EFFECT OF MALARIA CONTROL ON HAEMOGLOBIN LEVELS

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From 1954 to 1959 an experiment was in progress in the plains of the Taveta-Pare area of Kenya and Tanganyika, which are about 2,000 ft. (610 metres) above sea-level, to control rural hyperendemic malaria and to assess some of the effects of this, if successful, upon the health of the people. For the latter purpose several investigations were done, including the measurement of haemoglobin levels, and this paper describes the results of these.

After a year and a half for the collection of basic data, the first spraying of all native huts with the residual insecticide dieldrin was started in the latter part of 1955, the sixth and final spraying being completed in early 1959. Descriptions of the malaria before the spraying, and of the considerable reduction in transmission later effected, have been given by Smith and Draper (1959) for the Taveta area, and by Draper and Smith (1957, 1960) for the South Pare area. Serial measurements of haemoglobin, and other investigations, were done on a sample of about 2,000 people, of whom slightly less than one-third came from the Taveta area and the others from the South Pare area. The intention was to examine the same people on each occasion; and this was about 80% successful; of 100 people on the registers, about 80 would appear for examination at one survey. Infant clinics were run in the Pare area to study several aspects of infant health, and the results of haemoglobin estimations from these have been included here.

Table I shows the spleen and parasite rates, before and after three years of spraying, of those groups in

TABLE I.—Spleen and Parasite Rates, Before and After Three Years' Residual Spraying, of People on Whom Haemoglobin Estimations were Done

Age-groups	No. Examined	Spleen Rate %		Parasite Rate %	
		Feb.-June, 1955	Sept., 1958- Feb., 1959	Feb.-June, 1955	Sept., 1958- Feb., 1959
0-11 months	44-62	50	10	61	0
12-23 "	41-77	78	1	84	2
2-4 years	122-126	88	2	86	5
10-14 "	240-320	77	14	73	7
10-14 "	245-299	68	16	62	4
15-19 "	115-141	46	11	49	4
20-39 "	157-458	55	22	29	4
40+ "	134-379	56	31	33	3

Taveta and Pare on whom the haemoglobin estimations were done, and demonstrates the great reductions in the malaria indices by 1959. Before the spraying, malaria was hyperendemic, with heavy infection in infancy and childhood, but with evidence of the later development of some immunity to infection. This was typically manifested by a fall with increasing age in the density of infections, the highest densities occurring at the ages of 2 or 3 years. Over 90% of infections were of *Plasmodium falciparum*. At a preliminary medical survey in the Pare area, infections with *Schistosoma haematobium* and with hookworm were found to be common, and in the Taveta area infection with *S. mansoni* was common. There is no reason to think that there has been any change in the incidence of these infections during the period of these observations. There has, however, particularly in the Pare area, been a noticeable rise in the general economic level since 1955.

In addition, haemoglobin surveys were done in a school in the malaria-free Pare mountains, at an altitude of 4,000 ft. (1,220 metres), and in a lowland comparison area some 70 miles (112 km.) south of the sprayed zone, where malaria remained uncontrolled.

Estimations of haemoglobin were made with the M.R.C. photometer. Samples of blood were collected in the field in the mornings, and the estimations were done in the laboratory during the afternoons. The great majority of the estimations were done by me. Some total white-cell counts were done by the method given by Dacie (1950).

Results

Table II and the Chart show the mean haemoglobin levels in the Taveta-Pare areas at two surveys before the spraying and at three later surveys. Infants under 3 months old have been omitted because of the rapid physiological variations in haemoglobin during the first few months of life. Before the spraying, all groups showed some degree of anaemia, this being most pronounced in the infants and young children and in the adolescent and adult females. After the start of malaria control there has been a progressive rise each year in the mean levels; the figures for all groups at the last survey are significantly greater than those at the first survey, the differences between the means being from 3 to 10 times the standard errors of their differences. Table III shows, for each group, the percentage increases in the means from the first to the last surveys. The greatest proportional increases have been in the infants and young children, and the least in the girls and young

