERNATIONAL CO-OPERATION IN THE MATTER OF MALARIAL RESEARCH.

The Commission having come to the conclusion that it would be desirable to circumscribe investigation of the co-ordinated problems and to limit them in the future to two or three countries possessing experimental malaria stations, the Secretariat organised a mission of investigation to Roumania in May last.

Colonel James, accompanied by his assistant Mr. Shute and the Secretary of the Malaria Commission, proceeded to that country in order to ascertain at first hand how far laboratory and field conditions would allow of investigation of the problems, work on which had been started by the Malaria Commission, in accordance with the methods recommended by the Study Committee and also to establish co-operation between the experimental malaria stations and the Horton Malaria-therapy Centre in Great Britain.

They visited the permanent experimental research station at Socola where work is being done on cases of induced malaria with a view to malaria therapy on lines similar to those followed at the Horton Hospital at Epsom (near London). The members of the mission were more especially anxious to compare the data obtained on the susceptibility and immunity - in respect of the same strains of parasites - of malarial subjects in England and Roumania where epidemiological conditions are completely different, and also to exchange and preserve strains of the various species of malarial parasites. The experts were also desirous of organising experiments in the treatment of the disease with different anti-malarial products, at first in the laboratory and subsequently in the field, along the lines and in accordance with the programme laid down by the Study Committee in its report on treatment.

With this end in view the experts visited the Izolarea Hospital at Jassy and the stations at Gurbanesti and Tomesti the first of which is under the control of the Bucharest Health Institute and the second under the Jassy Health Institute, both being conducted as centres of research on malaria and its treatment.

These organisations are already making experiments with various medicaments and more especially with various samples of totaquina.

At the end of their stay the experts drew up a scheme of research in co-operation with the directors of the stations visited. This scheme includes investigation of the biology of the four types of parasite (including P. ovale) in two countries with differing epidemiological conditions: (a malarial country and a non-malarial country); research on acquired immunity in respect of various strains of the three types of parasite and experiments to ascertain the efficacy of cinchona alkaloids and synthetic products in the treatment of malaria.

Strains of parasites have been exchanged between the Horton and Socola stations and these are now being investigated in accordance with a definite plan.

Every fifteen to twenty days the secretariat of the Commission arranges for an exchange of observations in regard to patients undergoing malaria therapy and those undergoing treatment with the various substances. In order to enhance the results of this work research on anophelism has been begun by Professor Martini

of Hamburg and Professor Zotta of Bucharest in the areas in which the stations are situated.

The information collected by the Secretariat in Spain and Italy set forth how desirable it would be that this programme of international co-operation should be extended to these malarial countries where conditions of endemicity are different and where there are similar experimental study centres.

### Totaquina.

The following Institutions have consented to carry out experiments in treating malaria with this medicament:

The Pasteur Institute, Algiers,  
The Anti-malarial Institute Naval Moral de la Mata, Spain,  
Regio Spedale, Grosseto, Italy,  
Izolarea Hospital, experimental malaria stations at  
Gurbanesti, Socola and Tomesti, (Roumania),  
Pasteur Institute, Laboratory of Tropical medicine, Paris,  
Medical Clinical, Faculty of Medicine, Sofia,  
Malaria Survey of India, Kasauli, Punjab,  
Institute for Medical Research, Kuala Lumpur, F.M.S.,  
Wei Sheng Shu, Nanking,  
Central Sanitary Bureau, Tokyo.

The experts who have kindly consented to make experiments with this product have received samples of totaquina I manufactured by Burroughs, Wellcome and Co. London, and of totaquina type II manufactured by the State Quinine Factory, Turin, or the Quinine Factory, Madras.

A fourth sample of totaquina type II, the composition of which (quinine 26.90, cinchonidine 25.58, cinchonine 25.12, quinidine 5.40, amorphous alkaloids 15.30, ashes (1.70)) is very similar to that of totaquina type I as manufactured in London, has been submitted to the Commission by the State Quinine Factory, Turin (Totaquina Turin IIb). Thanks to a new process its price will be appreciably less than that of the previous sample. This product has been sent to the various experts.

A treatment record card has been drawn up in accordance with the method of study recommended in the report on the treatment of malaria and has been communicated to all the investigators in order to facilitate comparison of the results of their experiments. Certain modifications on points of detail were introduced after examination - by Colonel James, his assistant Mr. Shute and by the Secretary of the Malaria Commission during their visit in Roumania - of the results already obtained in that country. The Pasteur Institute, Algiers, the Grosseto Hospital and the Institute of Naval Moral and the Research Institute of Kuala Lumpur have also informed us that experiments are in progress.

The Commission's enquiries will be continued in 1934 in accordance with the same programme as in 1933.