# Relatively Benign Sickle-cell Anaemia in 60 Patients Aged Over 30 in the West Indies

G. R. SERJEANT,* M.B., M.R.C.P. ; R. RICHARDS,† M.B., M.R.C.P. ; P. R. H. BARBOR,‡ M.B., B.CHIR.
P. F. MILNER,§ M.B., D.C.P., M.C.PATH.

*Brit. med. J.*, 1968, 3, 86–91

**Summary: A study in Jamaica of 60 patients with sickle-cell anaemia over the age of 30 years showed that most of them were in full-time employment. Pains in the bones or joints, leg ulceration, and jaundice were the most frequent types of presentation, but only two patients had a haemoglobin level consistently below 6 g./100 ml. Most of the patients were well developed and of average height, and, though the development of secondary sexual characteristics was delayed, there was an average of 2.6 pregnancies per patient. These findings suggest that the course is more benign than has been realized.**

## Introduction

The frequency of sickle-cell anaemia in adults has always been a feature of the disease in the West Indies, and in 49 of the 114 cases so far described from Jamaica (Went and MacIver, 1958 ; MacIver and Went, 1958) the patients were over 15 years of age. Jonxis (1959) found four out of seven patients in Curaçao were over 18 years, one being 53. Since 1958 many adult cases of sickle-cell anaemia have been seen at the University Hospital, Kingston, Jamaica. Among adult admissions since 1958 there have been 18 deaths associated with sickle-cell anaemia, of whom six were over 30 years old, one being about 68 and the other about 62. Detailed laboratory and family studies are, however, lacking in some of these cases, and as the milder condition, sickle-cell thalassaemia, may closely simulate homozygous Hb S disease they cannot be used as evidence of prolonged survival in the homozygous form of the disease. To evaluate the true frequency and importance of sickle-cell anaemia in adults a special clinic was started at the University Hospital, Kingston, Jamaica, to which cases have been referred, and it is now clear that this disease is compatible with survival into and beyond middle age. An analysis of patients over the age of 30 years is presented in this report.

## Clinical Material

During the past three years 240 patients over the age of 15 who have sickle-cell anaemia have attended a special clinic. Seventy-three of them are now over 30 years old. Clinical and laboratory investigations were performed to confirm the diagnosis, and wherever possible parents, siblings, and offspring were investigated. On the evidence presented here we believe that 60 of these 73 patients are homozygous for Hb S, and this report presents the clinical and haematological findings in this large group of cases (see Table I).

* Wellcome Research Fellow.
† Lecturer in Medicine.
‡ Medical Registrar.
§ Senior Lecturer in Haematology.
University of the West Indies, Kingston, Jamaica, W.I.

## Methods and Laboratory Diagnosis

Haemoglobin electrophoresis on starch gel was used to demonstrate Hb S, Hb F, and Hb $A_2$ and to detect small proportions of Hb A, which would indicate a non-homozygous form of disease. Hb SC disease was also excluded. In each case the proportion of Hb $A_2$ was measured by column chromatography (Huisman and Dozy, 1965). Hb F was measured by the alkali denaturation method of Singer *et al.* (1951) modified by Went and MacIver (1961), for which the upper limit of normal is 1%. Agar gel electrophoresis (Marder and Conley, 1959) was used to detect other haemoglobins such as Hb D or Hb G and to rule out examples of Hb SD and SG disease. Solubility tests (Itano, 1953) confirmed these findings. Sickling preparations and Hb electrophoresis were performed on the blood of parents, siblings, and progeny where possible. Extended blood grouping was carried out in some but not all the parents of patients. Stained smears of capillary blood were examined on several occasions in each patient. Serum iron and iron-binding capacity were measured on many occasions in each patient by the method of Beale *et al.* (1961, 1962). Serum bilirubin was measured by the method of Lathe and Ruthwen (1958).

The diagnosis of homozygous sickle-cell anaemia was based on the red cell morphology in the smear, and the Hb electrophoresis in starch gel supported by the Hb $A_2$ value, and was confirmed in some instances by finding the sickle-cell trait in both parents and in all the offspring. The mean level of Hb $A_2$ in the 60 cases was 2.325% (S.D. = 0.22) and we considered the upper limit of normal to be 3.5%. In the sickle-cell thalassaemia cases excluded from this series the mean level of Hb $A_2$ was 4.245% (S.D. = 0.16). The standard error of the difference of these means is 0.033, which is highly significant.

## Clinical Features

There were 28 male and 32 female patients in the series. There was no significant difference in the distribution of the sexes in the different age groups (Table II). Most of the patients had full-time employment. Nine of the men were cultivators, five were labourers, and 12 were constantly employed in sedentary occupations ; two were unemployed, Among the women 21 were either housewives or in domestic employment. The remaining 11 held a variety of sedentary occupations such as dressmaking, hairdressing, and secretarial work. Most patients admitted missing occasional days from work on account of complications such as bone pains or leg ulceration, but several patients denied that the condition made them miss any days from work.

### Presentation of the Disease

The type of presentation is shown in Table III. The average age at presentation was 20.9 years for the men and 16.7 years for the women. There is little difference in the type of presentation with age, and it is doubtful whether the age at presentation bears any relation to the severity of the disease.