TABLE II.—Mean Haemoglobin (g./100 ml.) at 5 Successive Surveys

Sex and Age	Feb.-June, '55			Aug.-Nov., '55			Feb.-June, '57			Feb.-June, '58			Aug., '58-Feb., '59		
	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.
Both Sexes:															
3-11 months	40	9.2	1.6	112	9.4	1.7	131	10.9	1.4	176	10.7	1.3	106	10.9	1.2
12-23 "	40	8.9	1.8	68	9.4	2.1	73	10.9	1.6	84	10.8	1.3	87	11.2	1.1
2-4 years	108	10.4	1.5	68	10.2	1.7	105	11.5	1.5	119	11.6	1.3	102	12.2	1.4
5-9 "	245	11.6	1.5	110	11.2	1.4	254	12.4	1.6	296	12.5	1.4	250	12.9	1.1
Males:															
10-14 years	156	12.0	1.5	48	11.5	1.6	130	12.9	1.4	123	12.9	1.4	132	13.1	1.2
15-19 "	44	12.9	1.5	27	13.2	1.5	32	13.7	2.4	71	14.2	1.7	63	14.8	1.7
20-39 "	182	13.5	1.8	130	13.1	1.9	147	14.3	1.8	139	14.7	1.5	121	15.2	1.5
40+ "	163	12.6	1.9	107	12.6	1.9	153	13.6	1.8	196	13.9	1.9	133	14.5	1.5
Females:															
10-14 years	104	12.3	1.6	33	11.6	1.5	108	12.8	1.6	119	13.0	1.2	87	13.2	1.1
15-19 "	82	12.0	1.9	51	10.9	1.9	59	12.0	1.8	56	12.4	1.8	57	13.0	1.5
20-39 "	215	11.6	1.8	145	11.2	1.5	191	12.4	1.6	219	12.3	1.6	182	12.9	1.4
40+ "	130	11.6	1.6	86	10.9	1.8	134	12.2	1.7	159	12.5	1.8	92	13.4	1.4

No. = Number examined. S.D. = Standard deviation.

adult females. Pregnant females were 5 to 10% of the age-groups 15 to 19 years and 20 to 39 years, the higher proportion being at the later surveys, as another effect of malaria control was to increase the fertility rates. Their haemoglobin levels were generally lower than those of other females: 37 pregnant women examined at the first two surveys had a mean level of 10.0 ± 1.8 g., and 80 examined during the last three surveys had a mean level of 11.5 ± 1.2 g.

As analysis of some of the individual surveys suggested that there might be some relation between haemoglobin and splenomegaly, an analysis was done of the figures for the first and the last three surveys together, comparing the mean haemoglobin levels of those with and without palpable spleens. This is given in Table IV. There are differences in all groups, which are statistically significant except for the males aged 15 to 19 years and 40 and over.

Table V shows the haemoglobin levels, at several surveys, of children in the comparison area and in the Pare mountain school. The former show no changes over the period of observation. The latter initially had higher levels than the children in the Pare plains, perhaps in part due to the altitude, but they also show changes over three years. These, though statistically significant, are less than the changes in the plains, and may be due to general improvement in living conditions, this area being one of the most developed in the Pare district.

Despite the improvement in haemoglobin levels in the plains after malaria control, anaemia was still common, especially in children and young women. To see if this would respond to additional iron in the diet, a group of 23 schoolchildren, with a mean haemoglobin before treatment of 10.9 ± 0.7 g., were given 1 g. of ferrous

TABLE III.—Percentage Increases in Mean Haemoglobin Levels from First to Last Survey, by Age and Sex

Age	Both Sexes (% Increase)	Age	Males (% Increase)	Females (% Increase)
3-11 months	18.5	10-14 years	9.2	7.3
12-23 "	25.8	15-19 "	14.7	8.3
2-4 years	17.3	20-39 "	12.6	11.7
5-9 "	11.2	40+ "	15.1	15.5

TABLE IV.—Mean Haemoglobins (g./100 ml.) by Spleen Size

Sex and Age	Spleen Palpable			Spleen Not Palpable		
	No.	Mean	S.D.	No.	Mean	S.D.
Both Sexes:						
3-11 months	11	9.2	1.7	160	10.8	1.5
12-23 "	11	8.4	1.4	155	11.0	1.3
2-4 years	82	9.8	1.4	305	11.8	1.5
5-9 "	279	11.8	1.7	599	12.8	1.4
Males:						
10-14 years	191	12.3	1.5	319	13.2	1.2
15-19 "	61	13.5	2.0	144	13.8	1.9
20-39 "	188	14.1	1.8	347	14.7	1.6
40+ "	245	13.5	1.8	357	13.7	1.8
Females:						
10-14 years	128	12.4	1.4	274	13.1	1.3
15-19 "	58	11.6	1.3	177	12.5	1.7
20-39 "	201	11.9	1.6	510	12.5	1.5
40+ "	173	11.9	1.8	321	12.6	1.6

sulphate daily for five days a week over a month. At the end of this period their mean haemoglobin had risen to 12.3 ± 1.6 g.

The results of two series of total white-blood-cell counts, before and after malaria control, are given in Table VI. All groups show an increase, but the changes are statistically significant only for the two younger age-groups.

Changes in mean haemoglobin levels, by age and sex, after malaria control.

TABLE V.—Mean Haemoglobins in Comparison Area and in Mountain School (g./100 ml.)

