PYRIMETHAMINE ("DARAPRIM") IN THE TREATMENT OF VIVAX MALARIA

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At a meeting of the Royal Society of Tropical Medicine and Hygiene in July, 1952, it was suggested that pyrimethamine might prove of value in effecting a radical cure of vivax malaria by destroying the late exoerythrocytic forms of the parasite which are presumed to be responsible for relapse. The investigations here recorded were undertaken with the object of testing this theory.

The parasite used was the Madagascar strain of *Plasmodium vivax* which has been maintained at Horton for the routine treatment of neurosyphilis for the past 28 years. A peculiar characteristic of this strain of *P. vivax* is its tendency to give rise to attacks of fever with parasitaemia between the 30th and 40th weeks after mosquito infection. In most cases these attacks represent relapses following a primary attack which has begun 9 to 15 days after infection. In some instances the incidence of the primary attack itself may be delayed until this period.

The subjects of the trial were 12 patients, none of whom had a previous history of malaria. Each of them was subjected to the bites of 10 to 12 mosquitoes from an infected batch of *Anopheles atroparvus* on September 6, 1952. An overt malarial attack developed in each case after an incubation period of 9 to 11 days.

Each patient underwent a course of 50 mg. of pyrimethamine given as a single daily dose over a period of five days (total 250 mg.). Treatment was begun in all cases on the day when parasites were first found in the

peripheral blood. In two cases this was on the day before the first rise of temperature, but in the remainder it was on the first or second day of fever.

Result

In three of the subjects relapses (pyrexia with parasitaemia) occurred 55, 74, and 88 days after the last day of treatment (see Chart). Each relapse was treated, as in the primary attack, with a five-day course of 50 mg. of pyrimethamine daily. The patient who relapsed on the 74th day experienced a second relapse on the 14th day after completing his second five-day course. He was treated for this with a single dose of 50 mg. of pyrimethamine, but relapsed again 22 days later. A fourth subject relapsed on the 99th day. It was thus already clear that treatment of the primary attack with pyrimethamine in full dosage was not an effective method of preventing relapse of this strain of *P. vivax*.

It was now decided to test the effect of a weekly dose of 25 mg. of pyrimethamine given over a period of two months on the incidence of late relapses, which, as noted above, may be expected to occur with this strain of *P. vivax* between the 30th and 40th week after infection. Accordingly, on the 99th day after completion of the first course (the day on which the fourth patient (D) relapsed), the whole group, with the exception of the individual (A) who had already relapsed twice, received a single dose of 25 mg. of pyrimethamine, which was repeated at weekly intervals for the next seven weeks (eight doses in all).

Fifty-nine days after the last weekly dose (32 weeks after the infecting feed) the patient (B) who had relapsed on the 55th day experienced a second relapse. Every other member of the group, without exception, relapsed on one or more occasions between the 32nd and 41st weeks after the infecting feed (see Chart). There was thus no indication that the eight-weeks course of pyrimethamine given from the 17th to the 24th weeks after infection had had any effect on the subsequent relapse rate.

The results afford a striking example of the very high rate of relapse which occurs with this strain of *P. vivax* following early treatment of the primary attack. In patients who are allowed to have a dozen or more peaks of fever with this strain of parasite before the primary attack is terminated (as in the routine treatment of neurosyphilis with malaria therapy) the relapse rate is in the region of 50% only.

Effect of Pyrimethamine on Clinical Attack.—As was to be expected from the experience of other observers, the clinical response to pyrimethamine in the primary attack was slow. Fever persisted for seven days in one case, for six days in three, for five days in five, for four days in two, and for three days in the remaining one. It is clear that pyrimethamine unaided is not a satisfactory drug for the treatment of vivax malaria in a non-immune subject.

Toxicity

One of the patients (F) developed pyrexia on the eighth day after completing the five-day course of 50 mg. of pyrimethamine given for treatment of the primary attack. Fever continued in an irregular fashion for eight days, but no parasites were found at any time in the peripheral blood despite repeated and intensive search of both thick and thin smears. Two days after the onset of fever there was epistaxis over a period of 12 hours. On the following day the red blood cell count was 4,000,000 per c.mm.

Chart showing results of pyrimethamine treatment of 12 patients suffering from primary attacks of mosquito-induced malaria.

and the white-cell count 2,000 (polymorphs 22%, lymphocytes 70%). The patient was given one litre of blood intravenously and was treated with penicillin, crude liver extract, and pentnucleotide. Under this regime his condition progressively improved, and 15 days after the first rise of temperature the white-cell count had returned to normal. A sternal puncture specimen taken on the eighth day of his illness showed maturation arrest of the granulocytes.