TABLE I.—*Details of Cases*

| Case No. | Sex and Age | Hb F (%) | Hb $A_2$ (%) | Haemoglobin (g./100 ml.) | | Average Retics (%) | Bilirubin (mg./100 ml.) | | Leg Ulcer | Cardio-megaly | Hepato-megaly (cm.) | Splenomegaly (cm.) | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Highest | Lowest | | Direct | Total | | | | | |
| 1 | M 30 | 7·8–12·2 | 2·0 | 12·0 | 8·6 | 9 | 0·96 | 3·7 | + | + | 3 | – | D.U. Brother of Case 29 |
| 2 | M 30 | 2·7 | 2·5 | 9·0 | 8·5 | 8 | 0·6 | 2·31 | – | + | 2 | | Splenectomy |
| 3 | F 30 | 4·65 | 3·5 | 9·5 | 9·2 | 4 | 0·4 | 1·1 | – | – | – | – | D.U.* |
| 4 | M 30 | 3·0–4·5 | 2·8 | 13·3 | 12·0 | 8 | 0·4 | 0·8 | + | – | – | – | * |
| 5 | M 30 | 1·56–1·8 | 3·4 | 8·3 | 5·5 | 7 | 1·2 | 4·5 | + | – | 2 | – | |
| 6 | F 30 | 3·5 | 2·2 | 5·8 | — | 7 | 1·0 | 2·5 | + | – | 2 | – | |
| 7 | M 31 | 9·8–11·7 | 2·2 | 10·0 | 8·7 | 6 | 0·7 | 1·2 | – | – | – | – | |
| 8 | F 31 | 1·5 | 2·7 | 8·5 | — | 5 | 1·0 | 7·3 | – | – | – | – | Cholecystectomy |
| 9 | M 31 | 5·8–6·1 | 2·3 | 9·6 | 8·0 | 12 | 0·7 | 7·0 | + | + | 2 | – | |
| 10 | M 31 | 2·5–3·4 | 2·3 | 9·7 | 8·0 | 11 | 0·7 | 2·7 | + | – | 3 | – | |
| 11 | M 31 | 3·3–4·2 | 2·4 | 8·3 | 6·4 | 15 | 1·1 | 6·3 | + | + | 3 | – | D.U. |
| 12 | F 32 | 3·3 | 1·1 | 7·6 | 7·5 | 9 | 1·4 | 3·2 | – | – | – | – | |
| 13 | M 32 | 0·5–1·0 | 2·5 | 8·1 | 7·8 | 10 | 0·8 | 1·7 | – | + | 3 | – | |
| 14 | M 32 | 0·3 | — | 7·7 | — | 3 | 1·0 | 3·3 | – | – | – | – | Perforated D.U. |
| 15 | F 32 | 2·8–3·5 | 2·0 | 6·6 | 5·7 | 22 | 1·0 | 4·7 | + | – | – | – | |
| 16 | F 32 | 12·6 | 1·6 | 10·0 | 9·2 | 10 | 0·1 | 3·8 | + | + | 2 | – | Sister of Case 28 |
| 17 | F 32 | 2·4 | 2·4 | 6·0 | 2·8 | 12 | 0·9 | 2·0 | + | + | 4 | – | |
| 18 | F 33 | 1·2–1·9 | 3·0 | 8·5 | 7·4 | 12 | 0·65 | 1·6 | + | – | – | – | * |
| 19 | F 33 | 3·2–4·4 | 1·9 | 7·5 | 5·9 | 6 | 0·5 | 1·1 | + | – | 4 | 5 | |
| 20 | M 33 | 7·2–8·1 | 1·5 | 8·0 | 7·5 | 9 | 1·2 | 3·5 | + | + | 3 | – | D.U. |
| 21 | F 33 | 14·3 | 2·7 | 6·6 | 6·2 | 8 | 0·5 | 1·5 | + | – | 1 | – | |
| 22 | M 33 | 8·25 | 1·6 | 9·0 | 5·7 | 6 | 0·7 | 1·1 | + | + | 1 | 2 | |
| 23 | M 34 | 1·1–2·9 | 2·9 | 9·5 | 8·6 | 5 | 0·8 | 1·7 | + | – | – | – | |
| 24 | F 34 | 6·4 | 2·6 | 8·6 | 7·7 | 7 | 0·4 | 1·1 | + | – | – | – | |
| 25 | F 34 | 2·7–5·1 | 2·9 | 8·6 | 7·5 | 12 | 1·3 | 2·7 | + | + | 4 | – | * |
| 26 | F 34 | 9·3–9·8 | 2·5 | 10·0 | 8·7 | 13 | 0·3 | 1·9 | – | – | – | – | Half-brother SS |
| 27 | F 34 | 11·0–12·7 | 2·3 | 9·1 | 8·5 | 8 | 0·4 | 1·8 | + | + | – | – | * |
| 28 | F 34 | 10·9–14·8 | 1·6 | 7·1 | 7·0 | 9 | 1·2 | 3·8 | + | – | 4 | 2 | Sister of Case 16 |
| 29 | M 35 | 4·6–5·4 | 2·6 | 11·0 | 9·5 | 14 | 0·7 | 4·0 | + | – | 3 | – | D.U. Brother of Case 1 |
| 30 | M 35 | 2·4–2·6 | 2·6 | 7·7 | 6·4 | 7 | 1·3 | 3·1 | + | + | – | – | |
| 31 | F 35 | 5·6–7·5 | 2·2 | 9·2 | 7·2 | 7 | 0·3 | 1·4 | + | – | 2 | – | * |
| 32 | M 36 | 5·6–7·6 | 2·5 | 11·0 | 8·6 | 11 | 1·4 | 4·2 | + | + | – | – | D.U. |
| 33 | M 36 | 3·1 | 2·5 | 10·3 | 9·0 | 11 | 1·4 | 6·2 | + | – | 2 | – | * |
| 34 | M 36 | 1·94 | 2·8 | 7·5 | — | — | 0·6 | 1·8 | + | – | 2 | – | * |
| 35 | F 36 | 9·4 | 1·1 | 9·3 | 9·3 | 7 | 0·7 | 1·4 | + | + | 3 | – | |
| 36 | F 36 | 4·9 | 2·5 | 6·5 | 6·3 | 14 | 1·9 | 2·3 | + | + | 5 | – | |
| 37 | F 36 | 13·7 | 1·9 | 10·8 | 9·5 | 4 | 0·2 | 1·6 | + | – | – | 2 | |
| 38 | F 37 | 4·4–5·6 | 2·2 | 9·4 | 9·0 | 9 | 1·4 | 2·4 | + | – | – | – | |
| 39 | M 37 | 5·6–6·6 | 2·7 | 8·3 | 5·9 | 11 | 1·5 | 2·7 | + | + | 3 | – | D.U. |
| 40 | M 37 | 4·2–8·0 | 2·9 | 11·0 | 8·7 | 8 | 0·5 | 1·1 | + | + | 1 | 1 | * |
| 41 | F 38 | 12·6–13·6 | 2·3 | 6·5 | 6·0 | 5 | 0·6 | 2·4 | + | – | 3 | – | Rheumatic heart disease |
| 42 | M 38 | 0·5–2·2 | 1·4 | 11·1 | 10·3 | 12 | 0·7 | 1·4 | + | – | 2 | 2 | |
| 43 | F 38 | 2·2–2·8 | 2·6 | 6·0 | 6·0 | 10 | 0·7 | 1·9 | + | + | 2 | – | Sister of Case 50 |
| 44 | M 38 | 2·5 | 2·6 | 9·4 | 7·9 | 10 | 1·0 | 2·5 | – | + | 3 | – | |
| 45 | F 39 | 11·0–12·0 | 2·6 | 9·0 | 6·8 | 23 | 0·1 | 1·2 | + | – | 2 | – | * |
| 46 | F 39 | 4·3 | 2·6 | 8·0 | 7·6 | 11 | 0·2 | 1·1 | + | + | 3 | – | Epilepsy |
| 47 | F 41 | 11·0–14·7 | 1·8 | 7·3 | 5·5 | 10 | 0·3 | 1·1 | + | + | – | – | * |
| 48 | F 41 | 5·5–6·1 | 2·7 | 9·5 | 8·8 | 10 | 0·6 | 1·4 | + | + | 4 | – | |
| 49 | M 42 | 1·2 | 2·5 | 8·1 | 7·7 | 8 | 1·0 | 2·5 | + | – | 2 | – | |
| 50 | M 43 | 0·5–1·7 | 3·1 | 8·8 | 7·2 | 9 | 0·6 | 1·4 | + | – | – | – | Brother of Case 43 |
| 51 | F 43 | 10·0–18·2 | 1·6 | 6·7 | 6·3 | 5 | 0·6 | 1·1 | – | + | – | – | Cholecystectomy |
| 52 | F 45 | 3·3–4·3 | 2·4 | 8·8 | 6·9 | 7 | 0·5 | 1·0 | + | + | 2 | – | |
| 53 | F 47 | 9·6–9·9 | 1·7 | 8·0 | 6·9 | 8 | 1·0 | 3·2 | – | + | 3 | – | Cholecystectomy |
| 54 | M 51 | 0·54 | 3·2 | 7·4 | — | 11 | 1·4 | 3·1 | – | + | 3 | – | Laparotomy–nil abnormal found |
| 55 | M 51 | 9·8–12·6 | 2·2 | 5·7 | 5·0 | 7 | 1·2 | 3·9 | – | + | 3 | – | |
| 56 | F 51 | 3·7–10·7 | 2·2 | 7·9 | 7·0 | 6 | 1·2 | 2·8 | – | + | 6 | – | |
| 57 | F 52 | 7·3–9·7 | 1·7 | 7·5 | 7·0 | 8 | 0·4 | 2·1 | + | + | 1 | – | Epilepsy |
| 58 | M 52 | 1·1 | 2·4 | 8·2 | 6·1 | 10 | 0·9 | 3·4 | – | – | 2 | – | |
| 59 | F 53 | 6·1–8·4 | 1·7 | 7·2 | 6·6 | 8 | 0·6 | 2·1 | + | – | 3 | – | |
| 60 | M 56 | 4·2–7·8 | 2·2 | 6·9 | 6·3 | 16 | 0·9 | 3·9 | + | + | – | – | D.U. |

