DEPARTMENT OF MEDICINE
MAKERE UNIVERSITY, KAMPALA.

CARDIOVASCULAR FINDINGS IN PATIENTS
WITH SICKLE CELL DISEASE

A DISSERTATION PRESENTED

FOR

THE DEGREE OF MASTER OF MEDICINE (MED). 197-

MAKERE UNIVERSITY, KAMPALA.

BY


SUPERVISOR:- P.G. D'ARBELA, M.B.,CH.B. (E.A), M.R.C.P.,
M.R.C.P.(E).
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CHAPTER I

SUMMARY OF CONTENTS OF THIS DISSERTATION
SUMMARY

Fifty homozygous sicklers and ten heterozygous sickle cell patients selected from the Sickle Cell Clinic Cardiac Clinic and inpatients on the medical wards of Mulago Hospital form the basis of this dissertation.

It starts with a historical review and pathology of sickle cell disease. Cardiovascular alterations in anaemia with emphasis on physiological and pathological considerations in sickle cell disease are then discussed. The findings among the patients studied are described dwelling mainly on presenting symptoms, cardiovascular findings notably cardiomegaly, murmurs, abnormal heart sounds, electrocardiographic and x-ray abnormalities. A discussion of findings with reference to work on the same subject by other writers is presented. Some of the possible haemodynamic alterations in sickle cell disease are outlined and a need for further elaborate studies in this condition is stressed.
CHAPTER II

HISTORICAL REVIEW AND PATHOLOGY OF SICKLE CELL DISEASE
CARDIOVASCULAR FINDINGS IN PATIENTS WITH SICKLE CELL DISEASE

HISTORICAL REVIEW AND PATHOLOGY OF SICKLE CELL DISEASE
Sickle cell anaemia was first described in 1910 by J.B. Herrick (1) in a West Indian youth. In 1927, Hahn and Gillespie, studying the sickling phenomenon, discovered that the distortion of the red blood cells is related to the state of oxygenation of the haemoglobin molecule and in 1949 Pauling and his associates demonstrated that sickle cell haemoglobin differed in its electrophoretic behaviour from normal haemoglobin. The chemical structure of the haemoglobin molecule was defined in 1959 by Ingram who illustrated that the abnormality in haemoglobin S is limited to a single amino acid substitution within a polypeptide B-chain of globin – valine being substituted for glutamic acid in the sixth position. In 1949 it had been shown by Neel, that the S-gene is inherited in the autosomal Mendelian pattern. Beares of sickle cell trait show no haematological abnormalities apart from a possible decrease in osmotic fragility.

Sickle cell anaemia occurs in the homozygous state in which nearly all haemoglobin is S, the remainder being F. The pathological effects of the sickling phenomenon depend on the presence of and to a certain extent on the concentration of haemoglobin S. The other factors are
the duration of exposure of cells to reduced oxygen tension, the type of any associated haemoglobinopathy and also the pH of the surrounding medium. The trait is only associated with hyposthenuria and occasionally haematuria apart from susceptibility to various infections. The hyposthenuria in the AS individual is associated with the high osmotic pressure which occurs in the interstitial fluid in the region of the renal papillae, causing increased viscosity, anoxia, and restricted blood flow to the cortex. Vascular occlusions may occur in the region of the papillae and pelvis and may be responsible for unilateral or bilateral haematuria (Bennett et al. 1967, Akinkugbe 1966).

In the homozygous individual, in the presence of high oxygen tension, most of the haemoglobin exists in the combined form as oxyhaemoglobin. In this state the red blood cells tend to remain entirely normal in shape and behaviour. Relatively slight reduction in oxygen tension, however, causes haemoglobin S to crystallise, so distorting the red cells into the sickle shape. The sickling leads to intravascular stasis, increasing blood viscosity, occlusion secondary to thrombosis, and varying degrees of local ischaemia associated with infarction, necrosis and haemorrhage. The circulatory stasis affords more time for the red blood cells to lose their oxygen and this enhances the sickling phenomenon and subsequent thrombosis. Moreover stasis leads
to a state of acidosis, another factor which favours sickling. An unbreakable vicious cycle of reduced oxygen tension → sickling → stasis → reduced oxygen tension is thus set up.

In the peripheral circulation vascular blockage tends to occur on the venous side of the circulation where oxygen tension is least. In both liver and spleen sickled forms are abundant rendering the flow of blood very slow. The subsequent thrombosis and infarction eventually lead to a fibrotic and contracted spleen. In the pulmonary circulation the oxygen relationships are reversed, arterial occlusions are the rule and lead to multiple and repeated pulmonary infarctions with subsequent cor pulmonale. Intravascular haemolysis does occur leading to active erythrophagocytosis and reticulo–endothelial hyperplasia. The above pathological processes can proceed in almost any organ leading to various haemodynamic changes depending on the degree of anatomical and functional derangement.
CHAPTER III

CARDIOVASCULAR ALTERATIONS IN ANAEMIA - PHYSIOLOGICAL
AND PATHOLOGICAL CONSIDERATIONS WITH EMPHASIS ON SICKLE
CELL ANAEMIA.
The circulatory adjustments to any type of anaemia have been reported on by various workers (Leight, L. et al; Sharpey-Schafer, et al; (3), Brannon, et al; (4), Bishop, et al; (5), Fowler, et al; (6), Wintrobe, (7), Hunter; (8). Blood viscosity is dependent on the concentration of the red blood cells. In anaemia the greatly decreased viscosity decreases the resistance to blood flow in the peripheral vessels so that far more than normal quantities of blood return to the heart. As a result the cardiac output increases two-fold or more. Also diminished oxygen transport by the blood leads to hypoxia. The latter causes tissue vessels to dilate, thus allowing further increased return of blood to the heart and hence increased cardiac output. The factor leading to a rise in cardiac output besides an increase in stroke volume is an increase in pulse rate. These two mechanisms of raising the cardiac output combine to produce the so-called hyperkinetic circulatory state.

Thus one of the major effects of anaemia is a greatly increased work load on the heart consequent upon increased cardiac output. The cardiac output is usually not increased in anaemia until the haemoglobin falls to about 50% of the normal. Under such circumstances the resting cardiac output may be increased 3-fold and the utilisation of available oxygen may be increased from the normal 33% to
up to 90%. In this way the increased cardiac output offsets many of the symptoms of anaemia for even though each unit quantity of blood carries only a small quantity of oxygen, the rate of blood flow may be increased to such an extent that almost normal quantities of oxygen are delivered to the tissue. When an anaemic patient begins to exercise, however, his heart is not capable of pumping much greater quantities of blood than it is already pumping and hence tissue hypoxia results leading to acute cardiac failure. Patients with sickle cell anaemia get into a viscous cycle in which low oxygen tension in the tissues causes sickling, which causes impendement of blood flow through the tissues causing still further decrease in oxygen tension.

The cause of the raised venous pressure in anaemia without cardiac failure is not clear, although the plasma volume is raised, unlike the red cell volume which is usually normal or diminished. Moreover the small arteries and arterioles are dilated although there is presumably capillary constriction and venoconstriction. In florid congestive cardiac failure, however, the plasma volume may be increased to an extent leading to a rise in circulating total blood volume.

When it occurs several factors probably operate simultaneous to bring about the syndrome of cardiac failure in chronic anaemia. Angina pectoris is a recognised symptom of anaemia.
Zimmerman and Banett have reported a case of sickle cell anaemia simulating coronary occlusion. Although anaemia per se may give rise to angina pectoris, there is usually associated coronary arterial disease. The subendocardial region, particularly of the left ventricle and papillary muscles, has the poorest blood supply and therefore necrosis tends to occur in these regions. In addition, a diffuse focal myocardial necrosis may result from anaemia. If prolonged, severe anaemia may lead to fatty degeneration of the myocardium, thus further leading to functional impairment. There have also been reported cases of actual deposition of iron in the myocardium. Myocardial disease can also result from thrombosis of small cardiac blood vessels. Escipion, Oliveira and Gomez-Patino\(^{9}\), reported an instance of a fatal thrombus formation in the vital organs of a 29 year old Negro man whose presenting symptoms resembled those of rheumatic fever. He had cardiomegally and a Grade II systolic murmur. The ECG demonstrated diffuse progressive myocardial damage. At autopsy, the coronary arteries were filled with sickled cells and there was extensive myocardial fibrosis with interstitial infiltration with macrophages and lymphocytes. That pulmonary arterial thrombosis occurs in sickle cell anaemia leading to pulmonary infarction is a well recognised fact.
Shriley Rubler et al.\textsuperscript{(10)} reported four cases of sudden death in patients having a sickle cell diathesis who were found at post mortem to have extensive pulmonary infarction secondary to thromboembolic phenomenon. In one case there was an old and a recent pulmonary artery thrombus. Both ventricles were dilated and hypertrophied with endocardial thickening extending up to the mitral valve leaflets. Microscopy revealed hypertrophied myocardial fibres especially involving papillary muscles. There was basophilic degeneration and vacuolisation of the cytoplasm with calcific deposits in areas of hypertrophy as well as extensive interstitial fibrosis. Coronary capillaries were filled with sickled erythrocytes. The second case had cardiomegally and pulmonary congestion plus demarcated gangrene of toes. Microscopy of the heart showed areas of interstitial fibrosis, degenerative changes of myofibrils and loss of strictions and capillaries dilated with sickled cells. The third case had pulmonary congestion with old and recent pulmonary thromboemboli. The pulmonary artery was occluded by an adherent thrombus. Microscopy showed focal areas of fresh haemorrhagic infarction and residual evidence of previous infarction. The intima of pulmonary arteries was thickened and the medium sized arteries contained old,
organised and re-canalised thrombi. Case IV had congested haemorrhagic lungs and right and left ventricular dilatation and hypertrophy. Microscopy revealed hypertrophy of myofibrils with interfascicular and endocardial fibrosis. The pulmonic valve cusps were thickened and the pulmonary artery was sclerotic. These authors further pointed out that of these four patients, three were chronic users of alcohol. It is known that cardiomyopathy predisposes to pulmonary infarction secondary to emboli from mural thrombi. Patients with sickle cell trait also have an increased susceptibility to pulmonary infarction. Thus from these cases it is difficult to decipher the role of sickle cell anaemia in causation of cor pulmonale. Moreover, the association of an obscure cardiomyopathy and pulmonary infarction in patients with sickling diathesis though not previously reported may represent a distinct pathological entity.

