

LEAGUE OF NATIONS.

C.H./Malaria/14th Session/
S.C.3./P.V.2.

HEALTH COMMITTEE.

THIRD SUB-COMMITTEE.

MALARIA COMMISSION.

SECOND MEETING HELD ON JUNE 28th, 1928 at 9.30 a.m.

CHAIRMAN:

- PROFESSOR ASCOLI.

Present:

- All the Members of the
Sub-Committee.

THE CHAIRMAN recalled that on the previous day the Sub-Committee had dealt with the question of quinine and of the mixture in the cases of malignant fever, tertian and quartan.

DR. SFARCIC recalled that the first item on the agenda was the question of the use of quinine against malaria. He noted that Professor Schuffner and Professor Ottolenghi prescribed for the moment of the attack, one gramme to one and a half grammes of quinine. He drew attention to the importance, in his opinion, of the biological and other factors which at present were playing an important part. Poverty and precarious conditions of existence were obviously a great obstacle to a favourable treatment. Contaminated persons living in normal conditions might be more rapidly cured than

others. The individual application of quinine was as important as the doses prescribed. A number of people suffering from malaria were unable to undergo treatment with quinine; vomiting often occurred, and therefore Dr. Sfaric recommended intravenous or intramuscular injections of one and a half grammes of quinine. It should be pointed out that a doctor attached to a hospital or a private doctor was entirely free to apply the method that he considered most suitable to his patient. It was not, however, possible for the social doctor to do this. He was obliged to apply a single method to all his patients. In the latter case the most appropriate medicinal treatment was, now as always, the classical method of Professor Koch; one gramme of quinine each day for seven days, an interruption and a continuation of the treatment which ended with one gramme of quinine on Saturday and Sunday only. This protracted cure was the surest preventative against a relapse.

Professor de BUEN said that he only wished to instance general cases and that he would not enter into particular cases. The usual formula in his country, Spain, was: a month's treatment and a curative dose of one gramme a day. This medicinal treatment was efficacious and procured the complete disappearance of the parasites, in the treatment, of course, for adults. Obviously, the treatment for children in the case of benign tertian fever was different. Moreover, the treatment of benign tertian fever was always a problem. Treatment with quinine often occasioned cases of relapse. On the other hand, benign tertian fever often disappeared of itself.

The CHAIRMAN noted that the Members of the Sub-Committee were agreed on the consecutive treatment to be adopted after attacks.

The Committee recommended the following formula:
consecutive treatment: One gramme, average daily dose
(1½ grammes in special cases) over a period of from two to three
weeks. This treatment might be protracted in case of relapse and the medicinal treatment might be prescribed according to the case (primary or relapse fever) several times a week only. It should never exceed the dose of 1½ grammes.

M. MARCHOUX brought up another factor: the district in which the patient was living. He instanced the case in which a benign tertian fever might disappear in a short time with a mixture of one gramme a week taken on two occasions (0,50) in the district of Paris, and the possibility of a patient being re-infected if he were in a contaminated country.

The CHAIRMAN agreed with Professor Marchoux; re-infection might obviously occur in an endemic country.

Professor MARCHOUX, speaking to Professor Nocht, expressed his surprise that the latter, as promoter of the dose of quinine to be administered, had not taken part in the discussion. He would be glad to hear him speak on this subject.

Professor NOCHT explained that he shared the view of the previous speakers and that he was convinced of the necessity of small daily doses. He had not pressed this point, knowing the differences of opinion that still existed on it. On the other hand he thought that control of the mixture was very difficult. Here a psychological factor intervened; peasants, for instance,

could not be trusted to dose themselves rationally, and therefore a small daily dose should usually be prescribed.

The CHAIRMAN asked whether the Sub-Committee agreed with Professor Nocht.

The Sub-Committee approved the general principle of the small daily dose of quinine.

