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The Chief of the Malaria Section
has the honour to communicate hereunder the
following note

CHEMOTHERAPY IN MALARIA
CONTROL

by

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Over the past 18 months studies investigating the effects of the suppressive doses of antimalarial drugs administered at monthly intervals have been in progress at our Institute. They are being carried out in the coastal region of the Central Province of Liberia where malaria is hyperendemic and the native population shows varying degrees of resistance to infection. Transmission occurs throughout the year but is generally more intense during the rainy season. Plasmodium falciparum predominates, P. malariae is also of frequent occurrence but P. vivax is rare.

A summary of the different investigations, completed or still in progress, with results obtained is presented below.

INVESTIGATION A

Schoolchildren numbering 184, ages five to 14, were studied here. They were given pyrimethamine or chloroquine, or both drugs in combination, at intervals of one month. Parasite rates were determined at monthly intervals in the treated groups and concurrently in suitable untreated control groups. Monthly drug dosages were as follows: pyrimethamine one tablet (25 mg), chloroquine one tablet (150 mg), and one tablet of each when given in combination. Children receiving

the two drugs together and their controls were situated in an area which had never been sprayed with residual insecticide and were probably exposed to the heaviest infection challenge. They were studied for six months. Children receiving chloroquine and their controls were located in an area where houses had been sprayed with residual DDT at 4-month intervals starting eight months prior to the experiment and continuing throughout its course; these children were probably exposed to the lightest infection challenge. They were studied for eight months. Children receiving pyrimethamine and their controls were located in an area where houses were sprayed with residual DDT for the first time coincidentally with the beginning of the experiment and re-sprayed four months later. These children were exposed to an infection challenge with an intensity somewhere between that of the above two groups. They were studied for eight months.

The results showed that pyrimethamine and chloroquine given in combination had a marked effect on the malaria parasite rate of treated children, and two weeks after initial drug administration the asexual parasite rate was reduced from a pre-treatment 69% to zero. It remained negative on all subsequent monthly blood examinations with the exception of the last when one child showed a low density parasitaemia which responded quickly to the regular dose of suppressive therapy. Meanwhile children in the control group showed monthly parasite rates which fluctuated between 50% and 100%.

Pyrimethamine alone also proved to be very efficient and by the second month of suppressive therapy the initial parasite rate of 68% had dropped to zero. It remained negative on all subsequent monthly blood examinations throughout the period of therapy. The control group showed monthly parasite rates ranging from 19% to 73%.

Children receiving only chloroquine did not show as good a response and the initial parasite rate of 44% was still 26% at the end of the first and 3% at the end of the second month. No parasites were seen in the third or fourth months but there was one clinical malaria break-through in the fifth month. For the final three months of the experiment the children were parasite-free. The low

infection challenge was reflected in the parasite rates of the control children which ranged from 11% to 39% throughout the course of the study.

Suppressive chemotherapy as used in this investigation appeared to inhibit gametocyte production. This was clearly seen in the groups receiving pyrimethamine alone or in combination with chloroquine: gametocytes were not found in the blood of any treated child after the second month of treatment.

Spleen rates and average-enlarged-spleen measurements were apparently unaffected by the drugs as used in this study and remained relatively constant throughout.

There was no indication of pyrimethamine-resistant strains of malaria developing during the course of this investigation.

INVESTIGATION B

Adults and children living in a plantation area were studied here. Two separate experiments are reported. In Experiment 1 the effects on the malaria parasite rates of monthly doses of pyrimethamine plus chloroquine as compared with monthly doses of pyrimethamine alone, were studied in a controlled population of adult females and children. In experiment 2 the effectiveness in reducing malaria parasite rates, of monthly pyrimethamine administration and residual DDT spray was compared in partially controlled groups of male plantation workers.

Experiment 1. Two groups of adult females and children were studied here. Group A initially included 175 individuals; each received pyrimethamine at monthly intervals. Group B initially included 196 persons; each received pyrimethamine plus chloroquine once a month. In both groups children under 10 years made up about 40% of the total. All individuals of three years or older received monthly dosages of 25 mg of pyrimethamine given alone or in combination with 150 mg of chloroquine depending on the group; children under three years were given half doses. All persons were identified and treatment history recorded. Those missing treatment were included with new arrivals each month to serve as

control groups for each treatment group. Malaria parasite rates were determined for all groups by monthly blood studies. The study has now been in progress for one year.

Results in Experiment 1 indicate that pyrimethamine alone was as effective as pyrimethamine plus chloroquine in reducing the malaria parasite rates in the groups studied. In Group A receiving pyrimethamine alone the crude parasite rate (all age groups combined) fell from 47% to zero by the end of the second month of treatment and fluctuated between 2.2% and zero for the remainder of the 12-month period. The control group showed crude parasite rates ranging from 13% to 53%. In Group B, which received both drugs, the crude parasite rate which was initially 46% fell to 1% by the end of the first month and monthly rates for the remainder of the year fluctuated between zero and 1.4%. The control group here showed crude parasite rates ranging from 9% to 53%.

In the group receiving pyrimethamine alone one three-year child showed asexual parasites of P. falciparum before and after the fourth monthly drug dosage. In the fifth month she was given double the regular dose of 50 mg and five days later her blood was found negative for parasites. This was the only evidence of parasite resistance to pyrimethamine seen throughout the study.