Namik et al. (11), studied 48 patients with sickle cell anaemia of whom 16 patients died and of these 9 had autopsies done. The causes of death were recorded as pneumonia (4) congestive cardiac failure (3) and pulmonary infarction and multiple other organ infarctions in (2). A pale flabby myocardium was found in 4 cases (44.4%). Definite dilatation of both ventricles was found in 4 and
one had left ventricular dilatation alone. Microscopic
examination revealed granulation, vacuolisation of
myocardial fibres with interstitial oedema and increased
fibrous tissue. A posterior myocardial scar was found
in 1 case. The lungs showed sickling of erythrocytes within
the pulmonary vessels and multiple pulmonary infarcts
were found in 90% of cases. Marked pulmonary oedema was
present in 66.6%. Only 1 patient had bilateral pleural
effusion.

In their study of 25 patients, Winsom and Burch\(^{(12)}\),
reported on autopsy findings of 9 patients who died, 3
dying in congestive cardiac failure. All nine cases
showed cardiac hypertrophy and dilatation, interstitial
oedema, myocardial degeneration, vacuolated sarcoplasm,
Zenker's degeneration, interstitial infiltration with
polymorphs and oblitative endarteritis of coronary and
pericardial vessels.

Other evidence for the occurrence of pulmonary
infarction in sickle states comes from the work of
Steinberg \(^{(13)}\) who in 1930 in reviewing the pathology of
sickle cells anaemia described marked congestion of the
pulmonary capillaries and the larger vessels in the lungs
as a constant finding. In one instance he specifically
noted the presence of numerous small and medium sized
pulmonary vessels containing fresh or organised blood thrombi with "as a consequence fresh and old pulmonary infarcts". Similar changes were present in the spleen and kidneys. Bauer (14), in a similar review, observed that the major pathological process in sickle cell disease was "stagnation and conglutination of disfigured red corpuscles" which "predisposes to thrombosis followed by endarteritis and infarction". He further comments that" the arterioles of the spleen, lungs and brain are particularly likely to be affected". The classical report of Yater and Hansman(15), described a 38 year old Negro woman with probable S–S disease who presented with the clinical features of cor pulmonale with right-sided failure. At autopsy many splenic vessels were found occluded, also, many thrombi were found in small and medium-sized pulmonary arteries. The right ventricle was enlarged. Sickled cells were demonstrated in the pulmonary vessels. In 1941 Mallory(16), described a most interesting case in point of a patient who died aged 20. This Italian lady had been followed up for several years because of recurrent febrile episodes during which evidences compatible with pneumonitis were present. Cor pulmonale with eventual right heart failure appeared over this period. At autopsy there was classical changes of sickle cell anaemia in the spleen. There were multiple areas of thrombosis and infarction throughout both lungs along with evidence of cor pulmonale.
Margolies\textsuperscript{17}, states that the lungs may be the site of multiple thrombosis and infarcts involving many lobes. The pulmonary picture may be due to plugging of arterioles with secondary anoxia and tissue damage producing a pneumonia-like picture.

From a purely clinical point of view symptoms due to anaemia per se can be difficult to delineate from those due to cardiac failure consequent upon severe anaemia. Dyspnoea, fatigue, palpitation, and angina can be due to anaemia. Oedema may occur in anaemia and may be due to hypoproteinaemia or due to increased capillary permeability secondary to hypoxia. Left ventricular failure rarely arises as a result of anaemia except during blood transfusion. When it occurs the evidence will be in the form of pulmonary congestion giving rise to orthopnoea and cough. Venous congestion will give rise to an elevated jugular venous pressure and to hepatic congestion. Cardiomegally, cardiac murmurs and dyspnoea per se are of no diagnostic import as far as establishing presence or absence of cardiac disease is concerned.

In 1857 Bamberger\textsuperscript{18}, mentioned association of cardiomegally with anaemia. Other observers including Goodhart\textsuperscript{19}, Herssmann\textsuperscript{20}, Goldstein\textsuperscript{21} made similar observations.
In 1899, Gautier\(^{22}\), demonstrated such increase in heart size by percussion and showed a decrease with relief of the anaemia. Ball was the first to show such an increase by radiological measurement with reduction to a normal diameter after recovery from the anaemia. Other workers, notably Porter,\(^{24}\), Tung,\(^{25}\), and Cabot,\(^{26}\), confirmed this observation and showed that this return to normal occurs within a few weeks. From the work of those investigators several observations were made.

1. The tendency for cardiomegally to occur with very low haemoglobin. There also appeared to be a correlation between age of the patients and frequency of enlargement - the older the patients the greater the degree of enlargement.

2. There were possible aggravating factors such as duration of anaemia, degree of physical activity and dietary deficiency.

3. In most cases a decrease in heart size ranging from 1 - 4.7cm occurred within a period of 3 - 12 weeks.

4. The greater the degree of anaemia the more likely was the heart to decrease in size with correction of the anaemia.

5. Bed rest during the treatment of the anaemia appeared to be an important factor to aid return of heart size to normal.

6. The observed rapid decrease in heart size implied dilatation was partly responsible for the cardiomegally.
(7) Cardiac hypertrophy — shown by an increase in heart weight — was a contributory factor. Cabot and Richardson\(^{(26)}\), showed an increase in weight in 18 out of 19 patients dying of pernicious anaemia.

(8) Porter\(^{(24)}\), believed that short term anaemia led to reversible dilatation while prolonged disease led to irreversible hypertrophy. Animal experiments have shown evidence of hypertrophy as a result of prolonged anaemia.

(9) Organic valvular damage due to anaemia appeared unlikely.

(10) Anaemia led to fatty degeneration characterised by yellow streaking visible on the endocardial surface.

The above authors also studied cardiac murmurs among their patient. Systolic murmurs were frequent at the apex and base and these were mid-systolic. They were high-pitched and blowing. The factors involved in their causation appeared to be mainly two. Increased velocity of blood flow through the aortic and pulmonary valves was considered responsible for the basal murmurs through the aortic ejection systolic murmur could also be heard at the apex. Cardiac dilatation with functional mitral regurgitation was considered responsible for the apical systolic murmurs. A mitral mid-diastolic murmur may appear probably due to increased velocity of flow and comparable to that produced across the mitral valve as a result of a left to right shunt in patent ductus arteriosus or ventricular septal defect.
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Both aortic and pulmonary diastolic murmurs have been recored in anaemia and are thought to be due to dilatation of the aortic and pulmonary valve rings, producing functionally incompetent valves. In general, the presence and intensity of the murmurs was roughly proportional to the degree of cardiac enlargement and to the severity
of the anaemia. In their series 19 cases were followed and in 14 of these the murmur decreased as the anaemia improved. In 9 out of 10 in whom a decrease in the murmur was noted, roentgenographic evaluation also showed a decrease in size whereas all patients with no change of murmur showed no change of size. Diastolic murmur were less common than systolic. In 1861 Friedreich et al. (27), commented on a case with clinical features of a diastolic murmur who at autopsy had normal valves. The murmurs in their series were usually early diastolic, blowing and best heard near left sternal edge. The murmurs of pulmonary incompetence occurred only in very severe anaemia. Goldstein and Boas (21), reported an incidence of 10% these murmurs in 39 cases of anaemia but this is a much higher incidence than that generally reported. Presystolic murmurs are said to be very rare. Their importance lies in the fact that they may be mistaken for organic mitral stenosis especially in cases with a loud first heart sound or pre-systolic gallop as may occur in anaemia patients. Such murmurs are of course more likely to be heard in thin chested people, after exercise or pregnancy.

The effects of anaemia on blood pressure have been reported on by Tung, et al. (25). There is a tendency for systolic and diastolic pressures to fall with an increase in pulse pressure in milder cases and a decrease in pulse
pressure in severe cases. Some of the factors responsible for a fall in blood pressure are a compensatory peripheral vasodilatation, diminished blood viscosity and diminished blood volume. There is however, a concurrent increase in cardiac output which tends to increase the blood pressure and thus counteract any further fall in blood pressure.