Professor SCHILLING gave details of several experimental cases in the hospital of Professor Koch of Berlin. He pointed out that intravenous injections of 20 centimetres of diluted quinine occasioned relapses. This same solution diluted seven times more, still occasioned some relapses. The same quantity of quinine diluted ten times more, arrested them. This experiment had proved to him that the more the quinine was diluted, the more efficacious it was. He had made the same experiment with Salvarsan on animals. He recommended, therefore, intravenous injections of a weaker, if this were wished, but always strongly diluted, dose.

Professor NOCHT laid stress on the fact that the general therapeutic rule was well known: the efficacy of medicinal treatment was in proportion to the dilution. Nevertheless, he had some objections to make concerning intravenous injections. He had noted many accidents. These injections could only and should only be made in clinics by experienced persons.

In his opinion, the term relapse was difficult to define since there were so many factors to be considered: general care, treatment, the winter, the heavy labour of the peasant, etc. He thought that in order to judge, it was necessary to have thousands of experiments and of proofs.

Professor MARCHOUX asked Professor Schilling whether the experiment of the dose of 0,20 centigrammes had been made once or several times.

Professor SCHILLING replied that paralytics had been treated with this dose. Experiments had also been made on laboratory animals. He repeated his view that the large dilution of the dose was the most efficacious.

The CHAIRMAN shared Professor Schilling's view concerning the dilution of quinine since the latter easily irritated the organism. He did not share his view concerning intravenous injections; these had often, he thought, a dangerous effect upon the heart. He had quite changed his opinion on the subject and he advised that these injections should only be prescribed with the greatest prudence.

Professor SCHUFFNER recalled an interesting observations of Professor Krogh concerning not the chemical effect of quinine but its indirect action.

The CHAIRMAN noted that every one was agreed on the whole concerning alkaloids although perhaps a little less so with regard to "quinetum cinchonine".

Professor CIUCA recalled that the Sub-Committee of April, 1927, had asked that the work on other alkaloids of "quinquina" should be continued.

The CHAIRMAN said that experiments had been made with certain "cinchona" barks from the Indies, but that they were not so rich in quinine.

Professor MARCHOUX wished to know whether experiments had been made in the cultivation of these barks. It would be extremely interesting to know the result of such experiments.

Professor OTTOLENGHI entirely agreed with Professor Marchoux. He explained that specimens of these barks were being cultivated in Italy, that the results of this experiment would be presented to the Italian Superior Health Council and that they would certainly be favourable. Tests might then be made with these barks, and the Commission should urge that these experiments should be continued.

Professor NOCHT asked whether this bark contained a minimum of quinine.

Professor OTTOLENGHI recommended two experiments, one with quinetum with a strong dose of quinine and the other with a smaller dose.

Professor de BUEN explained his method of using quinetum and of keeping charts.

Professor NOCHT read a statement from Bayer & Co. (Leverkusen, Germany) on 1,400 cases which had been treated by different alkaloids, and said that the percentage of relapses was as follows:

	No. of relapses.
Sulphate of quinine	65%
" quinine	82%
" cinchonidine	69%
" febrifuge cinchona	72%
Stovarsol quinine	69%
Plasmochine (pure)	22%
" (comp.)	0 (nil)

The CHAIRMAN asked his colleagues whether they had any views to express with regard to the use of other drugs.

Professor NOCHT said that Bayer & Co., had forwarded him a list of 6,000 cases which had been dealt with.

He did not advise the use of plasmochine save in clinics, as the symptoms were at times disturbing. He prescribed pure plasmochine three times a day in doses varying from 0.002 - 0.006.

Professor de BUEN referred to experiments made in anti-malaria campaigns according to the following system:

Plasmochine treatment for 10 days;

Quinine treatment for 10 days;

Plasmochine treatment for 10 days.

This was a mixed treatment and this method was intended so far as possible to prevent a relapse of mild tertian fever.

Professor SCHUFFNER explained that his Dutch colleague, Professor Snyders, had made experiments in the use of plasmochine in treating mild and malignant tertian fever.

Plasmochine and quinine combined had given a surprising result during treatment for relapses. The cressents had disappeared in five days. In his opinion plasmochine might well be used instead of quinine, but it would have to be improved.

