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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REFERENCES

Allison, A. C. (1954). *British Medical Journal*, **1**, 290.
Beet, E. A. (1946). *E. Afr. med. J.*, **23**, 75.
—— (1947). Ibid., **24**, 212.
Brain, P. (1952). *S. Afr. med. J.*, **26**, 925.
Edington, G. M. (1954). *British Medical Journal*, **1**, 871.
Field, J. W. (1949). *Trans. roy. Soc. trop. Med. Hyg.*, **43**, 33.
Moore, R. A., Brass, W., and Foy, H. (1954). *British Medical Journal*, **2**, 630.
Raper, A. B. (1954a). *E. Afr. med. J.*, **31**, 443.
—— (1954b). *British Medical Journal*, **2**, 1162.

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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TABLE I.—*Parasite Counts per c.mm. in 5 "Sicklers" and 5 "Non-Sicklers" after Inoculation with 500,000 Trophozoites of P. falciparum.*

Day After Inoculation	"Sicklers"					"Non-sicklers"				
	S1	S2	S3	S4	S5	N1	N2	N3	N4	N5
1	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0
4	20	10	30	40	50	20	20	90	20	60
5	10	10	10	10	0	0	10	50	10	0
6	460	810	900	44)	1,040	740	840	3,620	1,380	1,860
7	270	140	10	240	30	210	70	830	290	380
8	2,720	2,640	13,980	4,520	17,720	6,140	26,280	63,360 *	12,420	23,920
9	110	380	80	690	180	1,260	40	1,260	6,040	4,420
10	6,120	6,940	14,280	15,780	16,040	10,920	12,540	100	23,720	18,540
11	210	1,280	1,460	2,640	570	10,820 *	560	20	1,500	17,400 *
12	16,740 *	19,520 *	36,120 *	34,840 *	25,380 *	7,860	18,180 *	10	8,820 *	8,640
13	180	740	380	4,520	6,510	660	1,980	0	640	150
14	40 (25%)	60	40 (25%)	290	60	0	10	0	100 (25%)	0
15	20 (100%)	30	0	10	0	0	0		40 (100%)	0
16	50 (100%)	10	0	100 (100%)	0		0		40 (100%)	
17	0	0		20 (100%)					0	
18	0	0		20 (100%)					0	
19				10 (100%)						
20				0						
21				0						

* Chloroquine therapy instituted. Figures in parentheses represent percentage of gametocytes. Unless otherwise indicated, all parasites were trophozoites.

TABLE II.—*Parasite Counts per c.mm. in 3 "Sicklers" and 3 "Non-sicklers" After Inoculation with 50,000 Trophozoites of P. falciparum*

Day After Inoculation	"Sicklers"			"Non-Sicklers"		
	S6	S7	S8	N6	N7	N8
1	0	0	0	0	0	0
2	0	0	0	0	0	0
3	0	10	0	0	0	30
4	10	0	10	0	0	0
5	20	70	280	20	30	60
6	700	80	60	40	160	240
7	480	820	1,960	180	1,700	2,340
8	12,900	320	9,760	240	3,980 *	3,720 *
9	2,040	4,280	3,920	2,320	11,320	11,800
10	27,600	780	3,760	2,540	3,370	3,100
11	4,540	13,380	5,760	8,160	710	420
12	65,400 *	1,780	2,720	17,300	40	280
13	4,600	23,120	14,380	34,260 *	0	0
14	720 (1%)	4,480	6,480	8,340	0	0
15	200 (50%)	12,620	10,620	4,480		
16	90 (100%)	9,080	6,160	70		
17	50 (50%)	1,680	6,540	0		
18	90 (100%)	2,360 (20%)	7,220	0		
19		1,180 (50%)	4,420			
20	90 (100%)	820 (50%)	1,740			
21		920 (40%)	1,200			
22		1,060 (50%)	1,460			
23		820 (15%) *	1,620 *			

* Chloroquine therapy instituted.
Figures in parentheses represent percentage of gametocytes.
Unless otherwise indicated, all parasites were trophozoites.

sample of heparinized, Group O, Rh-negative blood infected with trophozoites of the El Limon, Panama strain PF 6 (Jeffery and Eyles, 1954) of falciparum malaria. In studies 2 and 3 the donor's blood was diluted in his own plasma, so that the injected volume could be measured more accurately. The parasites in 0.1 c.mm. of blood were counted directly on stained thick smears (Earle and Perez, 1932). The infection was terminated with chloroquine whenever it was considered necessary to do so for the patient's safety; the decision whether or not to interrupt the infection in any given case was based on the course of the parasite count and on the clinical condition of the patient. All patients remaining in the study for 23 days after inoculation were cured at that time.