Electrocardiographic abnormalities in chronic anaemia have been variously reported either to be of no significance or to have a high incidence, to disappear with relief of anaemia or to persist, and to be proportional to the severity of the anaemia or to show no correlation. The ECG changes have been attributed to ischaemia of the myocardium, subendocardial necrosis, increased vagal tone, myocardial scarring or coronary occlusion. In a study of 100 patients with anaemia of at least 3 months duration and haemoglobin values of 2 - 80% Sanghvi, L.M. et al.\(^{(28)}\), made several observations. They noted that the incidence and nature of the abnormalities was related to the haemoglobin level and cardiac size on admission, and that there was no relation to aetiology or duration of the anaemia. They noted a left ventricular hypertrophy pattern in 3 cases in the absence of cardiac enlargement. In all patients with cardiac failure an abnormal ECG was found. More specifically in sickle cell
anaemia various ECG abnormalities have been reported. Prolongation of the PR interval, non specific ST segment and T wave changes, left ventricular hypertrophy and strain and incomplete right bundle branch block have all been described.

**PURPOSE OF THE STUDY**

Sickle cell disease is a common disorder in Uganda. About 20% of the African population are carriers and it is estimated that 1% of babies born are homozygous. The highest carrier rate is among Bamba of Rwenzori mountains in West Uganda where it is estimated at 39%. Among Baganda carrier rate is about 17% with 1.5% being homozygous sickle cell anaemia patients.

From the above account and with further evidence to be presented later it is apparent that patients with severe anaemia, including sickle cell anaemia, often present evidence of cardiovascular involvement even in the absence of frank cardiac failure. Heart murmurs, clinical and roentgenographic evidence of cardiac enlargement, flooded lung field and electrographic abnormalities may be noted. Moreover symptoms of cardiac decompensation notably palpitations, dyspnoea, angina pectoris may occur in anaemia per se.

More important, however, from the cardiological point of view is the apparent similarity of sickle cell disease to
rheumatic fever with or without carditis due to the presence of murmurs, dactylitis, and bone tenderness which may be mistaken for joint involvement and the presence of similar radiological and electrographic abnormalities. Here differences in erythrocyte sedimentation rate and the response to salicylate analgesics would be points of differentiation.

Sickle cell disease could be mistaken for chronic rheumatic heart disease with mitral stenosis because dyspnoea, swollen ankles, a loud S1, mid-diastolic murmurs and even presystolic murmurs may occur in both (Samuel Gram—Clinical Heart Disease).

Subacute bacterial endocarditis has to be differentiated from sickle cell disease because both may result in low grade fever, collapsing pulse, pallor of skin, petechiae, apical or basal systolic murmurs and even aortic diastolic murmurs.

Sickle cell anaemia as a cause of pulmonary vascular occlusion, pulmonary hypertension and subsequent right ventricular hypertrophy has already been referred to. It has also been suggested that sickle cell thrombi in the coronary vasculature occasionally result in coronary insufficiency.

The object of this study was to delineate the nature and frequency of the abnormalities mentioned above in the sickle cell population in Uganda.
CHAPTER XIV

THE STUDY
The total number of patients included in the study was sixty. Of these twenty-six were selected from the Sickle Cell Clinic. Twenty-five patients were attending the Cardiac Clinic and nine patients were inpatients on the medical wards—see table 1.
Table I

Table showing the number of patients from different sources.

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of patients</th>
<th>Haemoglobin</th>
<th>Electrophoresis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SS</td>
<td>AS</td>
</tr>
<tr>
<td>1. Sickle Cell Clinic</td>
<td>26</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>2. Cardiac Clinic</td>
<td>25</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>3. Inpatients</td>
<td>9</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>
The Sickle Cell Clinic patients:—

The Sickle Cell Clinic is held once every week. It has a daily attendance of about forty patients.

It was established in the Department of Paediatrics at New Mulago Hospital in 1961. The purpose of its establishment was to study the effects of antimalarials on the incidence of complications in Sickle Cell anaemia. Only patients diagnosed by haemoglobin electrophoresis (Goldberg[20]), attend the Clinic. The clinic has a registered number of attendants. Most of these patients live in or around Kampala—the capital of Uganda with a population 330,000. They live in rural or semi-rural surroundings on a subsistence economy. Most patients live within a radius of 15 miles from the hospital and attend regularly, usually every 3 months. Besides receiving their malarial prophylaxis on such visits, the patients are treated if they have a crisis or any other illness either as outpatients or as inpatients depending on the severity of their symptoms. The patients are taught to manage minor painful crises at home.

If patients need transfusion (Hb 56%) this is done either as outpatient in acute admission unit of the Paediatric Department or as inpatients depending on the severity of the anaemia and any other associated problem.

The Baganda form a high proportion of the attendants. By December, 1971, of 623 patients registered, 503 (31%) were Baganda. Other tribes included Soga (12), Nyoro (13), Jaluo (10), Acholi (11), Ateso (10). The male, female sex ration was equal. Among the attendants the highest
figure is in the age range 5 - 9 years. For example in 1971 of 628 patients, 230 were in this age group. A total of 182 patients were aged 10 years and above and 7 of these were 20 years and above.

The author attended the clinic on a total of eight consecutive weeks. The daily turn up on each of these occasions averaged forty five patients. The doctors running the clinic had been requested to co-operate so that they carried out a complete cardiological examination on each patient who attended. If any patient was detected having some cardiac abnormality he or she was referred to the author who then re-assessed the candidate and made the necessary documentation. Thus case selection from the patients attending the Sickle Cell Clinic lasted two months during which a total of three hundred and forty patients were screened.

The Patients from the Cardiac Clinic:

A register containing all the patients attending the Cardiac Clinic is kept. This normally contains most of the relevant information including the clinical diagnosis and where done haemoglobin electrophoresis. The author studied this register and extracted all cases where sickle haemoglobin had been detected on electrophoresis. The
clinical diagnosis of the cardiologists who had seen the patients were recorded, so was any other information relevant to the study. Obviously using this method of case finding many of the sicklers with heart disease could have been missed out since haemoglobin electrophoresis is not done as routine in the Cardiac Clinic. However, despite the drawbacks of the method, twenty five cases were found of whom fifteen were SS and ten AS.

In addition nine homozygous sicklers who had been admitted on the medical wards because of sickle cell crisis during the period of the study were included bringing the total to sixty patients.

All the patients included in the study were required to answer a questionnaire which included questions referring to the patients symptomatology with particular emphasis on thrombotic, aplastic or haemolytic crises; and symptoms suggesting respiratory or cardiovascular embarrassment. The patients then underwent a general physical examination with particular emphasis on the cardio-respiratory and other vital organs. Twenty cu.cm. of blood were drawn from each patient for haemoglobin estimation by Sahli method, haemoglobin electrophoresis according to the method of Goldberg (29), erythroyrte sedimentation rate (Wintrobe), hematocrit, anti-streptolysin O titre and several liver function tests.
An ECG was obtained in all patients except five, looking for evidence of left ventricular hypertrophy, ischaemia, or right ventricular hypertrophy. An x-ray of the chest was done on each patient in order to assess presence and degree of cardiomegally, vascular markings and other radiological abnormalities.
CHAPTER V

CLINICAL FINDINGS
Among a total number of 50 patients with haemoglobin SS, the Ganda formed the majority with 44 patients (84%) in this category. This figure was in keeping with the tribal attendance at the sickle cell clinic as analysed by Ndugwa (1972). The other tribes were Dama (2), Nyoro (1), and /Nkole (1), Teso (1), Toro (1). The sex ration was 1:1.

There were 10 patients with the sickle cell trait of whom 6 were Baganda (60%) Nkole (1), Teso (1), and Rundi (2). The sex ratio again was 1:1.

The age distribution of the patients ranged from 2 years to 30 years, thirty of the patients being in the 10 - 15 years age group, 14 in age range 5 - 9 and 11 patients in the 16 - 20 age group. There were only 3 patients aged 26 - 30.

Among the sickle trait carriers 5 were aged below 10, and five were between 10 and 20 years.

Clinical findings among the SS group

General:

By far the commonest complaint at the time of presentation was jaundice which was present in 34 patients (68%). The other common complaints included joints pains (19) bone pains (12), cough and palpitations. The latter 2 were found in 20% of the patients. Chest pain and dyspnoea were uncommon and no patient gave a history of haemoptysis. See table 2.
### Table II

**Presenting Symptoms Among the Homozygous Patients**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of Patients</th>
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<tbody>
<tr>
<td>Jaundice</td>
<td>34</td>
</tr>
<tr>
<td>Joint Pain</td>
<td>19</td>
</tr>
<tr>
<td>Fever</td>
<td>14</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>12</td>
</tr>
<tr>
<td>Cough</td>
<td>10</td>
</tr>
<tr>
<td>Palpitations</td>
<td>10</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10</td>
</tr>
<tr>
<td>Difficulty in breathing</td>
<td>6</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>3</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>3</td>
</tr>
<tr>
<td>Swelling of feet</td>
<td>2</td>
</tr>
<tr>
<td>Leg ulcers</td>
<td>1</td>
</tr>
</tbody>
</table>
In general the patients were underweight and had disproportionately long extremities. Forty six patients (92%) were anaemic at the time of examination, most of them having a haemoglobin of or near 8G% (range 4.5G% – 12.8G%). Forty of the fifty patients were icteric and 28 had obvious bossing. Lymphadenopathy was noted in 20% of the patients. Fever and bone pains were each found in only 10%. Leg ulcers, swelling of joints and peripheral oedema were extremely rare being detected in only 2%.

