carried out, four-fifths of the stomach being removed; continuity was restored by an anterior Polya with Hofmeister valve anastomosis.

When last seen (November 15, 1954) he was working again and doing more than he had been able to do for many years, but had given up sport. He has remained completely free from angina of effort, despite the fact that his blood pressure has returned to the pre-operative level; recent readings have been 220/130 (October 30, 1953); 200/110 (September 3, 1954); 240/134 lying, 220/130 standing (November 15, 1954). Changes in the retinal arterioles have advanced, but the heart shadow remains normal radiologically, and the cardiogram was still physiological. During the past year he has from time to time had pain in the left upper abdomen, sometimes three hours after food, sometimes wakening him at night. A barium-meal examination showed normal progress from the remaining portion of the stomach to the jejunum, and no evidence of ulcer was seen: progress through the small bowel was accelerated.

### Discussion

Painful sensations arising in the abdominal viscera are transmitted by afferent fibres which accompany the sympathetic nerves and pass uninterruptedly through the sympathetic ganglia to enter the spinal cord by the posterior nerve roots. Dorso-lumbar ganglionectomy will abolish those forms of abdominal visceral pain which are normally transmitted through the sympathetic. When perforation occurs structures supplied by other afferents are involved, including the parietal peritoneum; pain from here reaches the spinal cord by way of the peripheral nerves and is not abolished by dorso-lumbar ganglionectomy.

Froehlich *et al.* (1942) reported four cases in which sympathectomy was performed as treatment for gastric ulcer. In all of them the distress was relieved and the ulcer craters showed radiographic evidence of healing. Sicard *et al.* (1945) carried out splanchnicectomy in eight cases of gastro-duodenal ulcer. Although there was some relief of ulcer pain, cure was not complete. Five required gastric resection within 18 months.

Harkins and Willard (1950) speak of the relief of pain as "a Pyrrhic victory" in reporting a case of peptic ulcer in which sympathectomy had adverse effects. Weeks *et al.* (1946) describe the case of a man with duodenal ulcer and malignant hypertension. A transthoracic vagotomy was performed and at the same time the left thoracic-lumbar sympathetic chain was removed from D 5 and L 2. Two weeks later the second-stage sympathectomy was carried out on the right side from D 5 and L 2, after which the patient became extremely ill and died on the 15th post-operative day. Necropsy revealed a perforated duodenal ulcer with general peritonitis. An interesting feature was the absence of abdominal pain in the presence of a perforated ulcer and peritonitis. The authors state: "His absence of pain may have been due to the removal of the viscero-sensory fibres associated with the sympathetic side of the autonomic nervous system." Blegen and Kintner (1947) describe a case with gastric ulcer which had three massive haemorrhages following extensive unilateral sympathectomy, and point out that the sympathectomy relieved the pain but the ulcer progressed.

Mason and Pollard (1949) found 13 instances of peptic ulcer in a group of 1,498 patients who underwent splanchnicectomy for hypertension during an 11-year period. They point out that frequent and severe complications developed in 12 because the normal epigastric pain sensation was either abolished or greatly reduced so that ulcers were permitted to advance without giving the usual warning.

The present case illustrates progression of a duodenal ulcer and development of pyloric stenosis after bilateral dorso-lumbar ganglionectomy and splanchnicectomy carried out for hypertension; a jejunal ulcer subsequently developed and later perforated. Pain was conspicuous by its absence while the original ulcer was progressing and while the jejunal ulcer was developing, but severe pain occurred when the latter perforated. After dorso-lumbar ganglionectomy and splanchnicectomy the pain which characterizes exacerbations of a peptic ulcer is abolished; it is therefore suggested that in such cases more attention should be paid to vague abdominal symptoms which may take the form merely of slight epigastric discomfort or fullness.

It is well known that the lowering of blood pressure which results from sympathectomy has often been transient. Hypertension has recurred within 5 to 10 years in a high percentage of cases (Smithwick, 1948). In the present instance hypertension was abolished for three years but had returned by the end of the fifth year. The mechanism underlying recurrence of hypertension after sympathectomy is not fully understood. During the fifth year abdominal visceral pain returned; but it may well have arisen in the colon. The sympathetic nerve supply from the colon was not interrupted by the original operations.