Sex and Age	Kiloza Comparison Area									Usangi School					
	Mar. and June, '56			May, 1957			June, 1958			May, 1955			May, 1958		
	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.
Both Sexes:															
2-9 years	28	10.8	1.7	52	10.1	1.1	22	10.4	1.3	—	—	—	101	13.3	1.1
5-9 "	99	11.9	1.4	91	11.8	1.3	97	11.5	1.1	79	12.7	1.0	—	—	—
Males:															
10-14 years	61	11.9	1.6	23	11.5	1.6	62	11.6	1.2	70	13.2	1.1	80	13.8	1.1
Females:															
10-14 years	46	12.2	1.6	30	12.7	1.2	48	11.9	1.2	43	13.3	1.1	48	13.8	1.0

TABLE VI.—Mean Total White-cell Counts per c.mm.

Age and Sex	1955			1958		
	No.	Mean	S.D.	No.	Mean	S.D.
Both Sexes:						
2-9 years	92	8,260	1,890	96	9,350	2,690
10-19 "	141	7,270	1,970	110	7,940	2,128
Males:						
Over 20 years	84	6,950	1,620	56	7,250	2,722
Females:						
Over 20 years	72	6,330	1,700	53	6,720	1,660

Discussion

The possible causes of anaemia in malaria are several. In the acute stage of infection there is intravascular haemolysis of parasitized cells at sporulation, and, of equal if not of greater importance, the lysis of normal cells, resulting from a disturbance of the normal balance of lytic systems in the blood (Maegraith, 1948). In the Taveta-Pare area these processes would be of importance only in the non-immune, such as infants and young children, in whom heavy parasitaemia occurred. The development of immunity is accompanied by the production of specific humoral antibodies, such as agglutinins and opsonins, and, in particular, by a proliferation of the cells of the reticulo-endothelial system, which removes the parasites from the blood. The latter occurs chiefly in the spleen, which enlarges because of the hyperplasia and increased vascularity. The phagocytosis of red cells, however, is not entirely specific, and some normal cells may be destroyed as well as parasitized cells, though the more the immunity the greater the specificity (Taliaferro, 1949). The stagnation of blood in an enlarged spleen may of itself be a factor in causing anaemia, by the segregation of a large number of red cells from the circulation. The bone-marrow in malaria usually shows erythronormoblastic hyperplasia as a response to the anaemia, but a megaloblastic reaction has occasionally been described. It is probable, however, that the latter is due to the overstimulation of a marrow the function of which is already disordered. Depression of leucopoiesis, affecting particularly the granulocyte series, is well recognized, and the findings here are in agreement with this.

Anaemia is widespread in tropical Africa, but the importance of malaria in its aetiology is disputed. Jordan (1954) and Welbourn (1955), in East Africa, considered it to be a cause of anaemia in infants, but Garnham (1949) found only a small effect. In West Africa, McGregor and Smith (1952) and Hendrickse and King (1958) incriminated malaria, but McGregor *et al.* (1956), who compared protected and unprotected infants, found little difference between the mean haemoglobin levels of the two groups at 3 years of age. There have been

few recorded observations of the effects of malaria in causing anaemia in adults who have acquired some immunity to the parasite. Macdonald (1939), in Assam, where malaria was hyperendemic, found that the response of anaemic women to iron therapy was increased by previous treatment with mepacrine hydrochloride. Foy and Kondi (1957, 1958) and Foy *et al.* (1958) discount the effect of malaria, and thought that the anaemia of warm lowland areas is mostly due to iron deficiency, from poor absorption and dermal losses, combined with the losses of menstruation or child-bearing in women. They point out that the iron liberated by destruction of the red cells in malaria can be used again by the body, and that malaria would not cause anaemia unless superimposed on an already strained haemopoiesis. It is important therefore, in assessing the effects of malaria, to consider not only the degree of its endemicity but also the nutritional background. Variations in the latter may account for some of the different views expressed.

In the Taveta-Pare area anaemia was common before malaria control. That malaria had some part in its causation is shown by the changes in haemoglobin levels that have followed control. Some of the increase may have been due to the general rise in living standards. The greatest increases have been in infants and young children who had not yet acquired much immunity, but it is interesting that the relative immunity shown by older children and adults was maintained at some cost. After three years of control the haemoglobin in most children and in adult males approached levels regarded as physiologically normal (Wintrobe, 1956): but in other children, and in females during adolescence and the reproductive period, there remained some anaemia, probably due to iron deficiency.

Summary

Estimations of the haemoglobin levels of the same group of people in a part of East Africa were made before and during a successful malaria-control scheme. They were compared over the same period with a nearby non-malarious group and with another group in which malaria remained uncontrolled.