The sickle cell trait carriers:–

Among the heterozygous sicklers joint pain was interestingly common, being found in 8 out of 10 patients – see table 3. There was a history of sore throat and fever in four patients and in 3 patients cough and palpitations were among the presenting complaints. Dyspnoea and abdominal pain related to liver enlargement was found in two patients. Jaundice, bone pains, chest pain, peripheral oedema and a history of angina were each recorded in 10% of the patients. Clinical examination revealed the presence of anaemia in six of the patients, other findings being fever, oedema and lymphadenopathy each in one patient. The jaundiced patient also happened to have pneumonia and massive splenomegally probably due to tropical splenomegaly syndrome so that these two associated disease could explain the jaundice and the anaemia.
### Table III

Presenting symptoms and signs among the heterozygous patients.

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint pain</td>
<td>8</td>
</tr>
<tr>
<td>Sore throat</td>
<td>4</td>
</tr>
<tr>
<td>Fever</td>
<td>4</td>
</tr>
<tr>
<td>Cough</td>
<td>3</td>
</tr>
<tr>
<td>Palpitations</td>
<td>3</td>
</tr>
<tr>
<td>Breadthlessness</td>
<td>2</td>
</tr>
<tr>
<td>Anaemia</td>
<td>6</td>
</tr>
<tr>
<td>Jaundice</td>
<td>1</td>
</tr>
<tr>
<td>Oedema</td>
<td>1</td>
</tr>
</tbody>
</table>
The remaining five anaemic patients had associated hookworm infestation. The history of joint pains appeared to be related to a previous attack of rheumatic fever because it was associated in a high proportion of patients (40%) with a history of sore throat and fever. The same patients also had a significantly elevated antistreptolysin O titre although as will be discussed later the diagnostic value of this investigation is difficult to assess in a Ugandan population.

**CARDIOVASCULAR FINDINGS**

**The homozygous patients**

Of fifty four patients, thirty four (63%) had a tachycardia despite correction for age. In 36% the pulse was full and bounding while only four patients had a small volume pulse. The systolic blood pressure tended to be low while the diastolic blood pressure was normal. Eight patients had an elevated jugular venous pressure, the elevation ranging between 3 - 5 cm. Significant cardiomegaly was detected in 35 out of the fifty patients (70%). A left parasternal leave thought to represent right ventricular hypertrophy was felt in sixteen patients (32%). A prominent apical impulse was felt at the left anterior axillary line in the fifth or sixth intercostal space in seven patient (14%). There were no thrills. The first heart sound was slightly
accentuated at the apex in twenty two patients (44%). The second sound over the pulmonic area was accentuated in twenty seven patients (64%). There was splitting of the second heart sound in only one patient and the split increased during inspiration and vice versa. A distinct "filling" third heart sound in early patients (22%) and was best heard at the apex. An early systolic ejection click was present over the pulmonic area in one patient. An opening snap of unexplained causation was heard between the apex and left sternal edge in one patient.

Systolic murmurs were common. In 29 patients apical systolic murmurs were heard of which seven were pansystolic and of Grade 3/6 intensity and 22 were mid-systolic ejection type murmurs of Grade 2/6 intensity. Diastolic murmurs were detected in only five patients. In three of these there was a combination of a mid-diastolic murmur and a murmur of mitral incompetence. One patient had aortic regurgitation besides the mid-diastolic murmur and the latter could have been an Austin Flint murmur because there was no opening snap and the first heart sound was not accentuated. The fifth patient had a lone mid-diastolic murmur. This was a short murmur and it was not associated with an opening snap or a loud first heart sound.
Twenty five patients included in this series were attending the Cardiac Clinic at the time of the study. It is interesting to note that these patients had been referred to the clinic by various doctors in the firm belief that they had organic valvular heart disease. Fifteen were homozygous for the sickle cell gene. Of the fifteen patients in the SS group twelve had no evidence to suggest organic heart disease. These patients had been seen by various cardiologist on different occasions who formed the impression that the murmurs heard and the haemodynamic changes detected were all due to anaemia. One of these had a mid-diastolic murmur simulating mitral stenosis, the other had murmurs of mitral regurgitation. Among the remaining three patients in the SS group one had mitral and aortic incompetence and evidence of bacterial endocarditis. The second patient was diagnosed as rheumatic fever with carditis and the third had evidence of deep vein thrombosis and pulmonary embolism on two occasions. She had a Grade 2/6 mid-systolic murmur which is unlikely to have been of rheumatic origin. The other two cases were possibly secondary to rheumatic heart disease. Antistreptolysis O titres were done in all these patients. Elevated values ranging between 300 and 300 Todd units were found in six patients. The results obtained showed very poor correlation with the clinical
impressions. In other words, patients suspected to have clinical rheumatic heart disease did not necessarily have high titres. On the other hand high titres were found in some patients who on clinical grounds were judged to have no organic valvular disease. It has been shown by Stanfield\textsuperscript{36}, that there is a very high streptococcal infection pressure from age of three months in children in Buganda region and higher levels are attained earlier than in most other regions of the world. Thus between three months and six years forty per cent have titres over 200 I.U. High titres over 600 I.U. occur as early as the second six months of life and in 20\% of the age group 1-2 years.

Most physicians are currently aware that the joint pains, fever, cardiomegally, systolic and diastolic murmurs and abnormal heart sounds can mimic rheumatic fever with carditis or chronic rheumatic heart disease with endocarditis. The mere finding of cough, palpitations dyspnoea, abdominal pain and swelling of feet is no longer considered diagnostic of cardiovascular derangement. Tachycardia, an elevated jugular venous pressure and hepatomegally can all be part and parcel of a hyperkinetic circulatory state as obtains in sickle cell anaemia.

It is therefore obvious that the limited diagnostic value of auxilliary investigations like ASOT makes it extremely difficult to establish or refute the presence of cardiac disease in a patient who presents with cardiac
symptoms but who at the same time happens to be a homozygous sickler. The co-existence of valvular heart disease with sickle cell disease is a possibility (84, 85) and in some cases an organic valvular lesion can only be proved or disproved by catheter studies. Since cardiac catheterisation was not performed it is impossible to draw any meaningful conclusions in the present series. The heterozygous patients:

There were ten heterozygous sickle cell patients and all were attending the Cardiac Clinic at the time of the study. At the time of first presentation seven of these ten patients were in congestive cardiac failure as evidenced by a raised jugular venous pressure, an enlarged liver and triple rhythm.

Among the seven with heart failure six had associated hookworm anaemia, with haemoglobins ranging from 5G to 11G%. A seventh patient had pneumonia with right apical consolidation. In these seven patients it was thought that the anaemia and chest infection were responsible for precipitation of cardiac decompensation. Among the remaining three patients one had a patent ductus arteriosus, another had combined mitral stenosis and incompetence with right hemiplegia and the third had a combination of aortic and mitral regurgitation. Antistreptolysin O titres had been done in all the patients. In five values of 200 I.U. or less were obtained. In the remaining five the titres ranged from
400 I.U. to 800 I.U. The electrocardiogram were normal in three patients. T wave inversion in right chest leads was found in two patients. Evidence of left ventricular hypertrophy with strain was a feature in three patients. Two patients showed P‐mitrale. In all these patients the clinical impression was that of organic valvular heart disease or congenital heart disease. After correction of the anaemia and digitalisation the cardiac failure abated but the auscultatory findings persisted. According to Winsor and Burch (12), the Criteria Committee of the New York Heart Association laid down some criteria for the diagnosis of heart disease in anaemia.

These were:–

1. The presence of marked anaemia
2. Disturbance of cardiac function
3. Disappearance of signs and symptoms after relief of the anaemia.

In this series the third criterion was not fulfilled among the seven patients. It is therefore very tempting to assume that these patients presented with cardiac symptoms and signs on the basis of pre‐existing organic heart disease. The anaemia and chest infection appear to have acted as trigger/mechanisms sparking off the development of frank myocardial decompensation.

Cardiomegally was found in six patients. A loud first heart sound was detected in one patient and accentuation of the
second pulmonary heart sound was recorded in four patients. An ejection click was heard at the pulmonary area in one patient and three had a third heart sound. Evidence of left ventricular hypertrophy was present in four patients and in another four a left parasternal heave was detected. Apical pansystolic murmurs of Grade 3/6 intensity were found in six patients and in three patients the murmurs were of an ejection type and of Grade 2/6 intensity. Left parasternal systolic murmurs were heard in three patients and in one patient and Grade 4/6 mid-systolic murmur was heard at the pulmonary area. The latter patient actually had a patent ductus arteriosus which was operated upon. Murmurs of aortic regurgitation and mitral stenosis were each heard in one patient. The heart rates varied between 90 and 100 beats per minute. Systemic blood pressures were normal in all instances.