### Summary

A case is presented showing the progression of a duodenal ulcer following bilateral dorso-lumbar sympathectomy and splanchnicectomy, the subsequent development of a jejunal ulcer, and its ultimate perforation. The effect of sympathectomy on the pain of peptic ulcer is described and its mechanism is discussed.

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## MALARIA AND THE SICKLING TRAIT

BY

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This paper reports confirmation of Allison's (1954) conclusion that the possession of the sickling trait confers some protection against *P. falciparum* malaria, but it presents somewhat different views on the nature and extent of this protection.

Of the two experiments performed by Allison, one determined the parasite rates in children under 5 years of age in the Kampala region, mostly (Allison, personal communication) in the out-patient department of Mulago Hospital. Forty-three sickling children showed a parasite rate of 27.9%, and 247 non-sicklers a rate of 45.7%. This difference seemed so striking that it was reasonable to wonder why it had not already been noticed, or whether some feature of the experiment had accentuated a difference that was real, but actually of lesser magnitude. Indeed, since *P. falciparum* clearly can establish itself in the peripheral blood of sicklers, and can even multiply in the erythrocytes of cases of sickle-cell anaemia (in which there is no normal adult haemoglobin), it seemed reasonable to suppose that the effect of the presence of sickle-cell haemoglobin could not be to prevent an infection, though it might well limit the extent to which an infection could develop. If this were confirmed, quite sufficient explanation would have been given of the way in which *P. falciparum* infection could act as a selective agent in preserving high sickle-cell gene frequencies in endemic malarial regions, because it is

well known (Field, 1949) that the mortality from falciparum malaria is related to the height of the parasite count. But in that case some explanation would have to be found for the apparent difference in parasite rates observed by Allison in sicklers and non-sicklers respectively. And, since the results of Allison's inoculation experiments do not fully accord with the view advanced above, this view would have to be reconsidered if confirmation of his results should be obtained. This last question is not considered further here.

It was decided to repeat Allison's first experiment on the same type of patient, with the addition that parasite counts should be performed on all falciparum infections encountered, and to continue certain other observations that were already in progress.

## Malaria Infection in Relation to Sickling

Three groups formed the basis for this study—two of children and one of adult women.

### Group I

The subjects examined were 1,200 children under the age of 10 years presenting for any reason (very often "fever") at the medical out-patient department of Mulago Hospital, Kampala. They were taken without selection during a two- to three-hour visit by a native laboratory assistant, who recorded their personal details, and collected from each a thick and a thin blood film and a few drops of blood in saline. All the specimens were examined by me. Sickling was tested for in a 24-hour culture of *Bact. coli* and read at two to four hours, and paper electrophoresis was performed if necessary. Malarial species diagnosis was made on thick blood films, but the thin films were used if any doubt existed.

Malaria was detected in 638 of the children—90 times in 191 sicklers (47.1%), and 548 times in 1,009 non-sicklers (54.3%). For this difference in favour of sicklers, $\chi^2 = 2.65$, n = 1, $0.2 > P > 0.1$, and thus the possibility that the difference had arisen by chance was rather high. But this does not take account of the species of parasite present. If we exclude the *P. ovale* infections (7 in number), and 11 cases in which the species could not be determined with accuracy (there were no *P. vivax* infections), and consider only infections with *P. falciparum* and *P. malariae*, a different picture emerges. In compiling Table I, cases in which these two species were present together have been counted as separate infections (in 36 children). In the whole 1,200 children there was no indication that the incidence of *P. malariae* was affected by the sickling state of its hosts, but the numbers showing this parasite were not great. *P. falciparum*, however, was very noticeably commoner in non-sicklers, except in the first year of life. It will be noticed that the apparent protection against all forms of malaria, and even against *P. falciparum*, is much less in this series than in Allison's (1954). It may be added that the two main tribal groups covered by this survey had closely similar sickle-cell frequencies; the largely rural Baganda showed a higher malaria rate than the urban and suburban Nilotics, but the apparent protection against *P. falciparum* was present in each to a significant degree.