* Both parents of these cases have the sickle-cell trait, and hence these patients are proved cases. D.U. : duodenal ulcer.

Five patients were first discovered during routine examinations when pregnant. Their ages were 22, 23, 24, 26, and 38 years. Only 16 patients had been in hospital during childhood. On inquiring into the family history of patients with sickle-cell anaemia it is often possible to find relatives with occasional attacks of bone and joint pains or yellow eyes who have never had symptoms severe enough to take them to the doctor or the local hospital. Nine new cases were detected in this way, and three of these patients were over 30 years old. The presence of leg ulceration is often the only major symptom that brings these patients to hospital, and many patients in this series first presented with an ulcer and were detected by routine haemoglobin electrophoresis.

Occasionally other symptoms are prominent. Epigastric pain alone or in association with a painful crisis is well recognized. In the second case to be reported Washburn (1910–11) stated that " after eating, the patient occasionally had severe abdominal pain and is often troubled with indigestion." Such symptoms are often attributed to gallstones, and, as in Washburn's patient, a cholecystectomy is performed. A history of epigastric pain after meals, awakening the patients at nights, and frequently relieved by milk, food, or alkalis, was obtained from 20 patients (33%) in this series. Nine of these had marked deformity of the duodenal cap, and in five ulcer craters were found on radiological examination. Two brothers had pyloric stenosis associated with duodenal ulceration. Case 14 first presented at the age of 33 with a perforated duodenal ulcer and a subphrenic abscess. Duodenal ulceration is said to be rare in sickle-cell anaemia (Hein *et al.*, 1927 ; Jones *et al.*, 1948 ; Margolies, 1951), though a further three cases have since been reported (Bogoch *et al.*, 1955 ; Marsden and Blackman, 1964 ; Klion *et al.*, 1964). In the past it was assumed that they had hypochlorhydria (Huck, 1923 ; Sydenstricker, 1924 ; Alden, 1927 ; Cooley

TABLE II.—*Age and Sex Distribution*

| Age Group: | 30–34 | 35–39 | 40–44 | 45–49 | 50+ |
|---|---|---|---|---|---|
| No. of men | 13 | 9 | 2 | 0 | 4 |
| No. of women | 15 | 9 | 3 | 2 | 3 |
| Total | 28 | 18 | 5 | 2 | 7 |

TABLE III

| Type of Presentation | No. of Cases |
|---|---|
| Joint or bone pains | 21 |
| Leg ulceration | 13 |
| Jaundice | 14 |
| Pregnancy | 5 |
| Ill as a child | 3 |
| Investigation of relatives | 1 |
| Abdominal mass | 1 |
| Aplastic crisis | 1 |
| Congestive cardiac failure | 1 |

and Lee, 1929) until Zarafonetis *et al.* (1961) demonstrated a normal gastric acid secretion in sickle-cell anaemia. With the augmented histamine test meal two of our cases had high acid production.