The fall in the human malaria indices was accompanied by a progressive rise in the mean haemoglobin levels. The greatest increases were in infants and young children and the least in girls and young adult females.

These changes were probably directly due to the reduction in malaria transmission, but a general rise in living standards throughout the period of observation may have had some effect.

There was also a small rise in mean total white-blood-cell counts.

The pathogenesis of anaemia in hyperendemic malaria is discussed.

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Medical Memoranda

Outbreak of Dysentery Caused by *Shigella boydii* 4

In Britain dysentery is almost entirely caused by *Shigella sonnei* and only a small amount by *Sh. flexneri*, but from time to time outbreaks are associated with the more unusual shigella types; this communication describes one such outbreak, the cause of which was found to be *Sh. boydii* 4. In a personal communication Dr. K. Patricia Carpenter, of the Dysentery Reference Laboratory, Colindale, states that the *Sh. boydii* subgroup is not indigenous to Britain, and infections caused by the various Boyd types are always "imported"—that is, either the patient himself or a contact has been infected outside this country. Over a nine-year period, up to 1958, the records of the Dysentery Reference Laboratory show that only 37 *Sh. boydii* strains are known to have been isolated in Britain, and of these only 2 were *Sh. boydii* 4 (P274); both these organisms came from patients known to have been infected abroad. An outbreak of dysentery in this country caused by *Sh. boydii* 4 is therefore noteworthy.

CLINICAL NOTES

In May, 1958, seven children, all from one family and all below the age of 9 years, were admitted to an infectious diseases hospital near Glasgow, suffering from what was described as mild dysentery; their parents are reported as not being affected. On admission the children were found to have mild diarrhoea, with no blood or mucus in the stools, and no fever; no chemotherapeutic treatment was given, and after two weeks in hospital they were discharged home. During their stay in hospital, bacteriological examination of faecal specimens revealed that all the children were excreting an organism which behaved biochemically like a shigella, but which was not one of the serotypes commonly found in this area (*Sh. sonnei*, *Sh. flexneri* 1, 2, and 3, and X variants). A few days after the seven children had been discharged home, their maternal uncle and his two children, aged 4½ and 2½ years, were

admitted to hospital suffering from dysentery. From the faeces of these three were isolated organisms which appeared to be the same as those obtained from the seven children. These three patients were well within a few days, and were discharged home seven days after entering hospital.

BACTERIOLOGICAL FINDINGS

The 10 strains isolated appeared to be identical—two were selected for detailed examination; one was from one of the seven children first admitted to hospital and the other from their uncle. Both produced identical biochemical reactions—namely, acid without gas was formed from glucose and mannitol within 24 hours; from sorbitol and rhamnose a faint acid reaction was produced after three days, while maltose showed a slight acid reaction after 15 days: the tests for motility, indole, H₂S formation, citrate utilization, gelatin liquefaction, and urease formation were all negative; the Voges-Proskauer test was negative and the methyl-red test was positive. After 30 days' incubation negative reactions were obtained with lactose, sucrose, inositol, raffinose, xylose, galactose, dulcitol, salicin, and adonitol.

Slide-agglutination tests with the two strains under investigation against all the shigella antisera issued by the Standards Laboratory showed positive results with a polyvalent *Sh. boydii* serum (serotypes 1-7), *Sh. boydii* 4, and *Sh. boydii* 1. Tube-agglutination tests with these antisera produced full titre agglutination with the polyvalent *boydii* and the individual *Sh. boydii* 4 sera, but agglutination to only a titre of 1/10 with *Sh. boydii* 1. (Dr. Carpenter states that this agglutination with *Sh. boydii* 1 is almost certainly due to minor alkalescens-dispar group relationships.) Rabbit antisera to the two strains under test were prepared using boiled vaccines. Both sera gave a titre of 1:6,400 against boiled suspensions of the homologous strain, the heterologous strain, and also a known strain of *Sh. boydii* 4 (NCTC 8214). Reciprocal and mirror absorption tests showed that both strains were identical with each other and with a classical *Sh. boydii* 4. These findings were subsequently confirmed by the Dysentery Reference Laboratory at Colindale.

COMMENT

In view of what was known about the occurrence of *Sh. boydii* 4 in this country, inquiries were made to discover if the present outbreak had a foreign source: it was learned that the children's uncle, the only adult patient, was in fact a native of Estonia, making frequent trips to this country in his capacity as a seaman. It seems reasonable to suppose that he was the vehicle by which the organism was transmitted to the children, but, as he visited several Continental ports shortly before the outbreak developed, it is impossible to be certain of the exact location of origin of the infection. It is of interest that the outbreak produced only very mild symptoms, requiring practically no treatment, and that a careful follow-up by public-health authorities showed that the infection did not extend beyond family limits.

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