

Preliminary Communications

Chemoprophylaxis of Homozygous Sicklers with Antimalarials and Long-acting Penicillin

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Clinicians who have had considerable experience in handling patients suffering from sickle-cell anaemia have for long expressed the opinion that infections predispose to sickling crises. As early as 1924 Graham expressed this view. At the Hospital for Tropical Diseases, London, Woodruff and Bell (1961) found that a transient fever for a few days commonly preceded intravascular thrombosis in retinal vessels in patients suffering from a haemoglobinopathy. Basu *et al.* (1963) produced sickling experimentally, using T.A.B. vaccine in five patients with Haemoglobin AS and one patient with sickle-cell thalassaemia. In Uganda and the Congo the early childhood mortality is known to be high in sickle-cell anaemia (Lambotte-Legrande and Lambotte-Legrande, 1955; Jacob, 1957; Trowell *et al.*, 1957).

It seemed that if the homozygous sickler could be protected against infection the incidence of crises might be reduced and possibly the expectation of life increased. The commonest early childhood infections in Uganda are malaria and respiratory infections.

In 1961 a clinic was started in the paediatric department of the Mulago Hospital, Kampala, to study the effect of chemoprophylaxis with an antimalarial and long-acting penicillin on the complications of sickle-cell anaemia. Lewthwaite (1962) gave an encouraging introductory report on the work. This paper reports the progress of the chemoprophylactic trial, with particular reference to the effect of therapy on the incidence of dactylitis and the haemoglobin levels.

MATERIALS AND METHODS

Since August 1962 the clinic has been held weekly in the paediatric out-patient department at the Mulago Hospital, and since March 1964 this has been raised to twice weekly to cope with the increasing number of patients. For admission to the clinic all patients must have homozygous S/S haemoglobin proved by electrophoresis and must be prepared to attend regularly. All ages are admitted. Patients are allotted at random to two groups: (1) prophylactic and (2) control. These two groups attend on alternate weeks. At each attendance all patients are examined by a clinic doctor. Weight and temperature are measured. Blood is taken for haemoglobin and malaria parasites. To help ensure attendance patients are given up to 2s. per attendance towards travelling expenses.

The prophylactic group receive 1,200,000 units of long-acting benzathine penicillin by injection and are given one 200-mg. tablet of chloroquine at the clinic and a similar tablet to take after one week. Children under 3 years receive half these dosages. The control group receive 0.5 ml. of sterile water (placebo) by injection. The placebo was given for the following reasons: (1) not to have given the control group an injection would have seriously affected their attendance and influenced their attitude to the clinic; and (2) to have given any drug might have vitiated the results of the trial. Strict sterile precautions were observed and no injection abscess occurred.

The results have been analysed in the following manner. The mean haemoglobin values, the dactylitis, and haemolytic crises rates for each individual per month were compared in the two groups by arranging the results in ascending order of magnitude and calculating the significance of the differences, using Kendall's method.

RESULTS

The growth of the clinic from August 1962 to 1 May 1964 is shown in Fig. 1. It can be seen that the two groups have grown together and equally. In all, 260 patients had been seen at the clinic by 30 May 1964.

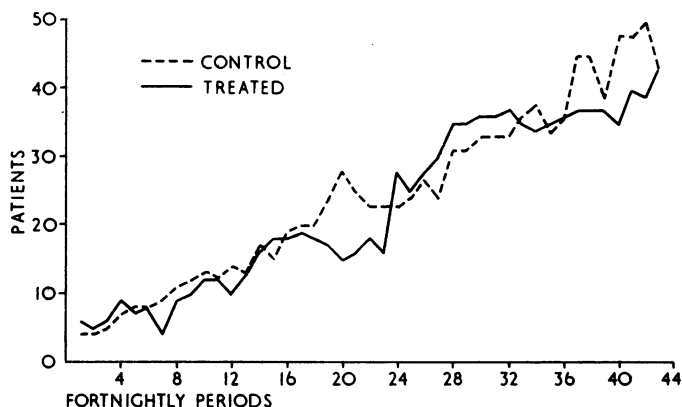


FIG. 1.—Attendances at the new Mulago Sickle-cell Clinic, August 1962 to May 1964.