### Conjunctival Sign

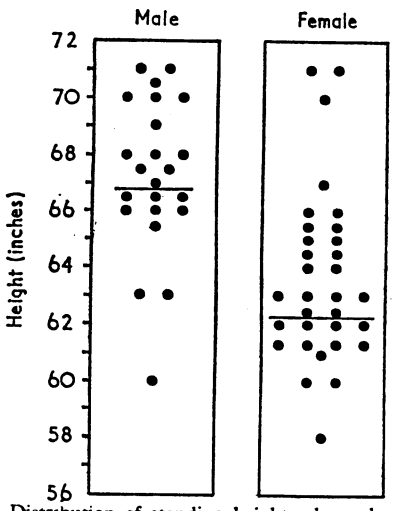
This abnormality of conjunctival vasculature in sickle-cell disease was first noted by Goodman *et al.* (1957). Later, Paton (1961, 1962) suggested that it was of diagnostic value when performed with a slit-lamp, but Comer and Fred (1964) observed it satisfactorily with an ophthalmoscope. Paton described the sign as "multiple, short, comma-shaped or curlicued capillary segments which are often seemingly isolated from the vascular network in that the afferent and efferent lumens have become devoid of blood." We have found it useful as a diagnostic sign in suspected cases of sickle-cell anaemia, and we have seen it in 59 of the 60 patients. It was absent in one patient (Case 14) who had recently received a blood transfusion during major surgery. Comer and Fred (1964) noted this effect of blood transfusion, and in their case the sign became positive when examined later.

### Painful Crises

In almost all the patients the frequency and severity of painful crises had diminished with age. In three patients the pains were still described as frequent or more than four a year, and in a further two patients symptoms had only recently begun. Thirty-six patients described them as infrequent, less than four a year, and most agreed they were less frequent than in childhood. Eleven patients had been free from attacks of pain for the preceding 10 years and a further eight denied ever having any pains.

### Habitus

Contrary to the conventional description of the disease (Winsor and Burch, 1944, 1945a) these patients were often well developed and of normal or above average height (see Chart). In a survey of heights of Jamaican adults Ashcroft *et al.* (1966) noted that the average height for a man over 30 from the urban area was 66.9 in. (170 cm.) and for a woman 62.4 in. (158.5 cm.). The average height for our male patients was 67.1 in. (170.4 cm.) and for the females 63.8 in. (162 cm.).




Distribution of standing heights about the average height for normal population according to Ashcroft *et al.* (1966).

### Leg Ulceration

Leg ulcers were present at some time in 75% of the patients. In 22 cases they were still present, but in 23 they had healed. In all cases the ulcers were in the typical site above the ankles, involving the left side three times more commonly than the right. In 35% they were bilateral. The initial cause of ulceration is usually trauma which leads to chronic infection, but in some instances we observed the formation of new ulcers, which had started as punched-out areas with avascular edges and a thick slough in the base with little evidence of suppuration. Chronic ulceration leads to foot deformity and can cause great demoralization. In our experience leg ulcers account for most of the disability that these patients feel, their anaemia and other symptoms being of much less importance to them. The increase in morale and general well-being when the ulcer is healed makes close attention to this aspect of the disease most rewarding. Major surgical procedures such as cross leg flaps are usually a failure, however, and more simple procedures such as pinch grafting (Walshe and Milner, 1967), which can be repeated many times if necessary, appear to give the better results.

### Anaemia

Individual patients tended to run a fairly steady haemoglobin level with only small variations from week to week. There was a wide range of values among patients (Table I). Eleven had at some time reached a level of 10 g./100 ml. or over, 28 had highest levels recorded between 8 and 9.9 g./100 ml., and 19 between 6 and 7.9 g./100 ml. Only two patients were consistently below 6 g./100 ml. The mean corpuscular haemoglobin concentration was at or above 31% most of the time in most patients, and in only three was it consistently below 31%. The average serum iron was 95 μg./100 ml. in the men and 102 μg./100 ml. in the women, and the average percentage saturation of transferrin was 32 and 35 respectively in these two groups. The levels fluctuated considerably, as they do in normal persons, but the results suggested that iron deficiency is uncommon, and in the few instances where the bone marrow was examined haemosiderin was usually plentiful. These patients had a very high serum iron turnover, between four and eight times normal, but a fall in serum iron and transferrin saturation can occur as a result of infections in the presence of considerable iron in the reticuloendothelial cells of the marrow (Bainton and Finch, 1964). Likewise, spasmodic rises of serum iron and transferrin are not to be interpreted as evidence of haemosiderosis, as they may be due to temporary depression of erythropoiesis and may be followed by a drop to subnormal levels.

On the whole patients with sickle-cell anaemia are in iron balance and should not be treated with iron unless there is an indication that negative iron balance has occurred. This happened in one male patient with an active duodenal ulcer when his serum iron dropped to 35 μg./100 ml. with a saturation of 8.6%. Folic-acid deficiency has often been reported in haemolytic syndromes, and is not uncommonly the cause of megaloblastic anaemia during pregnancy in patients with sickle-cell anaemia. Most of our patients had been treated prophylactically during pregnancy, but we did not routinely treat them in the clinic. The few folate levels that we have so far measured show a serum level around the lower limit of normal (2.5 mμg./ml.) but red cell folate levels in the normal range. The diet in Jamaica is rich in folic acid, and adult deficiency is extremely rare even in pregnancy. Finally, anaemia is not necessarily severe in these patients, and where haemoglobin levels below 6 g./100 ml. are encountered a serious complication such as renal failure may be the cause. Very few of our patients had received blood transfusions.