TABLE I.—*Incidence of P. malariae and P. falciparum Infections in Sicklers and Non-sicklers, Among 1,200 Children under 10 years of Age at a Medical Out-patient Department*

| Age in Years | Sickling State | No. of Cases | *P. malariae* | | *P. falciparum* | | |
|---|---|---|---|---|---|---|---|
| | | | No. | % | No. | % | $\chi^2$ (n=1) |
| Under 1 | Positive | 68 | 7 | 10·3 | 32 | 47 | 1·15 (P>0·2) |
| | Negative | 325 | 15 | 4·6 | 130 | 40 | |
| 1– | Positive | 59 | 6 | 10·2 | 20 | 34·4 | 10·13(P<0·01) |
| | Negative | 288 | 21 | 7·3 | 163 | 71·5 | |
| 2–10 | Positive | 64 | 3 | 4·7 | 21 | 32·8 | 7·11 (P<0·01) |
| | Negative | 396 | 37 | 9·3 | 201 | 50·8 | |
| Total | Positive | 191 | 16 | 8·4 | 73 | 38·2 | 7·4 (P<0·01) |
| | Negative | 1,009 | 73 | 7·3 | 494 | 49·3 | |

### Group II

Long before the above investigation was started, however, data were being collected from another group. These were children under the age of 5 years, attending child welfare clinics in and around Kampala, under the care of Dr. H. F. Welbourn, to whom I am indebted for permission to quote the following facts. At these clinics the children attend as families for general supervision, and not primarily because they are ill, though illness may often determine the first attendance of a family. A laboratory assistant attended all the clinics, and specimens were brought to the laboratory and examined in the same way as for the hospital series. Sickling and malaria were tested for on the first attendance of each child, and the results given below refer only to the first attendances, or to the first occasion when the tests were performed—in any case, before any antimalarial treatment had been given. Malarial species diagnosis was not quite so certain as in Group I, and the figures quoted here are for all species, though of course *P. falciparum* predominated.

From April, 1952, to October, 1954, 1,194 children were tested on first attendance; of 192 sicklers, 58 (30%) showed malarial parasitaemia, while of 1,002 non-sicklers 334 (33.4%) did so—a difference that is quite insignificant, but of the same nature as that for gross malarial parasitaemia in Group I. Among these children the malaria rate was lower, and the proportion of Nilotics higher, than in the hospital series, but again the two main tribal groups gave closely similar results. The apparent protection against malaria in the sicklers was less in this group than in Group I, and a possible reason for this is suggested below.

### Group III

One other group of persons was examined in the same way as the preceding; this was a consecutive series of 663 mothers of some of the children in Group I. They were not ill, and they were selected only in the sense that they had brought their sick children to hospital. Practically all would possess a considerable acquired immunity to the effects of malaria. All the 91 infections detected in them were of mild degree (only 5 showed more than about 1,000 parasites per c.mm.), and all were considered to be of *P. falciparum*, though proof was not always absolute when the parasites were very scanty. In the 135 mothers who were carriers of the sickle-cell trait there were 24 (18%) who showed parasites in the blood; in the 528 non-sicklers there were 67 (12.7%). These findings are the reverse of those for the children in Group I, but the difference is of about the same order of magnitude, and might with equal likelihood have arisen by chance ($\chi^2 = 2.35$, n = 1, $0.2 > P > 0.1$).

## Parasite Count in Relation to Sickling

The following findings refer only to the *P. falciparum* infections encountered in Group I and to the counts determined, for each child, only on the day on which it first attended hospital. Parasite counts were performed on 558 consecutive falciparum infections (they were omitted in the first nine cases). Counts were made against leucocytes in parts of the field where the distribution was even, and the result was recorded on the assumption that the leucocyte count was 5,000 per c.mm. Noticeable leucocytosis was very rare in malarial children.