Other clinical findings

Among the homozygous sicklers there were scanty respiratory signs. Bilateral basal crepitations were found in only two patients and one patient had a pleural rub. Hepatomegally was encountered in twenty-six patients (52%) and the liver enlargement ranged from 3 to 8 centimetres below the costal margin in the mid-clavicular line. Splenomegally was found in eight patients and in four it was
massive extending to eight centimeters below the costal margin. In none of these cases was a liver biopsy done and the cause of splenic enlargement was not established. Fundoscopy was done in thirty three patients. In sixteen patients (32%) there was moderate to marked dilatation and tortuosity of the retinal veins. This finding could not be correlated with the other cardiovascular abnormalities. One patient had optic atrophy and another patient had exudates. These patients were aged thirty and twelve years respectively. Both were anaemic. There was evidence of pulmonary congestion in eight of the ten, heterozygous patients and one of these had in addition consolidation of one of his lobes. Hepatomegally was present in eight and splenomegally in four of the patients.

**Laboratory Findings**

The haemoglobins ranged from 4.5 to 12.8G the majority of the patients (80%) being below 10G%. The haematocrit varied between 25 and 38 volumes percent, being over 33 percent in only six patients. The erythrocyte sedimentation rate was normal in twenty eight patients (56%) and was above normal in only four patients despite the anaemia. There was a leucocytosis (total white blood cell count over 10,000) in thirty eight patients (76%). Anti-
striptolylysis O titres were done in all homozygous sicklers.
Twenty five patients (50%) had values below 200 Todd units. In twelve patients (4.16%) values ranged between 200 - 400 Todd units. Five patients had values between 400 - 800 Todd units. Liver function tests were performed in all patients. High elevated direct bilirubin was the rule. No patient was found to have an elevated alkaline phosphatase to suggest biliary obstruction. This was in keeping with the lack of symptoms of biliary colick or evidence of biliary stones among the patients studied. However, it must be pointed out that liver function studies in this disease must be critically evaluated. The severe anaemia, possible kidney damage and nutritional status of the patient must all be considered. Urine urobilinogen studies are usually of no value for evaluating liver function since there may be severe haemolysis. The indirect-reacting bilirubin is of more importance as an index of haemolysis than of hepatocellular damage. Routine urinalyses were done in all patients. Twenty one (42%) patients revealed a trace of proteniuria. No pyuria was demonstrable in any of the patients. Specific gravity determinations done on twenty patients ranged between 1002 and 1015. Blood urea estimations were normal in all patients.

Among the 48 individuals five had haemoglobin values below 100% and only one patient had a normal haemoglobin.
Leucocytosis was a feature in four patients. The erythrocyte sedimentation rate was markedly elevated in three patients. Haematocrit was above normal in four patients. In fifty percent of the patients the antistreptolysin O titre was below 200 Todd units. In forty per cent of the patients values of 400–800 todd units were obtained. In one patient the result was not available.

**Roentgenography**

Generalised cardiomegally was found in thirty five patient (70%). The enlargement was moderate in twenty patients and slight in the rest. A globular contour was demonstrable in two patients. Four patients showed definite mitralisation. The pulmonary artery was slightly enlarged in three patients and moderately enlarged in twenty three. The pulmonary vascular markings were moderately increased in ten patients and slightly increased in four others. Twenty eight patients had lateral films after barium swallow but in no instance was there any displacement of the oesophagus by a disproportionate enlarged left atrium.

Among the ten sickle cell carriers, cardiomegally featured in five and pulmonary congestion in three. Mitralisation of the left heart border was detected in one patient and in one patient left atrial enlargement was demonstrated. The latter patient clinically had mitral regurgitation and stenosis and a right hemiplegia probably
on embolic basis. But the possibility of A2 predisposing to cerebral thrombosis can not be excluded.

**Electrocardiography**

At least one electrocardiogram was taken on every patient. The striking abnormalities were the frequency of partial right bundle branch block which occurred in sixteen patients, inversion of T waves especially in the right chest leads which was recorded in nineteen patients. Right ventricular hypertrophy was present in seven patients. The PR interval was normal in all cases being 0.12 sec. in 54 and 0.20 sec. in one patient. The QT interval ranged between 0.36 sec. and 0.40 sec. in all patients. In over 90 per cent of the cases QRS duration was 0.08 sec; in two patients it measured 0.07 sec. and 0.1 sec. respectively. Peaked T waves in leads V3 – V5 were present in eight patients and elevated ST segment was noted in three patients in leads V2 – V6. T wave inversion was a prominent feature in the right chest,
CHAPTER VI

DISCUSSION
The homozygous sicklers

GENERAL

Pallor and jaundice are usual findings consequent upon repeated episodes of haemolysis. This becomes particularly striking among those patients who do not have easy access to medical facilities and who therefore miss such protective measures like malarial prophylaxis or blood transfusion when their haemoglobin falls to critical levels. Leg ulcers reputed to be common in this disorder (Klinefelter, (30), were an unusual finding in this study. Hepatomegally is a finding that has been reported on by other writers, Klinefelter(30). It is said to be non-tender and non-pulsatile. From the cardiological point of view hepatomegally is difficult to evaluate as a sign of congestive cardiac failure because chronic anaemia per se can lead to enlargement of this organ. In addition there is generalised reticuloendothelial hyperplasia. Moreover sickling of red cells in the sinusoids with fibrin deposition and thrombosis may lead to obstruction of blood
flow and chronic venous congestion leading to enlargement. However, this is not the whole story because areas of necrosis, infarction and fibrosis have been demonstrated and cirrhosis is not uncommon (Edington\(^{32}\)). Haemosiderosis probably partly secondary to multiple transfusions is occasionally found. These two pathologic processes would be expected to cause shrinkage of the liver.

There is usually slight dependent oedema (Klinefelter\(^{30}\)). This could be due to congestive cardiac failure but as pointed out earlier anaemia by virtue of leading to capillary hypoxia may result in increased exudation of fluid. There may also be a concomitant hypoproteinaemic state.

In Klinefelter's series\(^{30}\), seven of twelve patients had dilatation and tortuosity of the retinal veins. This had been previously reported by Harden\(^{34}\). In this study the same observation was made but no explanation can be found. It could be due to a congenital anomaly or circulatory stasis. One patient had optic atrophy and for this a thrombotic catastrophe of the ophthalmic vessels is postulated. Another patient had exudates without evidence of hypertensive disease, diabetes or renal pathology. These could be secondary to retinal thrombosis, infarction or the result of chronic anaemia.

In his study of twelve patients Klinefelter\(^{30}\), noted that the pulse was normal in rate and volume and not collapsing-
He observed that there is frequently a sinus arrhythmia. Pulsations are prominent in the neck and often in the extremities (Klinefelter\(^{(30)}\), Wintrobe\(^{(35)}\)). In Klinefelter's series capillary pulsation was frequently visible and pistol-shot sounds were often audible over the arteries. In a study of the cardiovascular abnormalities in anaemia, Wintrobe\(^{(35)}\) reported that the praecordium is overactive—a phenomenon which is accentuated by a thin chest wall. A diffuse wavy impulse maybe visible in the fourth, fifth and sixth intercostal spaces to the left of the sternum. In cases with marked prominence of the pulmonary conus, there is a visible impulse and occasionally a bulge in the second and third interspaces to the left of the sternum. The point of maximum impulse is not well localised but is forceful and there is a praecordial lift (Klinefelter\(^{(30)}\)). A diastolic tap is usually present in the pulmonary area. A systolic thrill may be present over the praecordium and over the vessels of the neck, but no diastolic thrill has been noted.

Cardiac hypertrophy due to anaemia has been produced experimentally in dogs by Ludke and Schuller \(^{(37)}\). Cardiac enlargement has frequently been noted clinically and at autopsy in pernicious anaemia and these patients may also have physical signs suggesting valvular disease. In 1931
Ball\(^{(23)}\), reported the first case in which radiological evidence of cardiac enlargement in a young woman with hypochromic microcytic anaemia disappeared after 3 months as the anaemia responded to treatment. The patient also had symptoms of mitral stenosis which also disappeared with cure of the anaemia. Gunerwarden\(^{(38)}\), has reported several cases of chronic hookworm anaemia with cardiac enlargement, systolic and diastolic murmurs at apex and base, and "mild" congestive failure. There was however no objective confirmation by angiography. As the anaemia improved the unusual cardiac signs disappeared. Of his patients one died and at autopsy the heart was found to be hypertrophied and dilated, with normal valves and endocardium. In 1937 Porter\(^{(39)}\), carefully studied cardiac function in severe hookworm anaemia and found cardiac enlargement, confirmed by x-ray, with systolic murmurs. The heart rate and blood pressure were normal and the vital capacity was not reduced. Thus it is apparent that any severe anaemia of sufficient duration may be responsible for the cardiac signs that are present in sickle cell disease. The signs are probably more pronounced and more frequent in sickle cell anaemia because of its chronicity and resistance to treatment.

