Medical Memoranda

Pyrimethamine in the Prophylaxis of Malaria

Therapeutic trials with pyrimethamine ("daraprim") have indicated that the drug could effectively control a clinical attack of vivax or malariae infection in two to three days but might fail in a certain percentage of falciparum infection (Chakravarty and Chaudhuri, 1953). The present report on the prophylactic value of the drug is based on another investigation carried out simultaneously in a malarious village.

MATERIAL AND METHOD

The prophylactic trial was carried out on 311 boys in a village school about 35 miles from Calcutta from July to November, which is usually the heaviest transmission period in the locality. A preliminary survey was done to find out the spleen and parasite rates; it showed that 60% of malarial infection was due to *P. falciparum* and the rest to *P. vivax* or *P. malariae*. During the course of treatment the blood was examined every month except October, and on its conclusion a final estimate was made of the spleen and parasite rates (see Table). Alternate classes received pyrimethamine (172 boys) and dummy tablets (139 boys) respectively, the latter serving as control. Both were given once a week, the dose of pyrimethamine being 25 mg. (12.5 mg. for boys under 10 years). The tablets were administered personally by a member of the clinical research unit, financed by the Indian Council of Medical Research, except for four weeks during the October vacation, when they were handed over to the boys to be taken by themselves in their homes.

RESULTS

The effect of prophylactic regimen on the parasite and spleen rates is shown in the Table.

Effect of Pyrimethamine Prophylaxis on Parasite and Spleen Rate per 100

Group		July	Aug.	Sept.	Oct.	Nov.	Dec.
Pyrimethamine (172 boys)	Parasite	5·7	0	1·2	—	0·7	2·3
	Spleen	16·1	—	—	—	—	11·6
Control (139 boys)	Parasite	3·6	3·7	8·6	—	6·6	9·2
	Spleen	16·2	—	—	—	—	23·9

The parasite rate in the control group rose, as was to be expected, from 3.6 in July to 6.6 in November, while in the treated group it dropped from 5.7 to 0.7 during the same period. In December, after the conclusion of the experiment, there was an unexpected rise in the parasite rate, which might perhaps have been due to prolongation of the transmission period. The suppressive effect of pyrimethamine was also reflected on the spleen rate, which showed some reduction, while there was about 50% increase in the control group. In all the parasite-positive cases in the treated group only *P. falciparum* was seen throughout the period.

The incidence of overt malaria could not be accurately recorded, as it was not possible to examine the blood during febrile attacks. However, on inquiry at the weekly visits it was gathered that the incidence of fever was much less in the treated group.

COMMENT

Following the observation of Goodwin (1952) on himself that 5 mg. of pyrimethamine daily could suppress malaria, Vincke (1952) carried out a successful mass prophylaxis in the Belgian Congo with a weekly dose of 25 mg. Covell *et al.* (1953) obtained complete suppression of overt attack with 25 mg. of pyrimethamine weekly in non-immune subjects exposed to a West African strain of *P. falciparum*.

Our observation in a village school indicates that weekly doses of 25 mg. have an effective suppressive action against malaria. Both falciparum and vivax infections have been prevalent in the area, the majority being falciparum. The persistence of *P. falciparum* parasites in a few cases during pyrimethamine administration indicates that some falciparum strains are relatively less sensitive to the drug. However, the large majority of the cases were free from parasites during the prophylactic regimen.

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Fatal Case of Agranulocytosis Due to "Novalgin"

The danger of agranulocytosis due to amidopyrine and its derivatives is now so well known that few would wittingly advise the use of these drugs, yet this may be done unintentionally by prescribing certain proprietary preparations. Frequently the proprietary name gives no indication of the precise nature of the active principle, and thus cases of agranulocytosis due to amidopyrine or closely related compounds continue to occur. It seems that the exclusion by law of amidopyrine from proprietary preparations, as is done in Denmark, is the only sure way of preventing these fatalities (*Lancet*, 1951). Meantime, publication of cases may result in a wider appreciation of this hidden danger and so help to minimize it.

CASE REPORT

A married woman aged 67 was admitted to the surgical wards of the Western Infirmary, Glasgow, on November 7, 1953, complaining of vomiting and the passage of red blood per rectum of a week's duration. She had been operated on for haemorrhoids on two occasions and had received injections of liver extract for anaemia over the previous three to four years.

On admission she did not look very ill and her temperature was 100.4° F. (38° C.). The throat was red and oedematous; proctoscopy revealed an indurated, elevated sinuous ulcer on the anterior wall of the rectum. After three days in hospital she was still febrile and appeared slightly jaundiced. The diagnosis of agranulocytosis was established by blood examination, which showed: Hb, 13.4 g. per 100 ml.; P.C.V., 43%; red cells, 4,720,000 per c.mm.; white cells, 75 per c.mm.; icteric index, 25 units. The blood film showed normal red cells and adequate platelets, but white blood cells were extremely scanty. Of the first 50 leucocytes examined 2 were polymorphs, 10 monocytes, 36 lymphocytes, and 2 Türk irritation cells.

Inquiry revealed that, to control headache, novalgin had been taken occasionally for years, but during the last month 15 gr. (3 tablets) were ingested daily in divided doses up to the time of admission. The only other medicaments taken during the previous three months were a vegetable laxative and liver extract; in particular, no barbiturate drug had been used.

Intensive treatment with penicillin brought considerable improvement and a reduction in temperature, but five days after admission she suddenly became distressed and dyspnoeic. Treatment for massive pulmonary embolism was at once instituted, but she died within two hours.