Sickle cell haemoglobinopathies in England

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SUMMARY Ninety-six Birmingham children with sickle cell disease were studied prospectively between 1969 and 1979. Thirty-five were homozygotes for HbS (SS), 12 had sickle thalassaemia (S thal), and 23 were double heterozygotes for HbS and C (SC). Twenty-six whose family studies were incomplete were classified as SS or S thal although most were thought to be SS. The average length of follow-up was 5.1 years. Four SS children and 1 SC child died, the annual mortality rates being 1.3% for SS and presumed SS, 0% for S thal, and 0.9% for SC children. The incidence of pulmonary illnesses and anaemic crises was greater than reported from Jamaica, while leg ulceration described there and in New York was not observed in Birmingham. Severe infections were less common than in the series reported from New York and no case of salmonella osteomyelitis was observed in Birmingham. In general the S thal and SC children had milder illnesses than the SS, and the SS children often showed impairment of growth and sexual maturation.

The natural history of sickle cell disease in children varies greatly from country to country depending on socioeconomic and environmental factors. In west Africa, where child mortality rates were high, at least 40% of children with sickle cell diseases used to die during the first 2 years, mainly from infections and anaemic crises,¹ and fewer than 20% survived into adulthood.² It has been calculated that 40% of SS Jamaicans survive into middle age³ and similar mortality rates have been reported from North America,^{4,5} while Saudi Arabs have an unusually benign disease, which has been attributed to a genetically-determined ability to increase fetal haemoglobin (HbF) production.⁶

In 1971 about 93 000 of Birmingham's 1 million population were new commonwealth* immigrants⁷ and a survey of schoolchildren⁸ showed that among the 60% who were of African or West Indian origin, hetero- or homozygous HbS was present in 8%, HbC in 3%, and β -thalassaemia in 0.75%. Thus it can be calculated that about 155 children and adults with SS, SC, and S thal now live in Birmingham.

This report describes a prospective study started in 1969 of children with sickle haemoglobinopathies carried out at Birmingham Children's Hospital. It is the first account of the natural history of the disease to give mortality rates and to describe certain other

clinical and haematological features of children with sickle cell diseases living in the UK.

Patients and methods

Ninety-six children with SS, S thal, and SC were studied between January 1969 and December 1979. Children doubly heterozygous for HbS and hereditary persistence of HbF were excluded. Forty-eight patients were recruited into the study from clinics in the hospital during 1969-70 and 48 children newly diagnosed or referred from elsewhere were added subsequently. Their families had come to Birmingham from the West Indies (87), west Africa (8), and the Yemen (1).

With the exception of 5 asymptomatic S thal and SC children, all of them were reviewed regularly in a special clinic until their care was transferred elsewhere. At each clinic visit height, weight, and development (including sexual maturation, illnesses since previous attendance, Hb level, haematocrit, and reticulocyte count) were recorded. For the analysis of the growth data, heights and weights were plotted on the British standard growth charts⁹ for white children, since there are no such charts for black children living in Britain. Heights were expressed as standard scores defined as the number of standard deviations (SD) by which the measurements differed from the mean for healthy white populations of the same age and sex.¹⁰ Bilirubin levels were not recorded systematically.

*Comprising countries in the British Caribbean, parts of Africa, the Indian subcontinent, Sri Lanka, Singapore, Malaysia, Cyprus, Gibraltar, Malta, Gozo, etc.

Treatment consisted of folic acid 5 mg daily, provision of analgesia (generally aspirin) for painful crises, and antibiotics for infections as clinically indicated. Prophylactic penicillin was not given, except to one child who had two episodes of pneumococcal septicaemia and to another after splenectomy for recurrent sequestration crises. Eighteen children received sodium bicarbonate orally for a year during a clinical trial to test its efficacy in preventing painful crises,¹¹ and 5 received a course of anacrod in a double-blind study to determine whether this anticoagulant shortened established painful crises.¹² Prophylactic dental care was arranged, generally in the hospital's dental department.

