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TO THE MEMBERS OF THE EXPERT ADVISORY PANEL ON MALARIA

The Chief of the Malaria Section would greatly appreciate receiving the comments of the members on the attached paper.

The paper was prepared by the Pan American Sanitary Bureau (WHO Regional Office for the Americas) for its Advisory Committee on Malaria Eradication (second session, Maracay, Venezuela, November 1956).

It is understood that the Committee believed that the available experimental evidence justified extensive field trials; and we are informed that the Directors of the malaria eradication programmes in Brazil, Mexico and Venezuela indicated their desire in participating in such experiments.



EARLY TERMINATION OF MASS HOUSE-SPRAYING -
THE ROLE OF CHEMOPROPHYLAXIS

Malaria eradication campaigns could be shortened and the cost greatly reduced by abandoning the practice of continuing mass house-spraying for two years after the first year of full coverage. It is well known that when malaria transmission has been halted the major drop in the parasite rate is obtained by the end of the first year. It is therefore suggested that a test be made to determine the feasibility of eradicating malaria by terminating the mass application of residual insecticides after a single year of operation and completing the eradication campaign with a relatively large number of surveillance teams, their number progressively declining as circumstances warrant. In this procedure chemoprophylaxis would be a valuable adjunct as well as a means of extending the campaign to unsprayable areas.

When a surveillance team discovers a focus of infection, residual sprays should be used according to accepted practice but, in addition, chemotherapy should be introduced promptly. Administration of drugs is important because a focus of infection at this time is likely to consist of more than a single case, perhaps scattered cases throughout the community, and the malaria parasites should be rendered non-infective to the mosquito before a local epidemic occurs and before any of these infected people visit distant places. Speed is essential and drugs can be administered quickly. Active cases can thus be cured promptly and, through the use of pyrimethamine, the gametocytes of infected individuals can be rendered harmless.

An effective drug regimen which might be given as a single dose would be chloroquine or amodiaquine 600 mg (base) and 50 mg of pyrimethamine. This dual drug dose should be given to each person ill with malaria and to all persons who exhibit parasites in their blood. Individuals infected with parasites other than P. falciparum should be given 15 mg of primaquine daily for 14 days. All persons who might have been exposed to infection, i.e. those living within anopheline flight range of an infected person, should receive at least 50 mg of pyrimethamine. Quick treatment is important because after only one year of full coverage, there is still an appreciable amount of malaria, perhaps 10 per cent. of the original rate, and a small outbreak could occur.

As time passes and parasite rates become insignificant, single infections are not likely to trigger an epidemic. At this time, consideration may be given to using pyrimethamine only.

The efficacy of 600 mg of chloroquine or of amodiaquine in curing acute attacks of malaria is well established. Equally well known is the ability of primaquine to prevent relapses from vivax malaria by ridding the system of this species of plasmodium. Less well known is the remarkable action of pyrimethamine on gametocytes. Coatney reports (1952) that Young gave a single 25 mg dose of pyrimethamine to each of four patients infected with the Chesson strain of Plasmodium vivax and, after eight hours, mosquitos fed upon them did not develop sporozoites. Oöcysts appeared but none matured. This effect continued throughout the experiment which lasted for six days. Although therapeutically active levels of the drug persisted for 17 days no mosquito tests were made. Dr Coatney believes that continuation of the experiment would have shown this inhibitory effect for a full 30-day period.

He has subsequently shown that pyrimethamine in salt, eaten at the rate of 25 mg of the drug per week, prevents the development of acute attacks of malaria in experimental volunteers subjected to multiple bites of heavily infected mosquitos. Not until 28 to 40 days after cessation of the drug and infective mosquito feedings did active infections commence to appear. The experiments had to be terminated without testing these patients to ascertain their infectivity to mosquitos.

Dr Leon Schmidt's paper presented at the New Orleans meeting (October 1956) of the American Society of Tropical Medicine and Hygiene indicates the probable mechanism of the prolonged action of pyrimethamine in preventing the development of sporozoites. Dr Schmidt showed that when 12.5 mg of pyrimethamine were given, only half of the drug was metabolized within the first 72 hours. Thereafter, the remaining half disappeared from the blood stream at the rate of 3 per cent. per day. The percentage each day was calculated from the amount of pyrimethamine in the blood stream during the previous day. When the dose was doubled, i.e. 25 mg were given, the same thing happened - half of the drug was metabolized within the first 72 hours, thereafter of the remainder only 3 per cent. a day was lost from the blood stream.

Although not yet put to the test, these two workers believe that after a single 100 mg dose of pyrimethamine (maximum safe dose) an effective amount of the drug would still be present in the circulating blood 60 days later. An experiment is now under way to determine the actual number of days an effective blood level of the drug persists. It is hoped that this test may be accompanied by biting tests to ascertain the duration of the anti-sporozoite effect.

Special situations where residual spraying is without effect may be met by halting malaria transmission through the use of one or other of these remarkable drugs. When houses are without walls, where malaria-carrying mosquitos bit outdoors either during the day or night, or where people are nomadic, pyrimethamine or chloroquine should be combined with all ad lib salt. If this is not feasible because people drink from "salt wells" or get unmedicated salt from other sources, peripatetic drug teams should administer a maximum dose of pyrimethamine to each individual periodically. Although the maximum interval is still to be determined it is known that single doses are effective for a number of days and that pyrimethamine or chloroquine can be given in salt daily over long periods of time without evidence of toxicity and that this procedure has worked well under both controlled and field conditions.

Both pyrimethamine and chloroquine are excellent malaria suppressives and where ad lib salt is to be medicated the only factors influencing the choice of drug are cost and taste. Where the administration of the drug may be intermittent pyrimethamine is the drug of choice because it prevents development of sporozoites and thus halts transmission of malaria.

Wherever a drug regimen is to be added to an eradication campaign it is important that public health education programmes be inaugurated for the active co-operation of all individuals is a requisite.