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.

Our thanks are due to the Wellcome Foundation Ltd. for the supply of daraprim and to Sri C. L. Mitter, S. Mitter, and B. Dutta for their help in this work.

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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.

The significant post-mortem findings were as follows. Slight icterus; throat merely slightly injected. A coiled embolus 1 cm. in diameter lay across the bifurcation of the pulmonary artery. The embolus was massive and as much as 25 cm. could be removed in one piece; the right side of the heart was acutely dilated. On dissection of the leg veins both femorals were found to be clear, but the intramuscular tributaries on the right side contained thrombus; it was concluded that embolus had originated in the right femoral vein. On the anterior wall of the rectum there was an elevated irregular area of ulceration 4 by 2 cm. which extended into the anal canal. The necrotic tissue was greenish on the surface and dull yellow underneath. The necrosis extended into the bowel wall for 3 cm. and the adjacent tissues were severely inflamed and oedematous. The bone marrow was hyperplastic, red marrow extending half-way down the femur. The spleen weighed 250 g., and neither it nor any of the other blood-forming tissues showed evidence of leukaemia. The liver showed merely toxic cloudy swelling.

On microscopical examination the rectal ulcer showed the typical appearance of an agranulocytic lesion, the cellular infiltrate being composed almost entirely of mononuclears, and necrosis and inflammatory oedema being very severe and widespread. The marrow contained numerous foci of erythroblasts, and megakaryocytes were also plentiful; polymorphs were absent and myelocytes were scanty. The marrow thus showed a severe maturation arrest of granulopoiesis amounting to aplasia, but no evidence of either leukaemia or panmyelophthisis.

COMMENT

The post-mortem findings establish the cause of death as pulmonary embolism following right femoral thrombosis in a case of agranulocytosis. The neutropenia was clearly due to failure of granulopoiesis without there being any disease process in the marrow to account for it. Since there was nothing to suggest splenic neutropenia (Hutchison and Alexander, 1954), and no history of cyclic attacks, but a clear history of the habitual use of novalgin, a sulphonated compound of amidopyrine known to have caused agranulocytosis, it seems reasonable again to incriminate this drug. The findings in our case correspond closely with previous accounts of agranulocytosis due to novalgin (Benjamin and Biederman, 1936; Klumpp, 1937; Plum, 1937); in particular, the unusually low white-cell count which we observed has been met with in other novalgin cases (Fitz-Hugh and Comroe, 1933; Ridpath, 1934), and ulceration of the rectum is recorded in the case described by Buck (1929).

The introduction of antibiotics has altogether transformed the prognosis in cases of agranulocytosis by controlling the generalized infections which formerly proved rapidly fatal. It seems probable that had embolism not occurred this patient's life might not have been forfeit to novalgin, for under treatment with penicillin she was not profoundly ill and her blood culture was negative. It is, however, evident from examination of her marrow after death that several more days would have been required to see her out of the danger period due to agranulocytosis; the precursors of the polymorphs had not returned to the marrow, and so recovery was not yet in sight.

We are grateful to Professor C. F. W. Illingworth for permission to report this case.

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Thomas's Sign, or the Silver Stool in Cancer of the Ampulla of Vater

Dr. A. M. Thomas, pathologist to the Royal Masonic Hospital, has pointed out that in cancer involving the ampulla of Vater the patient sometimes passes "silver stools"—that is, motions having the colour of oxidized silver or aluminium paint. The silver or grey stool is a combination of the white stool of obstructive jaundice and the black stool of melaena.

Biliary obstruction, whatever its cause, will produce a clay-coloured stool. Such a stool may contain blood from many sources. If the amount of blood is small it will not colour the stool appreciably. If it is large it will dominate the picture and lead to the typical black stool of melaena, but massive intestinal haemorrhage is either intermittent or fatal. If the blood comes from low down it will be red and not black. The combination of deep jaundice with steady intestinal haemorrhage coming from high up in the intestinal tract is seen regularly in cancer of the ampulla, and only rarely in other conditions.

CASE 1

A married woman aged 46 was admitted on September 30, 1952, with a history of intermittent jaundice for three months. She did not appear to have lost weight, but was very anaemic. Tests showed the jaundice to be of the obstructive type, and the stools contained occult blood in large amounts. The barium meal was reported to be normal, apart from spasticity of the pyloric antrum.

A laparotomy was performed on October 16. A carcinoma could be felt at the ampulla. The gall-bladder and common bile duct were grossly distended, and both contained white bile only. Cholecystostomy was performed. The discharge from the drain soon became green in colour. On October 30 pancreatico-duodenectomy was performed with ligature of the stump of the pancreas and implantation of the bile duct in the jejunum. Apart from some blood-stained discharge, convalescence was satisfactory.

Since discharge on January 1, 1953, the patient has remained very well, needing only small doses of insulin. She dislikes fats, but that has benefited two people—her in that she has regained her youthful figure, and me in that she sends me a regular supply of Devonshire cream.

CASE 2

A man aged 78 was admitted on February 14, 1954, with a suprapubic fistula, following prostatectomy at another hospital in November, 1953. His haemoglobin level was 50% and his general condition poor. He was given two pints (1,130 ml.) of packed cells, and shortly afterwards developed jaundice which at the time was attributed to the transfusion. His stools were sent for analysis, and Dr. Thomas reported that they had the silvery appearance that he had previously noted in Case 1. On this appearance he made a tentative diagnosis of carcinoma of the ampulla of Vater.

The jaundice deepened and the patient died on February 22 in hepatic failure. At necropsy a carcinoma 3 mm. in diameter was found at the ampulla of Vater. The haemorrhage on which the diagnosis had been made had, however, come from a colonic diverticulum.

COMMENT

The diagnosis has since been made in two further cases. So far as I am aware the silver stool has never been described before. I bring the sign to the attention of surgeons because Dr. Thomas has not yet reported it himself and, being a pathologist, he is likely to report it in a journal read only by his brother pathologists. Thomas's sign, which can be observed by a house-surgeon or nurse who is aware of its importance, is diagnostic of cancer of the ampulla of Vater, and will enable instances of this eminently curable lesion to be recognized at an early and operable stage.

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