For surgical procedures intra- and postoperative intravenous hydration and 40% oxygen-anaesthetic mixtures were used. Preoperative blood transfusion to Hb level 10–11 g/dl was carried out if blood loss was expected or if the preoperative Hb level was <7 g/dl. Before the splenectomy and one cholecystectomy serial blood transfusions at weekly intervals to Hb level 13–14 g/dl for 3 weeks were performed to reduce the circulating HbS to <20%. Tourniquets were not used.

Haematological tests were performed using standard methods¹³ and HbF levels by alkali denaturation.¹⁴ Whenever possible clinical examination, Hb level, haematocrit, reticulocyte count, HbF and A₂ levels, and Hb electrophoresis were performed on the patient, the parents, and all siblings. Children with only HbF, A₂, and S, were classified as SS if both parents were heterozygotes (AS), or as SS or S thal if both parents were not available for testing. Only when one parent was shown to have β -thalassaemia and the other to be AS was the child classified as having S thal.

Results

Ninety-six children aged between 3 months and 19 years were studied for an average of 5.1 years a patient (Table 1). Thirty-seven children are still attending the clinic, 5 have died, 7 were lost to follow-up but have been traced and confirmed to be

Table 1 Patients studied, and deaths

Haemoglobinopathy	No of patient years	Average no of years per patient	Deaths	
			No	%
SS (n = 35)	203	5.8	4	1.9
SS or S thal (n = 26)	130	5.0	0	0
S thal (n = 12)*	42	4.2	0	0
SC (n = 23)†	117	5.1	1	0.9

*2 †3 patients discharged after diagnosis made.

Table 2 Presenting feature or source

	Age range (years)	SS	SS or thal	S thal	SC
Already attending Birmingham Children's Hospital*	1–15.6	21	14	5	8
Transferred from another hospital*	0.9–14.2	4	3		1
Painful crisis	2.7–13	4	1		3
Anaemic crisis	1.7–4	1	2		
Infection*	0.3–5.2	2			3
'Haemic' murmur	9.2		1		
Pallor	0.3		1		
Epistaxis	10.3				1
Splenomegaly	1.2		1		
Family study	3.9–8.7		3	1	2
School sickle survey	3.4–16.2	1		4	5
Blood test before surgery	3–8.8	2		2	

*3 children (2 SS, 1 SS or S thal) had first presented before start of survey with pneumococcal meningitis at the ages of 1, 1.6, and 2.8 years.

alive and well, while the medical care of the remainder has been transferred to the GP (n = 9), or to paediatric or adult clinics elsewhere in the UK (n = 29), or abroad (n = 9).

The presenting features are shown in Table 2. Most children were diagnosed because of painful bone or abdominal crises, but 3 presented with life-threatening anaemic crises, while 20 who were asymptomatic or had only mild symptoms (14 had the milder disorders S thal or SC) were diagnosed during family studies, in the Birmingham school haemoglobinopathy survey,⁸ or on routine testing before surgery. Three children who had presented before the start of the study did so with pneumococcal meningitis when aged 1, 1.6, and 2.8 years.

The mean Hb levels for each group of patients at entry to and exit from the study are shown in Table 3. From these findings, from studies on globin chain synthesis (K D Griffiths, J R Mann, and D N Raine, 1981, unpublished data), and from clinical similarities, it is considered that most of the children in the SS or S thal group were actually SS. However the possibility that some had S thal with a completely inactive β -thalassaemia gene (β^0) cannot be excluded. Two of the S thal children had S β^0 thalassaemia, low Hb levels (8.0–9.1 g/dl), and a severe clinical course, but the remainder had some production of normal adult HbA (S β^+ thalassaemia), higher Hb levels (10.6–13.1 g/dl), and few symptoms. In all groups of patients the Hb levels tended to rise with increasing age, possibly owing to 'auto-splenectomy'. As expected, the Hb levels were in general higher in S thal and SC children than in SS.