Results

Study 1.—Ten volunteers, five "sicklers" and five "non-sicklers," were inoculated with 500,000 parasites each. The parasite counts of these 10 men are presented in Table I. As this table indicates, it was necessary to interrupt the infections of three of the "non-sicklers" before it was necessary to interrupt the infections of any of the "sicklers." The parasite counts of the "non-sicklers" tended to be somewhat higher. On day 8 the difference between the means of the logarithms of the counts of the two groups slightly exceeded two standard errors, and may therefore be regarded as statistically significant at the 0.05 level. Earlier

TABLE III.—*Parasite Counts per c.mm. of 5 "Sicklers" and 5 "Non-Sicklers" (same subject as in Table I) after Reinoculation with 50,000 Trophozoites of P. falciparum.*

Day After Inoculation	"Sicklers"					"Non-sicklers"				
	S1	S2	S3	S4	S5	N1	N2	N3	N4	N5
1	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	30	0	0
6	50	30	20	60	20	30	10	150	30	20
7	0	0	0	0	0	0	0	10	10	10
8	380	220	150	340	390	30	320	7,380	130	1,450
9	20	30	10	20	20	10	10	380	10	30
10	7,240	4,020	3,260	8,740	7,240	380	6,680	130,050 *	5,440	28,200
11	110	70	60	270	450	30	90	3,640	210	200
12	11,800	39,600	30,200	57,480 *	84,640 *	1,800	12,040	680	7,460	57,600 *
13	90	320 *	380 *	460	90	10	70	140	40	170
14	9,920	20,520	9,760	90	20	880	3,540	0	1,640	470
15	70	2,360	1,640	20	0	30	150	0	40	220
16	2,860	90	70	10	0	510	7,500		1,820	20
17	190	0	0	0		30 (50%)	150		70	100
18	1,540 (20%)	0	0	0		170 (50%)	2,260 (50%)		2,200 (25%)	30
19	250 (95%)					110 (100%)	1,440 (100%)		530 (100%)	0
20	2,960 (15%)					270 (100%)	2,100 (80%)		1,780 (75%)	0
21	510 (70%)					360 (100%)	1,380 (99%)		1,080 (99%)	
22	4,720 (5%)					480 (98%)	2,180 (50%)		3,620 (80%)	
23	780 (50%) *					440 (100%) *	1,200 (99%) *		920 (99%) *	

* Chloroquine therapy instituted. Figures in parentheses represent percentage of gametocytes. Unless otherwise indicated, all parasites were trophozoites.

differences did not reach this level of significance; later comparisons were not valid because of the interposition of treatment of some of the volunteers.

Study 2.—Because it was thought that 500,000 parasites might have been an overwhelming inoculum, six other volunteers, three "sicklers" and three "non-sicklers," were given an injection of only 50,000 parasites. The parasite counts of these subjects are presented in Table II. It was necessary to interrupt the infection in two of the three "non-sicklers" before it was necessary to interrupt the infections of any of the "sicklers."

Study 3.—In an attempt to determine the effect of acquired immunity on the resistance of "sicklers" and "non-sicklers" to malaria, the same 10 volunteers who had been inoculated with 500,000 parasites in study 1 were reinoculated with 50,000 parasites after a lapse of four months. The parasite counts during this study are presented in Table III. Up to and including day 10, when treatment was started on subject N3, the means of the logarithms of the parasite counts of the "sicklers" and "non-sicklers" never differed to a statistically significant degree. Although it was necessary to treat two of the five "non-sicklers" relatively early in the course of their infection, the other three were able to continue for the remainder of the study, while only one of the "sicklers" was able to do so.