The stress engendered by prolonged increase in cardiac output due to anaemia is recognized as a possible cause of
cardiomegaly both through dilatation and later hypertrophy. The appearance or exaggeration of angina in the face of anaemia and the capacity of the anaemic state to produce or exaggerate congestive cardiac failure in patients with reduced cardiac reserve is generally recognized. Whether congestive heart failure ever supervenes in chronic anaemic states without some co-existing latent cause for reduced cardiac reserve is still debated but seems theoretically feasible. In 1937, Barteris(41), reported a case of severe congestive heart failure in a 76 year old white male who had a severe chronic post haemorrhagic anaemia from a bleeding peptic ulcer. The patient made rapid recovery when treated with bed rest and iron. No digitalis was administered and several years later there was no evidence of myocardial insufficiency. It has been stated above that in the present series no one was found to have florid congestive cardiac failure. Obviously it is possible these patients had a diminished cardiac reserve which was not detected by the bed-side technique used in this study.

Cor Pulmonale

Subjects with sickle cell disease are prone to small vessel congestion and stasis apparently due to mechanical and viscosity changes and may explain symptomatology. Margolies
(17), alluded to the experience of Henderson who reported that 26 per cent of his 54 patients with sickle cell disorders presented with "Pneumonia". Cough, productive of mucopurulent or blood streaked sputum with chest pain and fever were usual. However, routine examination of sputa were not conclusive. Response to therapy was unsatisfactory and slow clearing of the pneumonia was the rule. Cold agglutinins were absent in the cases tested. Wessler(42), has re-emphasised the problem of differentiating pneumonitis from pulmonary infarction. Cor Pulmonale in the form of multiple pulmonary emboli in non-sickle subjects is recognised (43, 44, 45). Less widely accepted is the tendency for pulmonary thrombosis and infarction to develop in sicklers with the emergence of cor pulmonale. It would appear that certain factors tend to favour sickle thrombosis in the lungs. A variable amount of "physiological shunting" is known to occur within the normal pulmonary vascular bed(46, 47). This shunting implies that some blood normally passes through poorly or non ventilated areas in the lung. Such areas of hypoventilation expose the capillary blood to alveoli in which the oxygen tension is markedly diminished thus potentiating the sickling process. Moreover narrowing of arterioles occurs in hypoventilated zones of the lung again predisposing to vascular stasis, tissue ischaemia, thrombosis and infarction. The effects of the above processes may be further accentuated
in sickle subjects by any situation calling for an increased supply of oxygen to the body such as performance of heavy work or exercise\(^{(43, 49)}\), or any further decrease in the oxygen capacity as may occur rather abruptly in the sickle subject during aplastic or haemolytic crises. Frequent recurrence of such infarctions eventually leads to reduction in pulmonary vascular bed and cor pulmonale. It would appear that cor pulmonale is most prone to develop in those individuals with severe anaemia or sudden lowering of the oxygen carrying capacity and in those with a high percentage of haemoglobin S. The presence of other auxilliary sickling potentiatators such as recurrent or extensive pulmonary infection, acidosis and left ventricular failure serve to make people with sickle cell anaemia more prone to the development of infarction and its ultimate consequences. While stressing the role of increased pulmonary artery pressure in causing right ventricular overload we should not overlook the fact that an increased cardiac output demands increased ventricular work. If this demand be prolonged, dilatation and hypertrophy ensue and eventually ventricular failure\(^{(49, 50)}\). One of the major mechanism of compensation for the low oxygen carrying capacity of the anaemic state is an increase in cardiac output (Hatcher\(^{(51)}\)) and in many sickle subjects this elevated cardiac output and increased ventricular work is demanded continuously due to the prolonged anaemia. This continuous stress leads to enlargement and failure of the right and left ventricles.
Thus two factors are operative in sickle states which may explain the occurrence of right ventricular abnormalities.

1. The cor pulmonale factor of increased right ventricular work due to an increased pulmonary vascular resistance resulting from extensive "sickle infarction" within the lung.

2. The anaemic factor of increased right ventricular load due to prolonged demand for an increase in cardiac output because of protracted anaemia.

Cardiomegally was recorded in thirty five patients. At the apex the first heart sound was louder than normal in twenty three patients. In thirty patients systolic murmurs were heard. This contrasted with Klinefelter's (30), and murmurs were Shubin's series (52) in which systolic murmurs were heard in all cases. It is well know that systolic murmurs may frequently be heard in normal children. The older age group studied in this series probably minimises this source of confusion since 80% of this series were over ten years of age. By means of intracardiac phonocardiography during right heart catheterisation, Feruglio (53) demonstrated a systolic murmur within the pulmonary artery in all sickle patients including those with normal catheterisation findings. Simultaneous phonocardiograms from the overlying anterior chest wall, however, failed to reveal a systolic murmur in over 50 per cent of these patients. Systolic murmurs have
been noted frequently in severe anaemias of various causes\(^{(7,8,30)}\), and have been reported as being most prominent either at the apex or of equal prominence at the apex and base of the heart \(^{(49)}\). In Shubin's series\(^{(52)}\), the murmurs were maximal over the upper left sternal border and a suspicion of interatrial septal defect was entertained. In all the children the cardiac and stroke indices were high suggesting that the murmur was due to increased flow into the pulmonary artery. In the present series the murmur was maximal at the apex in thirty five patients and the major factor appears to be functional mitral incompetence consequent upon chamber dilatation.

A third heart sound in early or mid-diastole was heard in 22\% of the patients in this series. No patient was in cardiac failure and none was on anti-failure regime. This is similar to the incidence in Hunter's series\(^{(8)}\), of non-sickle cell anaemias in which a third heart sound was heard in eight out of 34 patients. Six were however, in congestive heart failure and all the patients studied were over thirty years of age, a time when such sounds are apt to have more pathological significance than in children in whom a third heart sound frequently is a normal finding. None of the patients in the present series was in cardiac decompensation and this could not have been responsible for the third heart sound. In Shubin's series\(^{(52)}\), third "filling" heart sounds were heard in five of the seven
patients studied. This incidence was similar to that reported by Klinefelter (30).

An early systolic click which disappeared with inspiration was a rare finding being present in only one patient. This patient had pulmonary hypertension and radiological evidence of moderate enlargement of the pulmonary artery. Shubin\(^{52}\), reported an ejection click in one of seven patients. The pulmonary ejection click has been explained on the basis of sudden distension of dilated pulmonary artery\(^{54}\). Pulmonary ejection clicks are common in pulmonary hypertension, mild pulmonic stenosis, idiopathic dilatation of the pulmonary artery\(^{54, 55}\), and in some cases of atrial septal defect in the absence of pulmonary hypertension \(^{54, 56}\). In Shubin's case there was no pulmonary hypertension but the ejection click could be explained on the basis of a markedly increased stroke index.

The first heart sound was accentuated in forty four per cent of the patients. A similar finding has been reported on by Klinefelter\(^{30}\). Shubin\(^{52}\), also found a slightly accentuated first heart sound in fifty seven per cent of his series. Accentuation of the first heart sound is a common finding in any hyperkinetic circulatory state like anaemia, and fever. Since 92 percent of this series were anaemic and ten per cent had fever it was not surprising that this auscultatory finding was so common.
Abnormal splitting of the second heart sound was detected in only one patient. This patient had accentuation of $S_1$ and $P_2$ and right ventricular hypertrophy. In normal children and young adults, expiratory splitting may sometimes be heard in recumbency but almost always disappears on sitting or standing up. However, if splitting is also present when sitting or standing, heart disease is likely to be present. Abnormally wide splitting of the second heart sound is most often due to delay in pulmonary valve closure though sometimes it results from premature closure of the aortic valve. It has been pointed out by Leatham and Towers (57), that in normal patients the second heart sound is single or split by 0.03 second or less in the expiratory phase with the split widening to 0.05 second on average during inspiration. In patients with atrial septal defect, however, Leatham and Gray (56), found wide splitting of $P_2$ in the expiratory phase of normal respiration with little or no increase in the inspiratory phase and suggested this as a diagnostic sign of this condition.

The patient in question had no ECG evidence of right bundle branch block. There was no obstruction to right ventricular outflow, nor was there evidence of right ventricular failure. The patient was however febrile and was anaemic with a haemoglobin of 7G and had a bounding pulse with a rate of 110/min. It is possible that those factors led to an
increased stroke volume. According to Turner prolongation of right ventricular systole may result from a relative increase in stroke volume compared with the left as occurs in a left-to-right shunt through an atrial septal defect. Prolonged RV systole would result and consequently pathological splitting. In Shubin's series(52), the second sound over the pulmonic area was split in all his seven patients, with both components prominent. In these patients who had sickle cell anaemia the split in the second sound ranged from 0.03 to 0.05 second during the expiratory phase of normal respiration and increased 0.01 second or less during inspiration. Thus the split tended to be greater than normal during expiration but the increase in the split of the second heart sound during inspiration was less than normal. The majority of his patients had significantly increased stroke indices. He postulated that the filling of the right ventricle was greater than normal during expiration and the increment in filling with inspiration was less than normal.