Table II shows that more than half the falciparum infections in the sickling children were of low intensity, while non-sickling children showed predominantly heavy infections. It may be added that the highest count found in a sickler was 160,000 per c.mm., whereas counts up to 800,000 per c.mm. were not unusual in non-sicklers. For this analysis, grouping by parasite density has been made on a logarithmic basis (in powers of 10) for convenience, and because this accords with the process of multiplication of an

TABLE II.—*Distribution of Parasite Densities in 558 Consecutive Infections with P. falciparum in Children under 10 years, in Sicklers and Non-sicklers*

| Parasite Count per c.mm. | Sicklers (72 Cases) | | Non-sicklers (486 Cases) | |
|---|---|---|---|---|
| | No. | % of Total | No. | % of Total |
| Under 100 .. .. .. | 20 | 27·8 | 55 | 11·3 |
| 100– .. .. .. | 17 | 23·5 | 57 | 11·7 |
| 1,000– .. .. .. | 14 | 19·5 | 147 | 30·2 |
| 10,000– .. .. .. | 18 | 25·0 | 182 | 37·4 |
| 100,000+ .. .. .. | 3 | 4·2 | 45 | 9·4 |

TABLE III.—*Comparison of the Incidence of Parasite Counts under 1,000 per c.mm. in Sicklers and Non-sicklers at Various Ages, in 558 Children Infected with P. falciparum*

| Age in Years | Sickling State | No. of Cases | Cases with Counts under 1,000 c.mm. | | |
|---|---|---|---|---|---|
| | | | No. | % | $\chi^2$ (n = 1) |
| Under 1 | Positive | 30 | 16 | 53·3 | 11·99 (P < 0·01) |
| | Negative | 132 | 29 | 29·5 | |
| 1– | Positive | 20 | 12 | 60·0 | 14·5 (P < 0·01) |
| | Negative | 162 | 34 | 20·9 | |
| 2–10 | Positive | 22 | 9 | 40·9 | 2·36 (0·2 > P > 0·1) |
| | Negative | 192 | 49 | 25·5 | |
| Total | Positive | 72 | 37 | 51·4 | 21·94 (P < 0·01) |
| | Negative | 486 | 112 | 23·04 | |

organism. In this arbitrary scale a figure of 1,000 per c.mm. represents a point in the Table about which the difference between sicklers and non-sicklers is most pronounced, and Table III shows how a grouping of cases into those with counts of less than 1,000 per c.mm. and those with over 1,000 reveals a striking difference between sicklers and non-sicklers at all ages—least amongst the older children, but remarkable even in those under 1 year, in whom (Table I) falciparum infections were commoner in sicklers. Again, it may be added that these differences were as marked for the Baganda as for the Nilotic children.

## Nature of the "Protection" Enjoyed by Sicklers

The view put forward here is that the presence of sickle-cell haemoglobin in a person's erythrocytes does not prevent his infection with plasmodia, but does limit the extent to which at least a falciparum infection may develop. This probably means also that attacks of falciparum malaria will be on the whole briefer and less disabling among sicklers, and that, in them, dangerous attacks will be rare. This view is derived from the observations of parasite counts in a certain group of children, and therefore the validity of this experiment must be discussed.

The present experiment was not designed to detect the highest extent to which parasitaemia could develop in sicklers and non-sicklers respectively, nor was it possible to record the duration of each attack at the time the examination was made—and very marked changes are to be expected in the count as an attack develops and recedes. In this locality a visit to hospital is likely to be considered for some time before it is decided upon, and thus low counts are extremely unlikely to represent attendance early in an attack of malaria; they represent either the possession of immunity or attendance towards the end of an attack. Significant immunity can be excluded in practically all these children. If, therefore, we are to draw conclusions from the greater frequency of low parasite counts in sickling children, we must be assured that they attended, on the average, at about the same stage of the attack as did the non-sicklers; or if they attended at a somewhat later stage of their attacks than the non-sicklers did we must find an explanation for this. In spite of the lack of clinical data, there is some evidence on this point.