HbF levels (Table 3) were raised in most SS and S thal children, but varied widely and exceeded 10% in only 2 SS children (18.7 and 13.3%) whose illnesses were of comparable severity to those of

Table 3 Haemoglobin and HbF levels

Haemoglobinopathy	Haemoglobin (g/dl $\pm$ SD)		HbF (% $\pm$ SD)*
	At start of study	At end of study	
SS	8.2 $\pm$ 1.0	8.3 $\pm$ 0.9	4.7 $\pm$ 4.5
SS or S thal	8.0 $\pm$ 1.0	8.2 $\pm$ 1.0	5.1 $\pm$ 3.5
S thal	11.1 $\pm$ 1.3	11.5 $\pm$ 1.5	5.3 $\pm$ 4.5
SC	11.5 $\pm$ 1.3	11.8 $\pm$ 1.3	1.8 $\pm$ 2.0

*Children aged <1 year and levels measured before 1970 excluded.

other SS children. Two S thal children also had levels above 10% (11.2 and 14.5%). In the SC children HbF levels were normal or only slightly raised.

The principal complications are shown in Table 4. Painful bone and abdominal vaso-occlusive crises were the most numerous, but were not recorded in detail since the majority did not necessitate treatment in hospital, and a parallel study¹¹ had established much individual variation with an average frequency of 2 or 3 episodes per patient a year. Anaemic crises, which were often life-threatening and associated with infections, and the formation of red cell auto-antibodies,¹⁵ occurred on multiple occasions (maximum 8 times in one child). Pulmonary illnesses, generally diagnosed as pneumonia, although respiratory pathogens were seldom isolated and pulmonary infarction could not be excluded, were the next most common, and were also often recurrent in affected children. Often pulmonary illnesses and anaemic or painful crises occurred simultaneously. The serious infections, which occurred only in the SS and presumed SS children, were osteomyelitis due to coagulase-positive staphylococci (in 2) and klebsiella (in 1), pneumo-

coccal septicaemia (in 1, a 3-year-old boy who had originally presented at 1.6 years with pneumococcal meningitis), severe gastroenteritis (in 4), glandular fever with respiratory obstruction necessitating tracheostomy (in 1), and giardiasis (in 1).

Avascular necrosis of bone resembling Perthe's disease occurred in an SS boy, and necrosis and fusion of the 10th, 11th, and 12th thoracic vertebrae in an SS girl. Osgood-Schlatter's osteochondritis-like lesions of the tibial tuberosity were seen in 1 S β ⁰ thal and 3 SC children.

Serious central nervous system complications were confined to the SS and presumed SS children. Priapism is a recognised symptom of sickle cell anaemia.

The details of the children who died are shown in Table 5. The SC girl's final illness was preceded by hypersplenism and has been reported previously.¹⁶ The overall mortality rate for Birmingham children with sickle haemoglobinopathies (Table 1) was 1% per annum, but was higher (1.3%) in the SS and presumed SS children than in S thal (0) or SC (0.9%).

Table 4 Numbers of children with complications* and additional problems

	SS	SS or S thal	S thal	SC
Anaemic crises	17 (41)	12 (27)		1 (2)
Pulmonary illnesses	15 (26)	8 (10)	1	1
Other serious infections	5	5		
Nocturnal enuresis	5	2	1	
Severe/recurrent epistaxes	3	1		4
Avascular necrosis of bone	2		1	3
Hemiplegia $\pm$ epilepsy, low IQ	2	1		
Subarachnoid haemorrhage	2			
Atopy		2	1	2
Ventricular septal defect	1			1
Priapism		1		
Gastric ulcer		1		
Growth hormone deficiency		1		
Malabsorption, hepatitis, mental retardation	1			
Obesity			1	1

*Painful crises excluded.

Number of episodes shown in brackets.