Accentuation of the second heart sound was present in 54 per cent of the patients studied. Normally in adults $A_2$ is louder than $P_2$ because the diastolic pressure in the aorta exceeds that in the pulmonary artery. In children, $P_2$ may be as loud or louder because the pressure difference is
not so great and the pulmonary artery is relatively large and nearer to the chest wall. The loudness of either component of the second heart sound depends on intra-arterial pressure, dilatation of the main vessel and its proximity to the chest wall.

Among the 27 patients in this series who had \( P_2 \) accentuation, fifteen had radiological evidence of main pulmonary artery enlargement. Accentuation of \( P_2 \) has been noted by other observers in sickle cell anaemia \((7, 30)\). In Shubin's series \((30)\), it was found in all cases. Although in some instances, this accentuation has been attributed to pulmonary hypertension, in Shubin's study the pulmonary artery pressures were normal in all cases. It is possible that other factors like a thin chest wall, or a hyperkiretic circulatory state may be involved.

Diffuse radiological cardiac enlargement has been commonly observed in sickle cell anaemia \((30, 58, 17, 59)\). In many of these cases the heart has been shown to have a globular configuration \((17, 60)\). Typical mitralisation of rheumatic heart disease was reported by Henderson \((31)\) in one third of the patients who had cardiomegally. Leight et al. \((2)\), observed disproportionate left atrial enlargement on fluoroscopy in four of thirteen patients although one was believed to have rheumatic heart disease. Other observers notably Klinefelter \((30)\), and Winsor \((12)\), did not report disproportionate enlargement of the left atrium. All of the
patients in Shubin's series (52) had diffuse cardiomegally and the majority had globular-shaped hearts; none showed disproportionate chamber enlargement. Cardiac catheterisations were performed on all these patients and there was no evidence of mitral valvular disease or intracardiac septal defect. The authors concluded that these radiologic changes were on the basis of the sickle cell anaemia.

An enlarged pulmonary artery was recorded in 26 patients in the present series. The pulmonary vascular markings were accentuated in fourteen patients. Fluoroscopic evaluation was not performed. An enlarged pulmonary artery segment has been reported in sickle cell anaemia by Shubin (52), Klinefelter (30), Margolis (17), and Winsor (40).

Fluoroscopically, the pulmonary artery was enlarged and was observed to pulsate forcibly in all seven patients studied by Shubin (52). Increased pulmonary vascular markings were present in six of the seven patients. No elevation of the wedge pressure was found in any instance. It is of interest to mention that several investigators including Blumgart (61), suggested that the decrease in vital capacity was similar to that which occurred in pulmonary congestion or oedema. It is possible that the increased pulmonary vascular markings are on the basis of increased pulmonary blood volume leading to congestion despite the absence of congestive heart failure.
The other factor which may be operative in the pathogenesis of prominent pulmonary vasculature is thrombosis in situ due to the effect of sickled cells. It has been recognised that pulmonary thrombosis is one of the aetiological mechanisms for the development of pulmonary hypertension. Moser et al. (63), described a patient who presented with a picture simulating rheumatic carditis or rheumatic heart disease with bacterial endocarditis who however, showed an atypical response to therapy. On re-evaluation cardiopulmonary function studies indicated a "diffusion type" pulmonary defect and pulmonary hypertension on exercise. Such a defect implied a marked reduction in the functional pulmonary capillary bed. Fluoroscopy and review of chest radiographs showed enlargement of the pulmonary outflow tract and the main pulmonary arteries. The same authors reported a case who presented with praecordial tightness, chest pain and dyspnoea associated with a non-productive cough. The patient was pyrexial but the chest was clear and there was no murmur or cardiomegally and the second heart sound was not abnormally split. Initial chest radiography showed slight prominence of the pulmonary artery and a repeat x-ray showed a wedge-shaped area of infiltration at the left base. The patient was put on anticoagulants and the areas of infiltration healed with linear scarring.

Various electrocardiographic abnormalities have been described in anaemia in general. The explanation for the occurrence of the changes has attracted the attention of
many observers. Temporary coronary insufficiency leading
to transient myocardial ischaemia has been blamed for
causing ST depression because such changes often revert
to normal with correction of the anaemia. However, Bannerji,
Sanghvi and Misra(64), in their study of 100 patients with
anaemia of various aetiological factors reported that
several cases showed an increase of the abnormalities after
improvement of anaemia. This suggested to them that
myocardial scarring, hypertrophy and consequent relative
ischaemia and strain become manifest in the electrocardiogram
only when initial cardiac dilatation disappears with the
improvement of the anaemia. In sicklers the persistence was
attributed to myocardial scarring due to arterioles blocked
by sickled cells. These authors also suggested other possible
mechanisms for production of the abnormalities. Thus
congestive cardiac failure per se, abnormal thiamine
metabolism as in acute post haemorrhagic anaemia and increased
vagal tone may be operative. Wintrobe(7), referring to the
studies of Carter and Trant and Ellis and Faulkner (65), has
summarised the commonest ECG changes, often reversible, occurring in severe anaemia of any type as depression of ST segment, flat
or inverted T waves but without corresponding changes in QRS
complexes. He states that these ECG changes are similar
to those seen in sickle cell anaemia. Increased work load,
chronic myocardial anoxia, circulatory stasis in the myocardium due to sickling, disseminated occlusion of small pulmonary arteries leading to cor pulmonale may all be operative.

An analytical study of ECG's among 25 patients with sickle cell anaemia by Winsor and Burch (12), revealed no inversion of the T waves in lead I or lead II. Klinefelter (30), found no frank ECG evidence of myocardial damage in his twelve patients with sickle cell anaemia. Zimmerman and Barnett have reported a case of sickle cell anaemia simulating coronary occlusion who at autopsy had no evidence of coronary heart disease. Tung et al. (25), reported prolongation of the QT interval in anaemic patients. Elliot et al. found flat T waves in an anaemic patient with angina whose heart was normal at autopsy. Prolongation of the PR interval was reported by Klinefelter (30), in six of twelve patients. It was postulated that this was due to increased vagal tone. Winsor and Burch (12), reported slight prolongation of the P - R interval in 12 per cent of cases. Lindo and Doctor (67), found a prolonged P - R interval in 29 per cent of patients with sickle cell anaemia.

In Shubin's series (52), and in the present series the P - R interval was normal in all instances according to the criteria of Ashman and Hull (25).
Non specific S-T changes have been reported in sickle cell anaemia. Lindo and Doonoo (67), noted low, inverted or notched T waves in 56 per cent of patients and depressed S-T segments in 26 per cent. Non specific T wave changes were found in 20 per cent of the patients reported by Winsor and Burch (12), while Henderson (13), found evidence of myocardial ischaemia in twelve of thirty patients with three of these patients developing positive T waves following blood transfusion. In a study of one hundred patients with severe chronic anaemias of various causes, Sanghvi et al. (68), noted ST segment depression in fifty four cases and inverted T waves in sixty two. In some of these the persistence of such changes was attributed to irreversible cardiac changes as a result of prolonged hypoxaemia. In the present series S-T segment depression was not encountered in a single instance. These results concur with those of Shubin et al. (52), who found no ST segment depression in a study of seven sicklers. Three of his patients, however, had slight elevation of the ST segment in V4 to V6 together with tall, peaked, T-waves. In the present report three patients had slight S-T segment elevation in V2 to V6 together with peaked T waves. T wave inversion in V1 through to V6 was present in four patients. Twenty eight patients had inverted T waves in leads V1 to V3. The significance of an inverted T wave in leads
V₁–V₃ in my patients is difficult to assess as T wave. may not be upright in these leads in young adults. Lindo and Doctor (67), noted two cases of left ventricular strain in thirty four patients with abnormal electrocardiograms. Left ventricular hypertrophy was reported by Leight et al. (2), in four of thirteen cases of sickle cell anaemia. Shubin et al. (52), noted high QRS voltages over the left praecordial leads in three of seven patients but they confessed that the significance of these high praecordial QRS voltages was uncertain. Sokolow and Friedlander (68), have pointed out that such high QRS voltages may occur normally in children and do not necessarily indicate left ventricular hypertrophy.

In addition to the high QRS voltage in Shubin's three cases, there was S–T segment elevation and tall peaked T waves in leads V₄–V₆. In the present series SV₁ + RV₅ exceeded forty millimetres in eighteen patients. In seven of these patients peaked T waves were noted in leads V₃–V₅. Of these three patients had elevated S–T segment in association with high QRS voltages. The S–T segment elevation in association with the high voltage QRS in these leads is suggestive of diastolic overloading of the left ventricle as described by Cabrera and Monroy (69). Sodi-Pallares et al. (70), however, have pointed out the diagnostic limitations of this finding since it may occur
in the absence of diastolic overloading.