The CHAIRMAN said that he had pointed out that persons who caught mild tertian fever and were treated with undiluted plasmochine remained a long time without strength and in a weak condition. These persons had insisted on quinine treatment and had threatened to leave the clinic.

In his opinion quinine treatment was much more effective.

M. OTTOLENGHI told the Committee of experiments which had been made with plasmochine in treating mild and malignant tertian fever. Results had been obtained much more quickly than with quinine.

Professor CIUCA pointed out that treatment with pure plasmochine was extremely poisonous. He had noted cases where great weakness had been observed.

Professor NOCHT remarked that these toxic cases occurred particularly in Roumania. This might be caused by the method of manufacture of the drug.

Professor CIUCA expressed the view that the individual factor should be taken into account.

Professor NOCHT said that he concluded from the discussion that they should endeavour to obtain treatment by "plasmochin compositum".

The Sub-Committee decided to recommend treatment with plasmochin compositum.

Professor MOUTOUSSIS said that he had treated soldiers for malignant tertian fever with quinine in August 1927. When they were transported to Athens he treated them with small doses of plasmochin compositum. He used a more intensive treatment and the fever fell in a few days. He had not hitherto noted any cases of relapse.

Professor NOCHT advised the use of plasmochine when the patient could not bear quinine. He suggested, however, that these experiments should be left to the wisdom of the physician.

Professor MARCHOUX said that he would be glad to know whether haemoglobine fever was, in his colleagues' opinion due to the use of quinine.

Professor NOCHT replied that he had personally treated three cases where this fever had been due to the use of quinine.

Professor MARCHOUX expressed the view that stovarsol with an infinitesimal dose of quinine led to the best results.

The CHAIRMAN informed the Committee of a proposal of Professor Ottolenghi which would be discussed during the next plenary meeting. This proposal was for the examination of the following subject - "Practical importance of intensive treatment of malaria cases by quinine in anti-malaria prophylactic campaigns.

Professor LUTRARIO suggested that the Committee should decide whether this was a matter of international interest or whether it was merely a scientific subject for the laboratory. He emphasised the vital importance of protective measures by the use of quinine and emphasised the fact that only 700 tons of quinine a year were manufactured in the whole world, whereas the number of sick persons was incalculable. He therefore insisted that this question should be treated from the international point of view by all Governments Members of the League of Nations.

Professor SCHUFFNER remarked that paragraph 4 was a summary of the whole question. In other words mortal cases of malaria should occur no longer in marshy regions. Their occurrence would provide a basis for an accusation against the workers against malaria. The solution of the question by quinine treatment was a necessity.

Professor OTTOLENGHI said that he agreed with Professor Schuffner as regards quinine. It was absolutely necessary to treat sick persons by quinine, but he did not consider that this constituted protection against paludism. If the anopheles continued to breed, paludism would also continue. The treatment of sick persons should be undertaken at the same time as protective measures, and it was this action which should be recommended to the Governments.

Professor NOCHT remarked that he had not quite understood the proposal. Were the Governments to make experiments on the spot in contaminated areas or were they merely to study documents which had been compiled? He pointed out that there was a large documentation in existence in Italy and Spain.

Professor OTTOLENGHI expressed the view that although documents were extremely important their examination would not be sufficient for malariologists who were somewhat sceptical. He felt that it was the duty of the various Governments to examine the documents, to make investigations and to contribute their assistance to the important work.

Professor LUTRARIO asked that an international organisation should be set up for the study of paludism and the campaign against it.

Professor NOCHT insisted that experiments should be made in laboratories and on the spot in contaminated areas.

The Sub-Committee adopted the suggestions of Professor Lutrario and Professor Nocht.

Professor NOCHT asked that the examination be undertaken of the sexual development of mosquitoes.

This proposal was adopted.

The Sub-Committee asked Professor Nocht and Professor Ottolenghi to undertake the examination of this question.

The meeting rose at 12.15 p.m.