The age and sex distribution of those attending at the end of May 1964 are shown in Fig. 2. The two groups are similar in these respects. In the control group there were 31 males and 35 females, and in the prophylactic group 31 males and 29 females; 80% of the prophylactic group and 71% of the control group were under 6 years old. Of the 126 patients

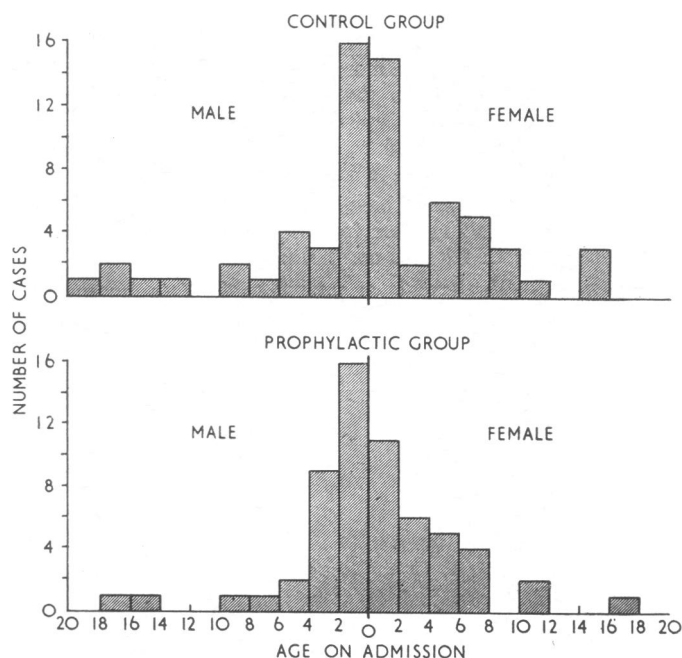


FIG. 2.—Sickle-cell Clinic, Mulago: Age and sex distribution.

attending at the end of May 1964, 115 (91%) were Baganda. The remaining 11 (9%) represented nine different tribes.

Table I shows the length of follow-up of those attending over three months and still attending.

TABLE I.—Period of Follow-up

Months	Prophylactic Group		Control Group	
	All Cases	Cases Under 6 Years	All Cases	Cases Under 6 Years
Over 3 ..	7	7	13	9
Over 6 ..	11	6	9	3
Over 9 ..	6	6	4	2
Over 12 ..	13	13	19	11
Totals ..	37	32	45	25

MALARIA STUDIES

An intensive search for malaria parasites was begun in April 1963, when adequate staff became available. The results of routine thick blood smears on 157 patients attending between April 1963 and April 1964 are shown in Table II. The high incidence of *Plasmodium malariae* is in keeping with recent findings in Uganda (Jelliffe and Jelliffe, 1963; Price and Lewthwaite, 1963). It is interesting that almost every positive finding of malaria was either preceded or followed by a fall of up to 2 g. Hb/100 ml. blood.

TABLE II.—Malaria Parasites in S/S Sickle-cell Patients

	Protected	Unprotected
Patients examined	73	84
Patients with malaria	7	21
Slides examined	897	740
Slides positive for malaria on first visit	2	4
Slides positive for malaria on subsequent visits	5	36
Parasites found :		
<i>P. falciparum</i>	4	9
<i>P. malariae</i>	1	7
<i>P. falciparum</i> and <i>P. malariae</i>	2	4
<i>P. malariae</i> and <i>P. vivax</i>	0	1

In keeping with other workers (Trowell *et al.*, 1957) our experience is that the mortality and the rate of crises are very high in the earliest years of life. It was therefore decided to analyse in detail those children under 6 years old and to concentrate on those who had been followed for 10 months or longer. Fig. 3 shows the proportion of children under 6 years in the treated and control groups analysed by the length of follow-up. The two groups are similar.