Experiment 2. Three groups of adult males, A, B and C, were studied. They lived in work camps which had received residual DDT spray at 4-month intervals for one year before the experiment started, but in Groups A and B spraying had been discontinued four months prior to the start of the experiment. In the camp housing Group C spraying was continued throughout the course of the experiment. All individuals in Group A received 25 mg of pyrimethamine once each month and constituted the treated group. Group C was protected by residual DDT spray; Group B served as a control. At monthly intervals blood smears were taken from 100 individuals at random in each group and parasite rates as well as crescent rates determined. The men in this study were only partially controlled and no attempt was made to identify the individuals of whom a variable and not inconsiderable percentage migrate within and in-and-out of the plantation area. Each group included a population which varied with the seasons from about 300 to 425.

This study has now been in progress for 11 months. During this period Group A, whose members received monthly doses of pyrimethamine, showed parasite rates ranging from 1% to 14% with an average monthly rate of 5.4% and an average crescent rate of 0.5%. Further analysis showed the average parasite rates for the first five months as compared to the last six months of the experiment to be 6% and 5% respectively. Group C, whose members lived in an area protected by residual DDT spray, showed parasite rates during the eleven months ranging from 13% to 37% with an average monthly rate of 24.5% and an average crescent rate of 1.1%. The average parasite rates for the first five months and the final six months were 30% and 18% respectively. The controls, Group B, showed a parasite rate range of 12% to 34% with an average monthly rate of 25.4% and an average crescent rate of 2.0%. Here the average parasite rates for the first five months and final six months were 23% and 26% respectively.

The results of this experiment indicate that chemotherapy was more effective than residual DDT spray in reducing malaria parasite rates. The reduction in average parasite rate seen in the second half of the experiment in the insecticide protected group, plus the absence of such reduction in the control group, suggests that the residual DDT spray was controlling malaria to some degree.

The inability to obtain better malaria control in these groups is probably explained in the main by the migratory habits of the individuals in each group. Nevertheless it is of interest to note how much more effective was chemotherapy control over residual insecticiding, and also the fact that even in an imperfectly controlled population a considerable measure of success was realized by the administration of monthly doses of pyrimethamine.

INVESTIGATION C

The effects of monthly suppressive doses of pyrimethamine in children and adults living under native village conditions in an unsprayed area, are being studied here. Four villages with 123 adults and 48 children (under 14 years) are being treated with pyrimethamine at monthly intervals; adults and children three

years or more receive 25 mg per dose, while children under three years get half doses. All treated individuals are identified and treatment history recorded. Three additional villages with 59 adults and 20 children receive placebos and serve as controls. Blood examination for malaria parasite rates are made monthly.

This experiment has now been in progress for four months. Results to date show that treated individuals are being well protected. Pre-treatment parasite rates which were 46% and 26% respectively for children and adults, have been 4% and 1%, 0% and 1%, 0% and 0%, and 0% and 0%, for the four months of suppressive therapy. The control subjects have shown parasite rates which ranged from 26% to 73% for the children, and 7% to 25% for the adults.

INVESTIGATION D

The malaria parasite and clinical histories of 20 adult West Africans has been studied continuously over a period of one year during which time specific anti-malarial treatment was withheld. Members of this same group are now receiving one tablet (25 mg) of pyrimethamine each month and blood studies for malaria parasites are being made weekly. This experiment will be continued for one year, at the end of which time the results will be compared with those of the previous year when no treatment was given. The second phase of this study has now been in progress for five months. During this period all subjects have been negative for parasites with one exception when one subject showed a transient low-grade parasitaemia with no clinical manifestations.

CONCLUSIONS

Although incomplete, the results of the foregoing studies indicate strongly that under conditions of our experiments the administration of suppressive doses of pyrimethamine alone or in combination with chloroquine, at intervals of one month, has a remarkable effect in reducing both the asexual parasite and crescent rates in the indigenous population of a hyperendemic malarious region. The numbers studied have not been great. Hence it cannot be stated on the basis of this work that

malaria strains resistant to pyrimethamine do not develop in our area. On the other hand there appears to be little doubt that resistant strains are not nearly as rapidly developed in our population as has been reported from East Africa.

The possibility that resistant strains are developed only rarely in our area together with the fact that pyrimethamine may be combined with chloroquine to obviate the persistence of resistant strains, suggests that these drugs may well be utilized in malaria suppression. Further, the marked control of both asexual and sexual malaria parasitaemia achieved with suppressive doses at monthly intervals, indicates that malaria control by chemotherapy may be a practical and efficient method in the semi-resistant population of West Africa. It is a fact that control by chemotherapy is more rapid in our area than that achieved by residual insecticiding, and from results reported by malaria control groups operating with residual insecticides in Liberia, control by chemotherapy may prove to be more efficient. This was certainly the case in the limited experiment reported in Investigation B.

Whether chemotherapy control of malaria by the method used in our studies will prove to be practicable in large population groups scattered over wide areas cannot be known until actual field tests have been carried out. Our experience leads us to believe that such tests may well prove successful and are definitely warranted.