### Jaundice

The majority of patients, though not all, were clinically jaundiced. A few were deeply jaundiced. Occasionally there were marked variations in serum bilirubin, but generally patients tended to maintain a relatively steady bilirubin level. In 26 the bilirubin was below 2 mg./100 ml., whereas in seven it exceeded 4 mg./100 ml. The remaining 27 patients had levels between 2 and 4 mg./100 ml.

### Hepatomegaly

The liver edge was palpable in 40 patients, and in 22 of these it was felt 3 cm. or more below the costal margin in the midclavicular line. It was smooth, soft, and non-tender. There was no evidence that the liver had been displaced downwards, nor was there any evidence of a raised central venous pressure to account for the enlargement. There was no relation between degree of hepatomegaly and bilirubin level, and there were no clinical stigmata of liver disease in any of the patients. Three patients had had a cholecystectomy for symptoms attributed to gallstones. Liver-function tests showed less abnormality than those in other series (Fenichel *et al.*, 1950 ; Green *et al.*, 1953 ; Bogoch *et al.*, 1955 ; Hilkovitz and Jacobson, 1961), but they were not done in great detail in this group. The serum alanine aminotransferase levels were all normal, and the alkaline phosphatase was raised in only seven cases (12%). In 30 patients (50%) the serum aspartate aminotransferase exceeded the normal range, but in view of the high levels of aspartate transaminase in red cells, this could result from haemolysis alone (Sass and Spear, 1958) and does not necessarily indicate liver-cell disease. Previous reports of liver function in sickle-cell anaemia are complicated by associated hepatic disease such as alcoholic cirrhosis and transfusion hepatitis in this group in the United States. There was no evidence of alcoholism in any of our patients, and their liver function is being studied more closely.

### Splenomegaly

Six of the patients (10%) had easily palpable spleens. An analysis of the $A_2$ values in these six show an average 1.9% ranging from 1.4 to 2.9%, whereas the average for the remaining 54 patients is 2.37%. It therefore seems very unlikely that these were examples of $\beta$-thalassaemia Hb S disease, in which splenomegaly is usually a feature. None of these six patients admitted to symptoms which could be attributed to episodes of splenic infarction.

### Cardiovascular System

The heart was clinically enlarged with an apex beat below or lateral to the fifth intercostal space in the midclavicular line in 30 out of 60 patients (50%). Midsystolic ejection type murmurs best heard at the apex were present in 53 out of 60 (88%). In most patients both components of the second heart sound were loud and moved normally with respiration. Accentuation of the pulmonary component alone was noted in two patients and marked accentuation of the aortic component was present in Case 47, whose B.P. was 130/90. Thirteen patients had third heart sounds, and two of these also had ejection clicks best heard in the pulmonary area. Case 41 had classic signs of mitral stenosis and incompetence. In all patients the jugular venous pressure was normal, and 10 patients had jugular venous hums, on the right side in eight and on the left side in two. Blood pressure varied from 180 to 110 systolic and from 105 to 50 diastolic. Three patients had a diastolic blood pressure of 90 mm., and one patient with associated multiple myeloma (Case 51) had a diastolic pressure of 105 mm. The average pulse pressure was 60 mm. Hg.

The cardiothoracic ratio measured from standard 6-ft. (1.8-metre) posterior-anterior chest *x*-ray films varied from 0.43 to 0.65, with an average of 0.54. Eight patients had a cardiothoracic ratio below 0.50.

The electrocardiograms showed the cardiac rate varying from 37 to 130. Two patients had rates exceeding 100/min. and 16 had rates of 60/min. or less. All patients were in sinus rhythm and eight showed sinus arrhythmia. The P–R interval varied from 0.14 to 0.34 and exceeded 0.22 in three patients. Four patients showed a dominant R in V4R suggestive of mild right ventricular hypertrophy (Goodwin and Abdin, 1959), and in 29 patients the combined voltages of SV1 and RV5 exceeded 35 mm. ST segment changes occurred in 11 patients, and in eight of them consisted of elevation in the right precardial leads V2–4. T-wave changes occurred in 39 patients (65%). In 16 there was only inversion of the T wave in lead III, in six there was inversion of the T wave in leads V2-3, and three showed both these changes. T-wave inversion in V5-6 occurred in three patients and seven showed peaking on T waves in the precordial leads.

The findings in the cardiovascular system are similar to those in other reports (Klinefelter, 1942 ; Winsor and Burch, 1954b). Cardiomegaly, systolic murmurs, third heart sounds, and other auscultatory signs are often present, and their association with fever and joint pain may mimic rheumatic heart disease (Higgins, 1949). Furthermore, the two diseases may be superimposed, as in Case 41. Systolic ejection clicks, third heart sounds, and venous hums have all been reported in this disease (Shubin *et al.*, 1960 ; Uzsoy, 1964), and are probably manifestations of a hyperdynamic circulation.

### Fertility

The development of secondary sexual characteristics was delayed in almost all patients. The average age of menarche was 16.4 years, with a range of 12 to 22 years. Only three patients had their menarche before the age of 14. There were 83 pregnancies among the 32 patients, with an average of 2.6 pregnancies per patient. If the seven patients who had never been pregnant are excluded the average pregnancies per patient rises to 3.3.

Of the 19 spontaneous abortions 10 occurred in three patients. There were five stillbirths. Normal delivery of live infants occurred on 56 occasions, and three patients were pregnant at the time of writing.

Early papers on pregnancy and sickle-cell anaemia stressed the problem of infertility and the high incidence of foetal and maternal mortality (Kobak *et al.*, 1941 ; Beacham and Beacham, 1950). Our own figures lend support to the optimistic attitude expressed by Anderson *et al.* (1960), also from this institution.