Dactylitis, mean haemoglobin values, and a fall in haemoglobin below 6 g./100 ml. have been chosen for full analysis,

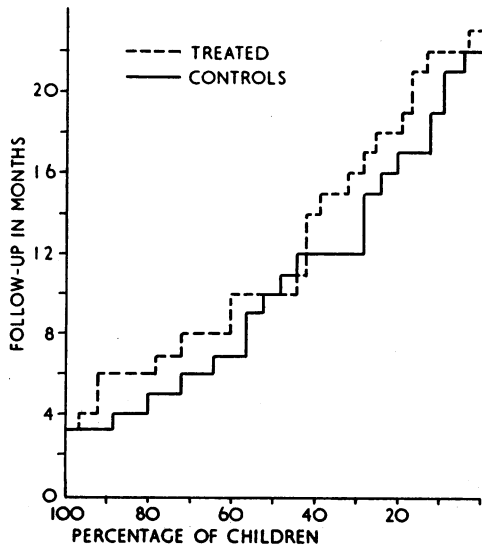


FIG. 3.—Follow-up of children under 6.

as these were the best objective measurements and reflect most accurately the incidence of crises. Dactylitis has been arbitrarily defined as any swelling or tenderness of bones, and has been measured as complete incidents, any one of which might last up to six weeks.

Table I shows the two groups to be comparable for follow-up over three months. Absentee and default rates were similar in the two groups. There is no evidence of selection among those who attended regularly. The two groups can therefore be considered comparable.

DACTYLITIS

Comparison of the individual rates of dactylitis per month in the two groups shows that the rate of dactylitis crises is significantly lower ($P < 0.1$) in the prophylactic group. The difference in the cumulative incidence of dactylitis in the two groups is shown in Fig. 4. The suggested advantage of the prophylactic group is borne out by the statistical analysis. This shows that after 24 months' treatment a child in the prophylactic group had an average of 1.8 attacks of dactylitis compared with 5.2 attacks per child in the control group.

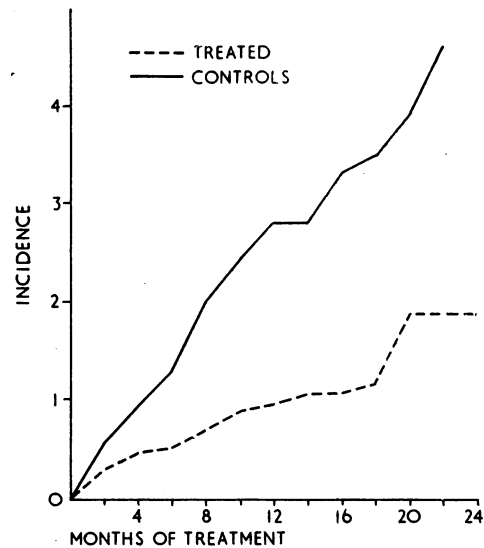


FIG. 4.—Difference in cumulative incidence of dactylitis in treated and control groups.

Mean Haemoglobin Values.—Analysis of the individual mean haemoglobin values for the period 19 December 1963 to 15 April 1964 in the two groups showed that the treated group's mean individual haemoglobin value was significantly higher than that of the control group ($P < 0.02$).

Fall in Haemoglobin.—By the same method results for the difference in incidence of falls in haemoglobin below 6 g./100 ml. blood are not yet significant ($P < 0.1$) but suggest that if one took a large enough sample the crises rate might also show a significant difference.

CONCLUSION

Therefore one can conclude that treatment as given reduced the rate of dactylitic crises and resulted in a higher average haemoglobin value and probably reduced the tendency for the haemoglobin to fall.