Incomplete right bundle branch block has been previously reported by Leight et al. (2) in one case. Shubin et al. (52) found the same abnormality in three of seven patients with sickle cell anaemia. Incomplete right bundle branch was detected in fifteen cases in the present report, an incidence of 33 per cent. Right ventricular hypertrophy was present in seven patients (15.5 per cent). Shubin et al. (52), found right ventricular hypertrophy in one of seven patients with sickle cell anaemia – an incidence of 14.3 per cent. Yater and Hansmann (15) has described two patients with sickle cell anaemia who died in right ventricular hypertrophy. The cor pulmonale was apparently due to widespread, disseminated thrombotic lesions in small pulmonary arteritis with thickening of the walls and narrowing of the lumen in the vessels. Mild or moderate pulmonary arteritis and thrombosis was found at necropsy in six of nine patients studied by Winsor and Burch (12). The authors however, did not consider the pulmonary lesions which were found of sufficient severity to produce cor pulmonale. Klinefelter (30), in a necropsy study of eleven cases of sickle cell anaemia found no striking changes in the pulmonary vasculature. In Mulago Hospital autopsy series, pulmonary lesions severe enough to cause cor pulmonale are infrequent (Owor – personal communication).
The QRS axis ranged from +30° to +60° in most patients. Among the seven patients with right ventricular hypertrophy the axis varied between +50° and +80°. Shubin (52), in his series found a QRS axis ranging from +30° to 60° in six of seven patients with sickle cell anaemia. One of his patients had right ventricular hypertrophy and an axis of +90°. Winsor and Burch (12) reported one case of right axis deviation in a series of twenty five patients with sickle cell anaemia. This patient was, however, believed to have had a recent pulmonary infarction.

Workers elsewhehere have carried out haemodynamic studies in sickle cell anaemia. Leight et al. (2), found normal pulmonary artery pressures at rest in all but two of thirteen patients with sickle cell anaemia. One exception occurred in a patient who was believed to have cor pulmonale and the other in a patient with concurrent rheumatic heart disease. With exercise however, significant pulmonary artery pressure elevations developed in four of his ten patients. Shubin et al. (52), did not demonstrate any rise in pulmonary artery pressures at rest or with exercise. They noted slight systolic gradients between the right ventricle and pulmonary artery in some instances but this was attributed to increased pulmonary blood flow rather than to pulmonic stenosis. Sproule et al. (64), found normal pulmonary artery pressures at rest in four of five patients with sickle cell anaemia.
Reduced pulmonary and peripheral vascular resistences in severe anaemia have been reported by various authors (3, 4, 5), and it is suggested that the associated hypervolemia is a contributing factor. However, Ferguson et al. (71), demonstrated that hypervolaemia without anaemia does not lower total, peripheral resistance in dogs. Fowler et al. (6), found that anaemic dogs with and without hypervolaemia showed comparable degrees of diminution in total peripheral resistance and this made them to suggest that other factors were responsible for the low resistance. Lowering of peripheral vascular resistance in severe anaemia has been attributed in part to a reduction in blood viscosity. In Shubin's series (52), the pulmonary vascular resistance was normal or low in all of the seven patients at rest and with exercise. In the same patients the total blood volume was markedly elevated while the red cell mass was considerably decreased. The resultant reduction in viscosity of the blood may have been a factor in reducing the vascular resistance. Sproule et al. (62), noted normal pulmonary vascular resistances in the patients in their series in the presence of appreciably elevated cardiac indices. These authors suggested that the total peripheral vascular resistance might be lowered on the basis of extensive arteriovenous anastomoses.

Bramon et al. (4), and Sharpey Schafer (3), have reported on increases in cardiac output in non sickle cell anaemias.
Sharpey-Schafer noted an increase in right atrial pressure in most cases of severe anaemia. Leight et al.\(^\text{(2)}\), however, found normal right atrial pressures in patients with sickle cell anaemia. Bishop\(^\text{(3)}\), on the other hand found lack of definite evidence of raised filling pressure on either side of the heart in patients with chronic severe anaemias from various causes.

In Shubin's series\(^\text{(52)}\), the cardiac indices were elevated in six of seven patients but no elevation of the wedge pressure or the right ventricular end diastolic pressure was found in their series. The heart rates tended to be normal or only slightly increased despite the severity of the anaemia. It therefore appeared that the greatly increased cardiac indices were achieved primarily by an increase in stroke indices. Experimental evidence in support of this was provided by Rushmer\(^\text{(72)}\), in a series of animal experiments in which he demonstrated that there may be a change in the diastolic distensibility of the myocardium without a corresponding change ineffective filling pressure.

Several authors have reported arterial oxygen unsaturation in sickle cell anaemia \(\text{(2, 62, 73, 74)}\), as well as in other chronic anaemias \(\text{(77, 78)}\). Leight et al.\(^\text{(2)}\) noted a fall in the arterial oxygen saturation during exercise in five of twelve patients. In Shubin's study\(^\text{(52)}\), arterial oxygen unsaturation was present in all patients.
but no significant changes in arterial saturation were noted with exercise in five patients. The explanation for the arterial oxygen unsaturation in sickle cell anaemia is not fully established. Several suggestions have however, been advanced. Abnormalities of the oxyhaemoglobin dissociation curve (77, 78, 79, 80, 74, 75), pulmonary diffusion defects (81), and venoarterial shunting in the lungs (62, 79) separately or in combination have been suggested.

The presence in sickle cell anaemia of abnormal oxyhaemoglobin dissociation curve which was shifted to the right was first suggested by Scriver and Waugh (77). These authors thought that the shift of the dissociation curve was not a function of the sickle cell abnormality per se, but probably was on the basis of the anaemic state with a decrease in the pH of the red blood cell occurring due to insufficient oxygenation. Becklake et al. (78), studied four patients with sickle cell anaemia and found the oxygen dissociation curve displaced to the right. They attributed this to the serum environment of the cell. They attributed this to the serum environment of the cell. Fraimow et al. (80) and Rodman et al. (74) also found displacement of the oxyhaemoglobin dissociation curve downward and to the right in patients with sickle cell anaemia and they suggested that this might be related to a reduction in pH of the red blood
cell. Other investigators notably Kennedy and Valtis\(^{75}\) have found rightward displacement of the oxyhaemoglobin dissociation curve in non-sicklaemic anaemias like Addisonian and hypochromic anaemia. They suggested a lowered red cell pH as a possible contributing factor but believed it was not the only factor because some displacement occurred even when results were corrected to a constant cell pH. Fowler et al.\(^{79}\), studied ten patients with sickle cell anaemia. They suggested the presence of a haemoglobin defect in which there is a deficient uptake of oxygen by sickle cell haemoglobin at a given oxygen tension thereby causing a rightward displacement of the oxyhaemoglobin dissociation curve. Moser and Shea\(^{81}\), postulated the occurrence of a pulmonary diffusion defect on the basis of recurrent pulmonary thromboses and infarctions. They drew attention to the accentuation of the pulmonary second heart sound (P₂) and the enlargement of the pulmonary outflow tract as suggestive evidence for associated pulmonary hypertension. In Shubin's seven cases\(^{52}\), however, accentuation of P₂ and enlargement of the pulmonary artery were found in every patient but cardiac catheterisation did not reveal pulmonary hypertension in any instance.

Intrapulmonary venoarterial shunting has been suggested as a cause of arterial oxygen unsaturation. Jensen et al.
(82), however, demonstrated that there was an increase in arterial oxygen saturation following transfusion of normal erythrocytes in patients with sickle cell anaemia. They concluded therefore that there was no significant venous admixture or venoarterial shunting in the lungs. If one assumes the presence of an abnormal oxygen dissociation curve in sickle cell anaemia, however, the transfusion of normal cells might well cause a shift of the curve toward normal and thus account for the higher saturations (44, 45).

From a review of the oxygen dissociation curves presented by Fraimow et al. (80), and Rodman et al. (74), it would appear that venous oxygen saturations were lower than normal in their cases. Brannon et al. (4), studying various non-sicklaemic anaemic patients found the oxygen saturation of mixed venous oxygen saturations were normal or only slightly decreased. Sproule et al. (62), have suggested the occurrence of peripheral arteriovenous shunting of considerable magnitude in sickle cell anaemia. Such shunts, if present, could account for the relatively high venous oxygen saturation which were found in Shubin's series (52), particularly after exercise.
CHAPTER VII

SUMMARY
Cardiovascular findings are described among fifty patients with sickle cell anaemia and ten patients with the sickle cell trait. The majority of the latter category also happened to be anaemic due to other causes notably hookworm infestation. Clinically features of note were:

1. Cough and palpitations and rarity of dyspnoea, chest pain and peripheral oedema.

2. A high frequency of murmurs which were detected in all but fifteen patients. These could have been functional but the presence of co-existing organic heart disease could not be excluded with the method/study used.

3. A third heart sound and accentuation of the first heart sound and the pulmonary component of the second heart sound.

4. X-ray evidence of cardiomegally and increased pulmonary vascular markings.

5. Abnormal electrocardiograms in many cases. Cases are cited to illustrate the possible role of repeated pulmonary infarctions in the causation of cor pulmonale in sickle subjects.

Some of the possible haemodynamic alterations in this disease are outlined.

A more comprehensive study of this subject is required. This should include fluoroscopic screening of the patients, cardiac catheterisation with measurement of intracardiac pressures, blood gas analysis and angiography.
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