## Discussion

Though in the first four cases of sickle-cell anaemia to be described the patients were all over 20 years of age (Herrick, 1910 ; Washburn, 1910–11 ; Cook and Meyer, 1915 ; Mason, 1922), the emphasis rapidly shifted to this being a disease with greatest importance in childhood. The natural history of the disease seemed to vary with the environment, but a particularly bad prognosis was observed in Africa.

The formulation of Neel's (1950) rule of inheritance acted as a powerful stimulus to work in Africa. In areas of very high trait frequency it was implied that sickle-cell anaemia may affect as much as 4% of the population. Initially such frequency was denied (Raper, 1950 ; Lehmann, 1951), but soon the Lambotte-Legrands (1951, 1955) and Vandepitte (1952), working in the Belgian Congo, and Welbourn and Raper (1954), working in Uganda, agreed that when populations of infants were examined the frequency of sickle-cell anaemia very nearly

matched the expected numbers obtained by calculation from trait frequencies. As Allison (1956a) states, " the disease is rare only when looked for in populations of older children and adults."

In the Belgian Congo the Lambotte-Legrands (1955) stated that the majority of patients with sickle-cell anaemia die in childhood, and Vandepitte (1955a), also from Leopoldville, estimated a 1% survival to adult life. Estimates of the survival rate of patients with sickle-cell anaemia have been made by comparing the observed incidence of the disease with the incidence predicted from a knowledge of the gene frequency. On the basis of a study of 70 adults with positive sickle tests of the Luo tribe in Kenya, Allison (1954a) noted two cases of sickle-cell anaemia and calculated a 35% survival rate, but on further studies of samples from adult populations in East and West Africa (Allison, 1954b, 1956a) he states (Allison, 1956b) that the survival rate to reproductive age is likely to be about 20%. On the other hand, Lehmann and Raper (1956) studied the Baamba tribe in Western Uganda, where the sickling rate had previously been estimated at 39.1% (Allison, 1954b) and 45% (Lehmann and Raper, 1949), and in a study of 478 subjects over the age of 5 years 35% had the trait, but no cases of sickle-cell anaemia were found. Lewthwaite (1962) stated that adult cases were not often encountered in East Africa.

However, even in this environment adult cases continued to be described. From Uganda Trowell (1945) described the cases of two patients aged 20 and 24 years. In 1952 Vandepitte and Pieters from Leopoldville described the case of a woman aged 22, and three years later Vandepitte (1955b) described the case of a woman aged 25 (presumably a follow-up of Vandepitte and Pieters's case) and a further case in a woman aged 21. Unfortunately, as Lehmann and Raper (1956) pointed out, none of these cases was substantiated by haemoglobin analysis. The first adult cases with such evidence were described by Allison (1954a). In a survey of 3,362 patients attending two out-patient clinics at Mulago Hospital Jacob (1957) was able to find three new cases in patients aged 18, 28, and 30, all attending the antenatal clinic. From an estimated sickling rate of 16.2% she calculated the survival rate at approximately 14%. Trowell *et al.* (1957) mention a further case in a Buganda woman of 25, and in a review of admissions to the medical wards at Mulago Hospital Shaper and Shaper (1958) noted three patients with sickle-cell anaemia aged 18, 20, and 27. Marsden and Blackman (1964) reported two adult cases—one patient aged 24 was a follow-up on the 18-year-old patient of Shaper and Shaper, and the other aged 20 was a further case. He concluded by saying, " It is likely that if a search were made, many others would be recognized as in Ibadan, where it was possible to build up a clinic of adults with sickle-cell anaemia." There are at least four patients over the age of 30 at present attending the sickle-cell clinic in Ibadan (Topley, personal communication).

In the United States Sydenstricker *et al.* (1962) reported 10 patients over the age of 30 with sickle-cell anaemia collected from their medical service over a period of four years, and Charache and Richardson (1964) reported the case of a 66-year-old woman with sickle-cell anaemia.

These reports of small groups and isolated cases in people of middle age tend rather to confirm the general impression that survival past 30 years is the exception rather than the rule. Our experience in Jamaica indicates that this is not a true picture of the disease, and with migration from this area it is likely that adult cases will be met more often in Europe and the United States of America.

Sickle-cell anaemia is the most widespread and numerically the most important haemoglobinopathy in the world today. In areas such as Jamaica, where the frequency of the Hb S gene is about 11% (MacIver and Went, 1958 ; Miall *et al.*, 1967) it can be calculated that approximately 0.32% of all children will have the disease. In a study of 741 men and 835 women between the ages of 35 and 64 who were selected at random from a rural and an urban population in Jamaica Miall *et al.* (1967) found two persons with sickle-cell anaemia, both women. This represents 0.127% of the whole sample taken and gives a survival rate into middle age of 39.2%.

The population of Jamaica is now about two million and increasing, so that a large proportion of these are under 20 years of age. There are probably about 4,000 persons of all ages who have homozygous sickle-cell anaemia. Similar numbers can be expected in immigrant populations abroad in the course of time.

It is difficult to say whether the disease is becoming more benign or whether it is just recognized more often in relatively asymptomatic patients. As social and economic conditions in Africa improve it is probable that many more people with the disease will reach adult life.

This work was supported by research grants from the Standing Advisory Committee for Medical Research in the British Caribbean ; the Ministry of Overseas Development, London, through the Tropical Medical Research Board of the Medical Research Council ; and the Wellcome Trust, London. We wish to thank Dr. Raymond Lewthwaite, Professor John Waterlow, Professor E. K. Cruickshank, and Professor H. Lehmann for their interest in this project. We are indebted to Mrs. L. Slifer and Mrs. B. Serjeant for technical assistance, to Mrs. A. Milner and Mrs. F. Gabay for secretarial assistance, and to the nurses and staff of the University Hospital of the West Indies.