Table 5 Deaths

Sex	Haemoglobinopathy	Age (years)	Cause of death
Male	SS	3.2	Found dead in bed at home. Necropsy showed bronchitis. Previously had had 8 anaemic crises
Male	SS	5.7	Found dead in bed at home. No cause detected
Male*	SS	8.6	Gastroenteritis. Previous cerebral crisis resulting in hemiplegia and epilepsy
Female*	SS	14.3	Found dead in bed at home. Necropsy showed subarachnoid haemorrhage (ruptured Berry aneurysm)
Female	SC	12.4	Splenic sequestration

*Brother and sister.

Table 6 Operations performed under general anaesthesia

	SS	SS or thal	S thal	SC
Dental	12	15	5	4
Ear, nose, and throat	5	3		
Cranial burr holes	2 (n = 1)			
Tracheostomy/closure/laryngoscopy	4 (n = 1)	1		
Cholecystectomy	2			
Splenectomy		1		
Hip manipulation	1			
Appendicectomy	1			
For osteomyelitis		7 (n = 2)		
Umbilical hernia repair			2	

Sixty-five operations were performed under general anaesthesia (Table 6) without any serious complications.

The growth of the children with SS and presumed SS is impaired compared with that of the black children with S thal and SC, and with standards for healthy white children (Figs 1 and 2). The standard

scores for height for children aged <10 years at the start and those aged >10 years at the end of the study are shown in Fig. 3; although there was considerable individual variation, all the children with heights >2 SD below the mean were SS or presumed SS patients, in whom there was also a trend towards further deviation below the mean

Fig. 1 Heights and weights of boys at start and end of study. Continuous lines represent 10th, 50th, and 90th centiles for standard white population.

during the second decade. The deviation was principally due to delayed pubertal development which is also illustrated by the later menarche in SS and presumed SS girls (Table 7). Lean body habitus was present in most of the SS and presumed SS children, whereas the S thal (except one S β^0 thal girl) and SC children were generally heavier (Figs 1

and 2). Obesity occurred in one S thal girl and one SC boy. Growth hormone deficiency as well as delayed puberty was detected in one SS or S thal boy, who showed a good spurt after treatment with growth hormone which was started almost concurrently with the onset of pubertal development at 16.8 years.

Fig. 2 Heights and weights of girls at start and end of study. Continuous lines represent 10th, 50th, and 90th centiles for standard white population.

Fig. 3 Standard scores for height. Dots on the left of each column show heights of children aged <10 years at start of study, and on the right of each column show heights of children aged >10 years at end of study. Mean and SD for each group of children is also shown.

Table 7 Age (years) at menarche

	Ages of girls over 10 years who have not yet reached menarche	Age at menarche	Average age at menarche
SS*	13.4, 13.8, 16.3, 17.1	13.5, 14, 14.3, 14.8, 15.2, 15.7, 18.1	15
SS or S thal	12.1	12.8, 13.7, 14, 14, 14.3	13.7
S thal*	11, 15.8†	11, 11	11
SC	10.9, 12.4	10.2, 12, 12, 12, 12	11.6

*Information not recorded for one child in group, †Sβ⁰ thalassaemia.

Discussion

In Africa,^{2 17 18} where the climate and infections create conditions in which childhood mortality rates are high, few SS individuals have survived into adult life, whereas SC disease is milder, presents later, and is compatible with a longer life-span. Malaria is a major cause of death in SS children (although AS individuals have some resistance to the parasite) and antimalarials with folic acid, antibiotics, and other measures to improve child health have been effective in reducing massive splenomegaly,² mortality, and morbidity.^{2 19 20} Nevertheless, the majority of African SS children still die.

The outlook is better in non-malarial countries such as the West Indies and North America. However, although the majority of Birmingham's black population is of West Indian origin, with a similar incidence of sickle haemoglobinopathies,^{8 21} this study suggests that the environmental differences between temperate industrial urban Birmingham and

tropical rural Jamaica have influenced the clinical manifestations.