Discussion

In comparing the resistance of individuals with and without sickle-cell trait to malaria, we have been able to demonstrate only unimpressive differences of questionable significance. These findings differ from those of Allison (1954). There are several possible explanations for this difference in results. While Allison used an African and a Malayan strain of falciparum malaria, we used a Panamanian strain. It is conceivable, although it does not appear very likely, that strain differences between the parasites used were sufficient to account for the different results. His subjects were highly immune; ours were non-immune in studies 1 and 2, and only slightly immune in study 3. It is also possible that any advantage which sickle-cell haemoglobin gives an individual infected with malaria is so slight in itself as to become manifest only when a high degree of acquired immunity already exists.

It would appear that further work is necessary to evaluate conclusively the role of sickle-cell haemoglobin in resistance to malaria.

Summary

Eight non-immune men with sickle-cell trait and eight non-immune men whose red cells contained only normal haemoglobin were inoculated with *P. falciparum* intravenously. Ten of these men were reinoculated four months after their initial course of malaria. The resulting parasitaemias tended to be somewhat less marked in the men with the sickle trait than in those without the trait, but the difference observed was unimpressive and of questionable significance.

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REFERENCES

Allison, A. C. (1954). *British Medical Journal*, **1**, 290.
Daland, G. A., and Castle, W. B. (1948). *J. Lab. clin. Med.*, **33**, 1082.
Earle, W. C., and Perez, M. (1932). Ibid., **17**, 1124.
Jeffery, G. M., and Eyles, D. E. (1954). *Amer. J. trop. Med. Hyg.*, **3**, 219.
Neel, J. V. (1951). *Blood*, **6**, 389.
Pauling, L., Itano, H. A., Singer, S. J., and Wells, I. C. (1949). *Science*, **110**, 543

EMERGENCY MITRAL VALVOTOMY AT FULL TERM

REPORT OF A CASE

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Several reports have appeared in recent literature on the value of mitral valvotomy during pregnancy (Baker *et al.*, 1952; Logan and Turner, 1952; Sellors *et al.*, 1953; Mulcahy, 1954). These emphasize that, in a limited and properly selected group of cases, this procedure may play an effective part in lessening disability, and thus help to reduce the maternal mortality rate due to heart disease. These reports advise that, when indicated, operation should take place during the first trimester or as early in pregnancy as possible, and most of the recorded valvotomies in pregnant women have been done during these early months.

We here record the case history of a patient with pure mitral stenosis who had a valvotomy performed at full term, ten hours before the birth of her ninth child. No such case has so far been recorded, though the feasibility of this procedure at all stages of pregnancy has been suggested previously (Mulcahy, 1954).

Case Report

A married woman aged 35 was admitted to the Coombe Maternity Hospital on November 29, 1954, in the early stages of labour. She had been a "defaulter" from the antenatal clinic. Apart from the normal labour pains, she was observed to be considerably distressed with dyspnoea, orthopnoea, cough, and cyanosis. On examination she was found to have pure mitral stenosis. She was in regular rhythm, and, though there was no evidence of heart failure, she was regarded at the time as a likely subject for a later pulmonary oedema. This impression was supported by the tachycardia, the loud slapping first sound following the unusually harsh mid-diastolic and presystolic murmur, the easily palpable right ventricle and pulmonary artery, and the evidence of early pulmonary venous congestion on the skiagram taken twenty-four hours after admission. The film also revealed a large left auricle and pulmonary artery, but only minimal cardiac enlargement. Further factors, obviously important in her case, were the six-weeks history of persistent non-productive cough and the presence of anaemia, her haemoglobin being 55%.

This patient had attended the antenatal clinic beforehand, but, despite a history of increasing distress on exertion and of a long-standing cough, she had failed to report anything abnormal. At no time had she complained of haemoptysis. During her earlier pregnancies, the last having been 22 months previously, she recalled no notable symptoms, nor was she informed of any abnormality in the heart. There was no previous history of rheumatic fever.

Treatment was started at once. It included penicillin, 500,000 units twice daily, digoxin, 0.25 mg. eight-hourly, sedation, and efforts to suppress the cough. Notwithstanding these measures and despite the cessation of labour pains a few hours after admission, her condition showed little or no improvement. Morphine, ¼ gr. (10 mg.) six-hourly, intravenous aminophylline, and streptomycin were added