Three features were encountered rather more often in the blood films of sicklers than in the rest—signs of erythropoietic activity (Raper, 1954a), well-grown trophozoites, and gametocytes. The latter were found in 31% of falciparum infections in sicklers, and in 21% of these infections in non-sicklers. None of these features can be ascribed directly to sicklaemia, but they are all indications of the early recovery phase of malaria. The experiment, therefore, had admitted a slight excess of sicklers in the early stages of recovery from malaria, and the reason for this must be sought. In this area, sicklers are not more common in the more remote population than in that close to the hospital, nor in the lower social classes than in the higher; indeed, they are less common in the more primitive tribes included in this experiment. Thus social and educational factors, producing different attitudes to the use of a hospital, are unlikely to have determined the later attendance of sicklers. The only explanation likely to account for all the observed facts is that falciparum attacks in sicklers are unusually mild and brief. This is the hypothesis advanced here; the low counts observed in sicklers are a feature of the kind of malarial attacks they experience, and, though the present results may slightly exaggerate this feature, they could not have been produced unless it existed.

The establishment of this point makes it possible to offer an explanation for the inconclusive reports regarding gross parasite rates in sicklers and non-sicklers, both among those recorded here and among those of Beet (1946, 1947), Brain (1952), Edington (1954), and Moore *et al.* (1954). All but the last of these referred to hospital patients, most included adults as well as children, and none except the last distinguished between the species of parasite. Among such non-immunes as were included, the sicklers would attend hospital less often because of their milder attacks, and so would form a smaller proportion of all malaria cases diagnosed, thus accounting for the general tendency to record fewer malarial attacks among sicklers. There must have been less selection of this sort in the child welfare clinic children recorded here (Group II), and in them the apparent protection against all forms of malaria was somewhat less than in the hospital series (Group I). Where no selection whatever is employed, as in the field survey of Moore *et al.* (1954), a very small difference between the two groups could be expected to arise from the probability that sampling at any moment would detect slightly fewer infections in sicklers, simply because their attacks are rather briefer than in non-sicklers. But the number to be sampled before this difference appeared significant would be very great, certainly several times 2,394, which is the number of partially selected cases recorded here.

In this connexion it may be remarked that since attacks of quartan malaria are normally of long duration, and on the whole mild, the results recorded here for *P. malariae* are quite inadequate in number to decide whether sicklers do or do not enjoy any protection against this species.

If the subjects of a survey possess any other means of resisting the growth of plasmodia, this must affect the degree of protection they exhibit from possessing or lacking the sickle-cell trait. In a region of heavy malarial endemicity adults possess this protection by reason of their acquired immunity (or "premunition"). How far this operates in sicklers and non-sicklers respectively is not revealed by the results quoted above for the 663 mothers (Group III), because they were neither selected by illness nor distinguished by the degree of their parasitaemia. But all experience suggests that acquired immunity is at least as potent a protection as the possession of the sickling trait. Hence the inclusion of adults in a survey in an endemic malarial region will obscure any protection that the sicklaemic children may enjoy.

It has been mentioned above that the relative protection of sicklaemic children against *heavy* falciparum infections is enough to account for that increased chance of survival that is required to explain the persistence, or the building up, of high frequencies of the sickling gene in parts of Africa. I have emphasized elsewhere (Raper, 1954b) that the process is a dynamic one, and that the present situation in that continent need not be treated as static. Field (1949) saw very few deaths from falciparum malaria in Malaya in persons whose parasite counts were under 10,000 per c.mm., and no death with a parasite count of fewer than 2,300 per c.mm.

It has been remarked above that the difference between sickling and non-sickling children is particularly marked at about this level of parasitaemia. It is important to notice that for natural selection to operate in favour of heterozygous sicklers it must exert its effect before reproductive age; the view advanced here is that it can operate only in the absence of acquired immunity, and in an endemic area it is precisely those below reproductive age who lack effective immunity.