## REFERENCES

Alden, H. S. (1927). *Amer. J. med. Sci.*, **173**, 168.
Allison, A. C. (1954a). *Ann. hum. Genet.*, **19**, 39.
Allison, A. C. (1954b). *Trans. roy. Soc. trop. Med. Hyg.*, **48**, 312.
Allison, A. C. (1956a). *Ann hum. Genet.*, **21**, 67.
Allison, A. C. (1956b). *Trans. roy. Soc. trop. Med. Hyg.*, **50**, 185.
Anderson, M., Went, L. N., MacIver, J. E., and Dixon, H. G. (1960). *Lancet*, **2**, 516.
Ashcroft, M. T., Ling, J., Lovell, H. G., and Miall, W. E. (1966). *Brit. J. prev. soc. Med.*, **20**, 22.
Bainton, D. F., and Finch, C. A. (1964). *Amer. J. Med.*, **37**, 62.
Beacham, W. D., and Beacham, D. W. (1950). *Amer. J. Obstet. Gynec.*, **60**, 1217.
Beale, R. N., Bostrom, J. O., and Taylor, R. F. (1961). *J. clin. Path.*, **14**, 488.
Beale, R. N., Bostrom, J. O., and Taylor, R. F. (1962). *J. clin. Path.*, **15**, 156.
Bogoch, A., Casselman, W. G., Margolies, M. P., and Bockus, H. L. (1955). *Amer. J. Med.*, **19**, 583.
Charache, S., and Richardson, S. N. (1964). *Arch. intern. Med.*, **113**, 844.
Comer, P. B., and Fred, H. L. (1964). *New Engl. J. Med.*, **271**, 544.
Cook, J. E., and Meyer, J. (1915). *Arch. intern. Med.*, **16**, 644.
Cooley, T. B., and Lee, P. (1929). *Amer. J. Dis. Child.*, **38**, 103.
Fenichel, R. L., Watson, J., and Eirich, F. (1950). *J. clin. Invest.*, **29**, 1620.
Goodman, G., von Sailmann, L., and Holland, M. G. (1957). *Arch. Ophthal.*, **58**, 655.
Goodwin, J. F., and Abdin, Z. H. (1959). *Brit. Heart J.*, **21**, 523.
Green, T. W., Conley, C. L., and Berthrong, M. (1953). *Bull. Johns Hopk. Hosp.*, **92**, 99.
Hein, G. E., McCalla, R. L., and Thorne, G. W. (1927). *Amer. J. med. Sci.*, **173**, 763.
Herrick, J. B. (1910). *Arch. intern. Med.*, **6**, 517.
Higgins, W. H. (1949). *Sth. med. J. (Bgham, Ala.)*, **42**, 39.
Hilkovitz, G., and Jacobson, A. (1961). *J. Lab. clin. Med.*, **57**, 856.
Huck, J. G. (1923). *Bull. Johns Hopk. Hosp.*, **34**, 335.
Huisman, T. H., and Dozy, A. M. (1965). *J. Chromatogr.*, **19**, 160.
Itano, H. A. (1953). *Arch. Biochem. Biophys.*, **47**, 148.
Jacob, G. F. (1957). *Brit. med. J.*, **1**, 738.
Jones, H. L., Wetzel, F. E., and Black, B. K. (1948). *Ann. intern. Med.*, **29**, 928.
Jonxis, J. H. P. (1959). Abnormal Haemoglobins. A C.I.O.M.S. Symposium, p. 300.
Klinefelter, H. F. (1942). *Amer. J. med. Sci.*, **203**, 34.
Klion, F. M., Weiner, M. J., and Schaffner, F. (1964). *Amer. J. Med.*, **37**, 829.
Kobak, A. J., Stein, P. J., and Daro, A. F. (1941). *Amer. J. Obstet. Gynec.*, **41**, 811.
Lambotte-Legrand, J. and C. (1955). *Ann. Soc. belge Méd. trop.*, **35**, 53.
Lambotte-Legrand, J. and C. (1951). *Mém. Inst. roy. colon. belge*, No. 19, 1.
Lathe, G. H., and Ruthven, C. R. J. (1958). *J. clin. Path.*, **11**, 155.
Lehmann, H. (1951). *Nature (Lond.)*, **167**, 931.
Lehmann, H., and Raper, A. B. (1949). *Nature (Lond.)*, **164**, 494.
Lehmann, H., and Raper, A. B. (1956). *Brit. med. J.*, **2**, 333.
Lewthwaite, C. J. (1962). *E. Afr. med. J.*, **39**, 196.
MacIver, J. E., and Went, L. N. (1958). *West Indian med. J.*, **7**, 109.
Marder, V. J., and Conley, L. C. (1959). *Bull. Johns Hopk. Hosp.*, **105**, 77.