It was at first thought that in the case of this individual the dosage of pyrimethamine administered (250 mg. in five days) had exceeded the limit of tolerance. He had been in the hospital for over 12 months and had received no previous treatment likely to give rise to such a syndrome. However, in the 36th week after the infective feed he experienced a malarial relapse attended with profuse epistaxis and leucopenia. The clinical picture, though considerably less severe, resembled that observed in the previous attack. Malaria parasites were seen in the peripheral blood, though in very scanty numbers. The only antimalarial drug given on this occasion was quinine (5 gr. (0.32 g.) thrice daily for 10 days).

The patient had had no pyrimethamine since his primary attack except the eight-weeks course of 25 mg. weekly which was completed three months before his relapse. It seems probable that his symptoms were attributable rather to an abnormal susceptibility to this strain of malaria parasite rather than to any effect of the drug. None of the other patients in this series (three of whom underwent a second five-day course of 50 mg. of pyrimethamine daily during their first relapse) showed any ill-effect from taking the drug, nor was there any abnormal feature in their blood count.

Summary

Twelve patients suffering from primary attacks of mosquito-induced vivax malaria (Madagascar strain) were treated with 50 mg. of pyrimethamine daily for five days. The clinical response to the action of the drug was slow, and for this reason alone we regard it as unsuitable for treatment of the clinical attack in non-immune subjects.

Four of the patients relapsed between the 55th and 99th days after completing the course, one of them on two occasions.

On the 99th day 11 of the group were given a single dose of 25 mg. of pyrimethamine, which was repeated at weekly intervals for the following seven weeks. All of them relapsed on one or more occasions between the 8th and 18th weeks after completing this eight-weeks course.

There is no indication that either of the two courses of pyrimethamine administered in this trial (50 mg. daily for five days during the primary attack and 25 mg. weekly for eight weeks, starting three and a half months later) were of any value in preventing the incidence of relapse, though it is possible that the attacks might have occurred somewhat earlier had the drug not been given.

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The British Standards Institution has issued a sectional list of British standards for hospital equipment. It catalogues standards for medical and surgical apparatus; laboratory glassware and scientific apparatus; furniture and fittings; textiles and clothing; photography and radiography; methods of testing; symbols, tables, and definitions; and electrical equipment. The list also includes a note on what new standards for hospital equipment are now being prepared. The list (P.D. 1644, dated June, 1953) is obtainable from the British Standards Institution (Sales Branch), 24, Victoria Street, London, S.W.1.

LEPROSY: REPORT ON FOUR CASES

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Although a temporary increase in the incidence of leprosy in Great Britain was expected following the second world war (Ryrie, 1947), the disease remains relatively uncommon. Compulsory notification was introduced in September, 1951. In England and Wales 48 cases were notified in 1951 and 65 in 1952, but at least 100 of these were existing known cases. In Scotland seven cases had been reported up to the end of 1952.

During the past four years the four cases reported below were encountered in routine hospital practice in one city. It will be seen, however, that not all were due to the aftermath of global war, at least two being attributable to factors peculiar to a jute-manufacturing seaport. Even in this small series the diverse symptomatology and varying clinical types of the disease are well illustrated.

Case 1

The Goanese wife, aged 23, of a British Service man was first seen in May, 1948, with a circinate lesion of the right lower leg of 18 months' duration (Fig. 1). The margin of the lesion was raised and infiltrated, while the central flat area showed marked loss of sensation to light touch and pinprick. No other skin lesion was present, nor could any thickened nerves be found. Biopsy of the active edge showed a tuberculoid histology; no acid-fast bacilli were demonstrated either here or in a nasal scrape. The lepromin test was positive.

FIG. 1.—Case 1. Circinate lesion of leg before treatment with solapsone.

Treatment with weekly intradermal injections of "moo-grol" for two months produced no improvement. In December, 1948, solapsone by mouth was started. The maximum tolerated dose of three 0.5-g. tablets was taken intermittently over a long period. When last seen in May, 1951, the leg lesion had almost disappeared and sensation in the area showed considerable improvement.

Case 2

A British man aged 30, who had served in Cyprus, Syria, and India during the second world war, attended in August, 1948, with a generalized non-itchy eruption of brownish-red slightly infiltrated patches over the whole body surface. The Wassermann reaction was negative. A tentative diagnosis of sarcoidosis was not confirmed by biopsy, which showed an infiltrate of mononuclear cells and lymphocytes surrounding sweat ducts and follicles. In view of the possibility of a pre-mycotic eruption x rays and thorium X were applied to selected areas, without clinical benefit.