In a retrospective review of 100 Jamaican SS children²² 74 had presented with symptoms before age 3 years and 2 had died, but precise mortality rates were not calculated. Their Hb levels were lower (6–8 g/dl) than Birmingham children's, and serum bilirubin level was increased (>1 mg/100 ml; 17.1 μmol/l) in 67% of determinations. Painful crises were not quantified but pulmonary illnesses and anaemic crises were recorded in fewer Jamaican (36 and 17%) than Birmingham SS children (43 and 49% respectively) while leg ulceration, present in 13 Jamaican children, the youngest aged 6 years, has not been seen in Birmingham. The incidence of other complications was similar. For example, the Jamaican series included 4 children with meningitis (1 pneumococcal), 2 with subarachnoid haemorrhage aged 9 and 11 years, 2 with hemiparesis, 1 with priapism, and 9 with epistaxis. Haematuria occurred in 1 Jamaican child and has been reported in other series, but was not observed in Birmingham children.

Subsequent reports have indicated that among Jamaican infants diagnosed since 1973 by cord blood Hb electrophoresis and studied prospectively, 87% of SS and 95% of SC, compared with 99% of normal control children, survived the first 2 years of life,²³ and about 40% of SS Jamaicans have survived into middle age.³ Most of the early deaths resulted from acute splenic sequestration and pneumococcal infections in young SS children,²³ while SC²³ and older SS children⁴ have been at smaller risk. However, the Birmingham deaths were in children aged >3 years, although others not included in this series might have died undiagnosed with apparent sudden infant death syndrome; in Los Angeles⁴ during a 10-year period 7 babies with apparent sudden infant death syndrome were found on Hb electrophoresis and blood culture at necropsy to have had SS and pneumococcal septicaemia. Further studies in Birmingham are attempting to assess the extent of this problem, and in Jamaica the value of prophylactic penicillin and pneumococcal vaccine in infants is now being assessed (G R Serjeant, 1980, unpublished data).

In the urban environment of New York,⁵ where between 1956 and 1973 in a study of 551 children annual mortality rates were 2% for SS, 0% for SC, and 1.5% for S thal, 67% of deaths occurred before age 4 years, most commonly from infections, cerebral thrombosis, or haemorrhage, or from splenic sequestration. New York children had fewer anaemic crises and a different pattern of infections from those in Birmingham: meningitis occurred in 6.9% of New York children (compared with 0% of Birmingham

children, or 3% including illnesses before the study), severe diarrhoea in 16% (compared with 4%), and urinary infections in 9% (0%). No case of salmonella osteomyelitis was noted in Birmingham whereas over half of cases in New York were caused by *Salmonella* sp. Cerebrovascular accidents and mental retardation were of similar incidence in the two cities but leg ulcers, haematuria, lead encephalopathy, and certain central nervous system manifestations—such as sudden blindness—seen in New York children have not been observed in Birmingham.

As in Jamaica²⁴ and elsewhere, Birmingham SC children have had less severe symptoms than those with SS, whereas those with S β^0 thal were affected to a similar extent as those with SS.²⁵ Children with S β^+ thal were often asymptomatic.

There have been a number of reports about the growth of children with sickle cell anaemia^{22–26–31} but interpretation of the results has been complicated by the small numbers in some studies. However, in general there is agreement that SS children are generally thin, while their heights show pronounced individual variation. In most series some children have been of subnormal height, while others have been tall. Sexual maturation has commonly been delayed,²⁹ as has skeletal development,³² but adults have generally been of average or above average height.³ In Birmingham, too, wide individual variation in the heights of SS children is evident, but the heights of the S thal and SC are similar to those of the English white standards. Eleven per cent of SS and presumed SS children aged <10 years and 16% aged >10 years had heights >2 SD below the mean for white standards, so it seems clear that their more severe illnesses have led in some to delayed growth and late sexual maturation.