DISCUSSION

Statistical analysis of our results has confirmed that the treated group is at a definite advantage over the control group. This bears out the clinical impression of other workers. However, the treated group are receiving both chloroquine and long-

acting penicillin. It will be important to decide to what extent each of these drugs is benefiting the treated group. We know that the chloroquine is effective (Table II), and we know clinically that whenever a patient has a positive slide for malaria it has either been preceded or followed by a fall of up to 2 g./100 ml. in the haemoglobin value.

In the meantime we feel justified in advocating that children with sickle-cell anaemia should be seen regularly, possibly at special clinics, and treated routinely with antimalarial chemoprophylaxis if they live in a malaria zone. For the present we reserve judgment on the place of long-acting penicillin.

SUMMARY

The results of a long-term chemoprophylactic trial of chloroquine and long-acting penicillin in homozygous sickle-cell anaemia at the Mulago Hospital, Kampala, show that those patients under 6 years old followed for 10 months or more who received chloroquine and long-acting penicillin had a significantly ($P < 0.01$) lower rate of dactylitis and higher average haemoglobin value ($P < 0.02$) than patients in a control group receiving only a placebo. In addition, the therapy probably reduced the tendency for the haemoglobin to fall.

It is recommended that children with sickle-cell anaemia in malarious zones should be treated with suitable chemoprophylactic doses of chloroquine and followed at special clinics, if possible, at least in the early years of life.

The role of long-acting penicillin is not yet clear and studies are in progress to try to clarify this.

(Note.—The full statistical analysis is available from Dr. M. A. Warley, Department of Paediatrics and Child Health, P.O. Box 2072, Kampala, Uganda.)

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Medical Memoranda**Alcohol-induced Pain Associated with Adenocarcinoma of the Bronchus**

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The occurrence of pain immediately after the consumption of an alcoholic beverage was first described by Hoster (1950) in patients suffering from Hodgkin's disease. This phenomenon has recently been studied in this department in a patient who had an adenocarcinoma of the bronchus and who presented with shoulder pain.

CASE REPORT

A 42-year-old post-office sorter developed a dull ache in his left upper chest and shoulder radiating to the ulnar border of his left arm and hand. Three weeks after the onset of symptoms a miniature chest radiograph taken as part of the routine examination at that time was reported as normal. A few days afterwards the patient first noticed weakness of his left hand. When first seen in this department, four weeks after the onset of symptoms, a full-size chest radiograph revealed a very small left apical opacity, and tomographs of this region showed an erosion of the neck of the third

left rib. There was no history of cough, sputum, haemoptysis, alteration in voice, or dysphagia. The results of a barium-swallow examination and bronchoscopy (Dr. L. J. Grant) were normal, and cytological and bacteriological examination of bronchial washings at the time of bronchoscopy and subsequently of sputum obtained by positioning and chest percussion gave negative results. The haemoglobin was 14.3 g. per 100 ml., white blood count 15,600 (polymorphs 82%, eosinophils 1%, lymphocytes 14%, monocytes 3%). Erythrocyte sedimentation rate (Westergren) was 20 mm. in the first hour, blood urea 36 mg. per 100 ml., serum alkaline phosphatase 12.4 K.A. units. Urine analysis, direct and indirect Coombs test, and Wassermann and Kahn reactions were also normal.

Shortly after admission the patient remarked that his symptoms were made very much worse within minutes of drinking a glass of beer or cider. He had noticed this about a week after the onset of symptoms and had since avoided any form of alcohol.

The left supraclavicular lymph node became palpable within a week of admission and a subsequent biopsy of this showed a fairly well differentiated mucus-secreting adenocarcinoma. The patient was treated with supervoltage x-ray therapy. However, he developed further metastases in his lumbar spine within weeks and died at home six months after the onset of the first symptoms. There was no necropsy.

Experimental Study.—With his full co-operation and knowledge the patient was given 30 ml. of 70° proof brandy (equivalent to approximately 10.5 ml. of ethanol). After seven minutes he suddenly developed a very severe and peculiarly unpleasant pain over the