All this evidence is of course indirect; the decisive information—accurate mortality statistics for sicklers and non-sicklers before puberty—is nowhere available, and will be difficult to collect. Nevertheless, there is enough evidence to give support to Allison's (1954) hypothesis, and to justify attempts to show exactly how the metabolism of the various species of plasmodia is affected by the molecular structure of the haemoglobin in the erythrocytes that they invade.


## Summary

In two large series of children living in the vicinity of Kampala, Uganda, the gross malarial parasite rate was found to be lower in those carrying the sickle-cell trait than in others, but not significantly so.

In a series of 1,200 children attending hospital the *P. falciparum* rate was significantly lower in sicklers than in non-sicklers.

Parasite counts in *P. falciparum* infections were very much lower in sickling than in non-sickling children.

It is maintained that the presence of sickle-cell haemoglobin in erythrocytes does not prevent, but limits, the severity of *P. falciparum* infections in non-immune subjects. Insufficient data are available to assess the effect of sickle-cell haemoglobin on other species of plasmodia.


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Television has been used by the American Medical Association since 1946 for health education, either in broadcasts to the public or on closed circuit to the medical profession, and the A.M.A. has recently published a handbook, *Television in Medical Education*, to give doctors guidance on the techniques of successful televising. The first part is devoted to the workings of television, which are clearly explained with the aid of photographs and diagrams. The second part gives practical help in producing a medical programme, suggesting ways in which information can be given, such as by monologue, interview, or documentary. Two scripts are reproduced, one for a public and one for a specialist audience. The reader is reminded that television is a visual medium, and he is shown how to include graphic and visual devices such as charts and sectional cut-outs in his programmes. Advice on dress, voice production, and approach is also given. The last section of the handbook describes what has already been achieved by this medium in medical education, and ends with a glossary of television terms. While, as the foreword points out, "learning by active participation has no peer," this publication is intended to enable doctors to make television a useful adjunct to their teaching programmes.

# EFFECT OF SICKLE-CELL TRAIT ON RESISTANCE TO MALARIA*


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Type S (sickle) haemoglobin is present in the red cells of a sizable percentage of members of the negro race. The presence or absence of this abnormal haemoglobin type is genetically determined. Heterozygous individuals, whose red cells also contain type A (normal) haemoglobin, suffer no ill effects from the presence of the abnormal haemoglobin, although sickling of the cells may be demonstrated when the oxygen tension is greatly reduced. Such individuals are said to have the sickle-cell trait. When, on the other hand, type S haemoglobin is inherited in the homozygous form, sickle-cell disease, a severe chronic haemolytic anaemia, results (Pauling *et al.*, 1949; Neel, 1951). Thus, unless individuals with the sickle-cell trait possessed some selective advantage, the gene for sickle haemoglobin would gradually be eliminated from the population by the early death of those with sickle-cell disease.

Allison (1954) has suggested that an increased resistance to infection with malaria may be such an advantage. He reviewed evidence that the incidence of malaria in endemic areas was lower in those individuals with the sickle-cell trait than in those without the trait. He also noted that the incidence of the sickle-cell trait was highest in those areas in which malaria was prevalent. Upon inoculation of a series of highly immune subjects with an African or a Malayan strain of *P. falciparum* intravenously and, in some cases, also with infected mosquitoes, Allison found that only 2 out of 15 "sicklers" (sickle-cell trait) developed malaria, while 14 out of 15 "non-sicklers" developed malaria. In the present study we have attempted to evaluate the effect of sickle haemoglobin on resistance to malaria under carefully controlled conditions.

## Materials and Methods

All subjects were inmate volunteers from the Stateville Branch of the Illinois State Penitentiary at Joliet, Illinois. Sixteen American negroes who had never previously had malaria were inoculated. Erythrocytes were examined for sickling by the 2% sodium metabisulphite method (Daland and Castle, 1948). In addition, haemoglobin from each volunteer was examined by filter-paper electrophoresis. Each of the eight "sicklers" had both type A and type S haemoglobin; each of the eight "non-sicklers" had only type A haemoglobin. In each of the three studies all subjects were inoculated with aliquots of a single freshly drawn

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