Davis³³ studied Hb levels in 75 children with sickle cell anaemia aged 4 days to 16 years and showed a progressive fall from mean levels of 9.75 at 1 month to 8.07 at 1 year, 8.18 at 5 years, 7.7 at 10 years, and 7.29 g/dl at 12–16 years. However some of the age groups contained small numbers of children and the Birmingham data suggest that after the first year of life 'steady state' Hb levels remain constant or perhaps rise slightly. As in Los Angeles,⁴ few Birmingham children had high HbF levels, and increased HbF did not convey clinical advantage; this was consistent with the reported similar survival of high and low HbF cells.³⁴

Good anaesthetic techniques and the other measures described have permitted many surgical procedures to be carried out safely on Birmingham children, confirming previous reports^{35–36} of the efficacy of simple management of patients with sickle haemoglobinopathies.

This study has demonstrated the natural history of the sickle haemoglobinopathies in children living in the UK and has further illustrated that the manifestations of these disorders vary from country to country, depending on many factors, which may include the weather, endemic infections, and the standards of nutrition and medical care.

I thank Professor J Stuart, the late Dr D N Raine, and Dr P H W Rayner for help, Dr K D Griffiths and Dr F G H Hill for Hb analyses and haematological tests, and Professor C M Anderson, Dr W H P Cant, Professor G W Chance, Dr H McC Giles, Dr S H Green, Professor D V Hubble, Dr J Insley, Dr R H R White, and Dr B S B Wood for allowing their patients to be included in the study.

Financial support was provided by the United Birmingham Hospitals (now Central Birmingham Health District) Research Endowment Fund.

References

- Lambotte-Legrand J, Lambotte-Legrand C. Le pronostic de l'anémie drépanocytaire au Congo Belge. *Ann Soc Belge Med Trop* 1955; **35**: 53–7.
- Konotey-Ahulu F I D. Effect of environment on sickle cell disease in West Africa: epidemiological and clinical considerations. In: Abramson H, Bertles J F, Wethers D L, eds. *Sickle cell disease diagnosis, management, education, and research*. St Louis: Mosby, 1973: 20–38.
- Serjeant G R, Richards R, Barbor P R H, Milner P F. Relatively benign sickle-cell anaemia in 60 patients aged over 30 in the West Indies. *Br Med J* 1968; **iii**: 86–91.
- Powars D R. Natural history of sickle cell disease—the first ten years. *Semin Hematol* 1975; **12**: 267–85.
- Robinson M G. Clinical aspects of sickle cell disease. In: Levere R D, ed. *Sickle cell anemia and other hemoglobinopathies*. New York: Academic Press, 1975: 87–112.
- Perrine R P, Brown M J, Clegg J B, Weatherall D J, May A. Benign sickle-cell anaemia. *Lancet* 1972; **ii**: 1163–7.
- Neale A B, Haine G, eds. *Birmingham statistics 1977–8*. Vol. 20. Birmingham: City of Birmingham Central Statistical Office, 1979: 32–3.
- Stuart J, Schwartz F C M, Little A J, Raine D N. Screening for abnormal haemoglobins: a pilot study. *Br Med J* 1973; **iv**: 284–7.
- Tanner J M, Whitehouse R H, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. Part I. *Arch Dis Child* 1966; **41**: 454–71.
- Tanner J M, Whitehouse R H, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. Part II. *Arch Dis Child* 1966; **41**: 613–35.
- Mann J R, Stuart J. Sodium bicarbonate prophylaxis of sickle cell crisis. *Pediatrics* 1974; **53**: 414–6.
- Mann J R, Deeble T J, Breeze G R, Stuart J. Ancrod in sickle-cell crisis. *Lancet* 1972; **i**: 934–7.
- Dacie J V, Lewis S N, eds. *Practical haematology*, fifth edition. Edinburgh: Churchill Livingstone, 1975.
- Betke K, Marti H R, Schlicht I. Estimation of small percentages of foetal haemoglobin. *Nature* 1959; **184**: 1877–8.