Margolies, M. P. (1951). *Medicine (Baltimore)*, **30**, 357.
Marsden, P. D., and Blackman, V. (1964). *E. Afr. med. J.*, **41**, 305.
Mason, V. R. (1922). *J. Amer. med. Ass.*, **79**, 1318.
Miall, W. E., Milner, P. F., Lovell, H. G., and Standard, K. L. (1967). *Brit. J. prev. soc. Med.*, **21**, 45.
Neel, J. V. (1950). *Cold Spr. Harb. Symp. quant. Biol.*, 15, 141.
Paton, D. (1961). *Arch. Ophthal.*, **66**, 90.
Paton, D. (1962). *Arch. Ophthal.*, **68**, 627.
Raper, A. B. (1950). *J. trop. Med. Hyg.*, **53**, 49.
Saas, M., and Spear, P. W. (1958). *J. Lab. clin. Med.*, **51**, 926.
Shaper, A. G., and Shaper, L. (1958). *E. Afr. med. J.*, **35**, 647.
Shubin, H., Kaufman, R., Shapiro, M., and Levinson, D. C. (1960). *Amer. J. Cardiol.*, **6**, 875.
Singer, K., Chernoff, A. I., and Singer, L. (1951). *Blood*, **6**, 413.
Sydenstricker, V. P. (1924) *Sth. med. J. (Bgham, Ala.)*, **17**, 177.
Sydenstricker, V. P., Kemp, J. A., and Metts, J. C. (1962). *Amer. Practit.*, **13**, 584.
Trowell, H. C. (1945). *E. Afr. med. J.*, **22**, 34.
Trowell, H. C., Raper, A. B., and Welbourn, H. F. (1957). *Quart. J. Med.*, **26**, 401.
Uzsoy, N. K. (1964). *Amer. J. Cardiol.*, **13**, 320.
Vandepitte, J. M. (1952). *Brit. med. J.*, **1**, 920.
Vandepitte. J. M. (1955a). *Docum. Med. geogr. trop. (Amst.)*, **7**, 154.
Vandepitte, J. M. (1955b). *Ann. Soc. belge méd. trop.*, **35**, 501.
Vandepitte, J .M., and Pieters, G. (1952). *Ann. Soc. belge. Méd. trop.*, **32**, 281.
Walshe, M. W., and Milner, P. F. (1967). *West Indian med. J.*, **16**, 10.
Washburn, R. E. (1910-11). *Virginia Med.*, semi-monthly 15, 490.
Welbourn, H., and Raper, A. B. (1954). *Brit. med. J.*, **1**, 1440.
Went, L. N., and MacIver, J. E. (1958). *Lancet*, **2**, 824.
Went, L. N., and MacIver, J. E. (1961). *Blood*, **17**, 166.
Winsor, T., and Burch, G. E. (1944). *Hum. Biol.*, **16**, 99.
Winsor, T., and Burch, G. E. (1945a). *Arch. intern. Med.*, **76**, 47.
Winsor, T., and Burch, G. E. (1945b). *Amer. Heart J.*, **29**, 685.
Zarafonetis, C. J., Joseph, R. R., McMaster, J. D., and Kalas, J. P. (1961). *J. Lab clin. Med.*, **57**, 600.

# Clinical Use of Atrial Pacing Test in Angina Pectoris

RAPHAEL BALCON,* M.B., M.R.C.P.; WILLIAM C. MALOY,* M.D.; EDGAR SOWTON,* M.A., M.D., M.R.C.P.

*Brit. med. J.*, 1968, **3**, 91–92

**Summary: Atrial pacing can be used as a safe test in the assessment of patients with angina pectoris. The results are useful in clinical judgements, and this method of investigation may be indicated for patients in whom the diagnosis of angina pectoris is in doubt or who are being considered for surgical treatment of ischaemic heart disease.**

## Introduction

The difficulties in evaluating patients with angina pectoris are well known and are assuming greater importance with the increasing application of surgical techniques of revascularization of the heart. Since angina is a symptom, it cannot be evaluated objectively, and clinical interpretation of the state of the disease may be greatly influenced by a placebo response or by wide variations in effort tolerance from day to day. This spontaneous variation may also confuse the interpretation of exercise tests, while electrocardiographic (E.C.G.) changes as an end-point do not always correlate with the time of onset of pain. The purpose of this paper is to describe our clinical experience with the use of an atrial pacing test over a period of one year. This test relies on the temporary production of an artificial supraventricular tachycardia by pacing from the right atrium of resting patients.

## Methods

The technique has been described in detail elsewhere (Sowton *et al.*, 1967), but it essentially depends on the percutaneous passage of a bipolar pacing electrode from a peripheral vein to the right atrium. The heart rate is then controlled by an external adjustable pacemaker and the systemic pressure is simultaneously recorded from a very fine (1 mm.) Teflon catheter introduced by the Seldinger technique. The heart rate is increased in increments until the earliest detectable sensation of substernal oppression is reported by the patient, and the tension-time index at this point is calculated from the pressure trace. This tension-time index has been shown to be a highly repeatable measure of the "angina threshold," provided there is no sudden increase in heart size (Sowton *et al.*, 1967). We suggest that measurements of the angina threshold in this way may be useful in following the progress of individual patients over a period of time, but do not claim that valid comparisons can be made between different patients. All the manifestations of cardiac ischaemia, including the substernal oppression, can be very rapidly reverted to the control state by reducing the pacing rate. The entire test procedure can be performed on an outpatient basis, several confirmatory measurements of angina threshold being made within 60 minutes.

* Institute of Cardiology and the National Heart Hospital, London W.1.

## Results

The detailed haemodynamic and E.C.G. findings at the onset of pain and during treatment with various anti-anginal drugs have already been reported both by ourselves and by others (Sowton *et al.*, 1967; Lau *et al.*, 1967b; Friesinger *et al.*, 1967; Frick *et al.*, 1968). The first 42 patients studied had a clear clinical history of angina, and 39 of them had ischaemic changes on the E.C.G. They were investigated as part of an assessment for revascularization surgery, and in addition had the usual full clinical and radiological examination and often went forward to selective angiography by the Mason Sones technique. The Table shows the results of the atrial pacing test in these patients grouped according to the clinical severity of their disease.

*Results of Atrial Pacing Test*

| Clinical Grade | No. of Patients | | | Mean Age | Angina Induced | | Percentage of Group with Induced Angina |
|---|---|---|---|---|---|---|---|
| | M | F | Total | | Yes | No | |
| 1 | 5 | 1 | 6 | 50·2 | 1 | 5 | 17 |
| 2 | 15 | 1 | 16 | 54·4 | 11 | 5 | 69 |
| 3 | 11 | 1 | 12 | 52·2 | 11 | 1 | 92 |
| 4 | 5 | 3 | 8 | 54·4 | 8 | 0 | 100 |

*Group 1:* Pain occurs only occasionally, on exceptional effort or emotion—for example, hurrying uphill.

*Group 2:* Pain occurs during ordinary activity; walking is restricted to 200 yards (180 metres) at normal pace.

*Group 3:* Pain after 50 yards (46 metres) or less.

*Group 4:* Pain at rest.

Pain was produced during atrial pacing in only one patient in group 1 (17%), 11 out of 16 had pain in group 2 (69%), 11 out of 12 in group 3 (92%), and all in group 4 (100%).

From these results it was felt that the test might have diagnostic significance in cases where there were atypical features and diagnosis was in doubt. The first two of the following case histories are taken from the original series of 42 patients; the other two are of patients subsequently tested.