- ¹⁵ Mann J R, Cotter K P, Walker R A, Bird G W G, Stuart J. Anaemic crisis in sickle cell disease. *J Clin Pathol* 1975; **28**: 341-4.
- ¹⁶ Topley J M, Obeid D, Mann J R. Acute splenic sequestration crisis preceded by hypersplenism in haemoglobin SC disease. *Br Med J* 1977; **i**: 617-8.
- ¹⁷ Vandepitte J M. Present-day aspects of sickle cell problem. *Doc Med Geogr Trop (Amst)* 1955; **7**: 154-63.
- ¹⁸ Lehmann H, Raper A B. Maintenance of high sickling rate in an African community. *Br Med J* 1956; **ii**: 333-6.
- ¹⁹ Konotey-Ahulu F I D. Letter: Treatment and prevention of sickle-cell crisis. *Lancet* 1971; **ii**: 1255.
- ²⁰ Adeyokunnu A A, Topley E. Sickle cell anaemia: diagnosis and care in a Nigerian health centre. *Trans R Soc Trop Med Hyg* 1977; **71**: 416-20.
- ²¹ Went L N. Incidence of abnormal haemoglobins in Jamaica. *Nature* 1957; **180**: 1131-2.
- ²² Gray R H. Clinical features of homozygous SS disease in Jamaican children. *West Indian Med J* 1971; **20**: 60-8.
- ²³ Rogers D W, Clarke J M, Cupidore L, Ramlal A M, Sparke B R, Serjeant G R. Early deaths in Jamaican children with sickle cell disease. *Br Med J* 1978; **i**: 1515-6.
- ²⁴ Serjeant G R, Ashcroft M T, Serjeant B E. The clinical features of haemoglobin SC disease in Jamaica. *Br J Haematol* 1973; **24**: 491-501.
- ²⁵ Serjeant G R, Sommereux A M, Stevenson M, Mason K, Serjeant B E. Comparison of sickle cell—beta⁰ thalassaemia with homozygous sickle cell disease. *Br J Haematol* 1979; **41**: 83-93.
- ²⁶ Winsor T, Burch G E. The habitus of patients with sickle cell anemia. *Hum Biol* 1944; **16**: 99-114.
- ²⁷ Scott R B, Ferguson A D, Jenkins M E, Clarke H M. Studies in sickle cell anemia. VIII. Further observations on the clinical manifestations of sickle cell anemia in children. *Am J Dis Child* 1965; **90**: 682-91.
- ²⁸ Whitten C F. Growth status of children with sickle cell anemia. *Am J Dis Child* 1961; **102**: 355-64.
- ²⁹ Jimenez C T, Scott R B, Henry W L, Sampson C C, Ferguson A D. Studies in sickle cell anemia. XXVI. The effects of homozygous sickle cell disease on the onset of menarche, pregnancy, fertility, pubescent changes, and body growth in Negro subjects. *Am J Dis Child* 1966; **11**: 497-504.
- ³⁰ McCormack M K, Dicker L, Katz S H, *et al.* Growth patterns of children with sickle cell disease. *Hum Biol* 1976; **48**: 429-37.
- ³¹ Lowry M F, Desai P, Ashcroft M T, Serjeant B E, Serjeant G R. Heights and weights of Jamaican children with homozygous sickle cell disease. *Hum Biol* 1977; **49**: 429-36.
- ³² Lowry M F, Desai P, Ashcroft M T, McCall I W, Serjeant G R. Skeletal development of Jamaican children with homozygous sickle cell disease. *Hum Biol* 1978; **50**: 115-9.
- ³³ Davis L R. Changing blood picture in sickle-cell anaemia from shortly after birth to adolescence. *J Clin Pathol* 1976; **29**: 898-901.
- ³⁴ Dover G J, Boyer S H, Charache S, Heintzelman K. Individual variation in the production and survival of F cells in sickle-cell disease. *N Engl J Med* 1978; **299**: 1428-35.
- ³⁵ Oduro K A, Searle J F. Anaesthesia in sickle-cell states: a plea for simplicity. *Br Med J* 1972; **iv**: 596-8.
- ³⁶ Homi J, Reynolds J, Skinner A, Hanna W, Serjeant G R. General anaesthesia in sickle-cell disease. *Br Med J* 1979; **i**: 1599-601.

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Received 25 June 1980