

THE PATHOLOGY OF SICKLE CELL HAEMOGLOBIN C DISEASE AND SICKLE CELL ANAEMIA

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The purpose of this communication is to describe the necropsy findings in three patients dying of sickle cell haemoglobin C disease and two of sickle cell anaemia. In southern Ghana there is a high incidence of abnormal haemoglobins in the population, the incidence of haemoglobin S being 18% and of haemoglobin C 12% (Edington and Lehmann, 1954a). Haemoglobin G has also been described (Edington and Lehmann, 1954b), a form of thalassaemia is present (Edington and Lehmann, 1955), and congenital haemolytic icterus has been diagnosed. Little information is available on the pathology of the "mixed abnormal haemoglobin diseases" and, indeed, the discovery of haemoglobin C by Itano and Neel (1950) invalidates much of the pathology attributed to sickle cell anaemia before this time, as sickle cell anaemia was not distinguished from sickle cell haemoglobin C disease. In a previous communication (Edington, 1955) the pathology of sickle cell disease in West Africa was discussed. This term was employed to describe those conditions in which the sickling phenomenon was considered to be a factor in the cause of death. At necropsy two different types of lesion were demonstrable in the spleen. In some cases death occurred in subjects in which the small siderofibrotic type of spleen was found and the cause of death in these instances was considered to be sickle cell anaemia. In others the spleen was grossly enlarged and congested and death was believed to be due to a "sickle cell crisis." It was pointed out that the sickle cell crisis in many instances was not likely to be due to the homozygous inheritance of the S gene, but probably represented a number of conditions in which the sickle cell trait was in combination with other inherited anomalies of the blood.

In an attempt to elucidate the pathology of some of the abnormal haemoglobin diseases paper electrophoresis was performed on the blood of 99 subjects coming to necropsy and the following patterns were seen.

TABLE I
ELECTROPHORETIC PATTERN OF THE BLOOD IN 99 NECROPSIES

AA 68 SS 2	AC 6 SC 3 ASC 1	AS 18 CC 1
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The pattern ASC was due to blood having been transfused before death and is discussed elsewhere (Edington, 1956). A male aged 55 years died from disseminated miliary tuberculosis. The haemoglobin on paper electrophoresis showed the pattern CC. The spleen was grossly enlarged, but the overall pathology of pure haemoglobin C disease was unfortunately obscured by the presence of the widespread tuberculous lesions. The blood of 18 subjects showed the electrophoretic pattern AS and in certain instances the spleen was engorged with blood, the pulp packed with sickled erythrocytes, and haemorrhages were present. The histopathological findings in these spleens appeared to be typical of the sickle cell crisis although free iron pigment in the sinusoidal lining cells was only present in three instances and in

TABLE II
DATA FROM 10 NECROPSIES ON SUBJECTS WITH THE SICKLE CELL TRAIT WITH SPLEENS RESEMBLING MACROSCOPICALLY AND MICROSCOPICALLY THE TYPE SEEN IN SICKLE CELL CRISIS

Necropsy	Age	Sex	Spleen	Liver	Cause of Death
91	36	M	290 g.	Erythrophagocytosis	Undetermined; thought to be sickle-cell crisis
102	4	F	210 "	Congestion	Sudden death, gastro-enteritis
196	20	F	1,380 "	Doubtful changes	Primipara, thought to be sickle-cell crisis
239	9	M	Enlarged	Congestion	Burns
264	18	F	320 g.	Haemorrhages	Primipara, eclampsia
297	3	F	105 "	Congestion	Congenital heart, basal meningitis
309	30	M	495 "	Doubtful changes	Injury, subarachnoid haemorrhage
317	8	M	150 "	Congestion	Gunshot wound
348	5	F	Enlarged	"	Burns
349	1½	M	"	"	Typhoid, kwashiorkor

only one of the liver sections was erythrophagocytosis noted. Doubtful changes were present in two other liver sections. Table II summarizes the findings in these necropsies.

Previously, the cause of death in at least three of these necropsies would have been diagnosed as a sickle cell crisis from the macroscopic appearance of the viscera and the histological changes in the spleen. In the absence of family studies, ante-mortem investigations, and foetal haemoglobin estimations, however, the part played by the sickling phenomenon in the eventual cause of death of these subjects must remain conjectural.

No abnormalities attributable to the presence of the haemoglobin C trait were found in those subjects whose haemoglobins on electrophoresis showed the pattern AC.

Three Necropsy Reports of Cases of Sickle Cell Haemoglobin C Disease

Three females of the Ga tribe aged 19, 19, and 22 years respectively died suddenly in their first pregnancy. The findings are given briefly below.

Necropsy No. 1 (51/55).—A.A.L., a Ga woman aged 19 years, was admitted to the Maternity Hospital, Accra, on January 21, 1955, complaining of rheumatic pains and backache. She was 30 weeks pregnant. Haemoglobin was 8.9 g./100 ml. (grey wedge); sickling positive; no malarial parasites were seen in a blood film; a few pus cells were found in the urine. Her temperature was 99° F., and she was considered to be suffering from pyelitis and treated with penicillin, sulphatriad, and sonalgin.

On February 5 the patient suddenly complained of abdominal pain and collapsed and died.

Necropsy Findings.—The body was that of a reasonably well-nourished African girl. The conjunctivae were slightly jaundiced. The lungs were congested and showed a few scattered haemorrhages. On section the heart appeared normal, but the right side contained much blood. The spleen was the only organ which showed gross macroscopic changes. It weighed 635 g. and was bound down by adhesions. There was much perisplenitis. It appeared to be packed with blood. The cut surface was dark red and dry and the Malpighian corpuscles could not be distinguished. The liver weighed 2,151 g. The mid-femoral marrow was greyish red. The blood on paper electrophoresis showed the pattern SC. A female child weighing 1,875 g. was removed from the uterus. Post-mortem examination of the child revealed no abnormality apart from congestion of the brain. The blood did not sickle, but the electrophoretic pattern was FS.

Histological Examination.—All sections were fixed in formol saline. The sinusoids of the liver were distended and grossly congested. The red cells were sickled and there was marked erythrophagocytosis.

No iron was present and no areas of extramedullary erythropoiesis were seen. The reticulin pattern appeared to be normal. The pulp cords of the spleen were packed with sickled erythrocytes and the appearance was that of lakes of blood widely separating small Malpighian corpuscles. Haemorrhages were present. There were iron deposits in the capsule.

The lungs were grossly congested with scattered areas of oedema and pneumonitis. Haemorrhages were present and there were masses of recently agglutinated erythrocytes in a number of the smaller capillaries.

The kidneys were grossly congested and the proximal tubules were dilated and contained an albuminous exudate. Traces of iron pigment were present in the tubules of Henle's loop. The sternal marrow was hyperplastic, but no iron was present.

Apart from gross congestion of the capillaries, the adrenals, heart, aorta, pancreas, brain, pituitary, stomach, and placenta were normal.

Necropsy No. 2 (P175/55).—A.O.T., a Ga woman aged 22 years, had a sudden attack of "fever" in the 30th week of her first pregnancy. She died while being conveyed to hospital. The father stated that the patient had suffered from rheumatism as a child but had otherwise been well. The deceased was the second of eight children. The other seven children are alive and well.

Necropsy Findings.—The body was that of a well-nourished African female. There was gross pallor of the internal organs with the exception of the liver and spleen. The lungs were pale and grossly oedematous. The heart weighed 200 g. and no abnormality was noted. The liver (1,800 g.) was reddish and the lobular markings were accentuated. The spleen (850 g.) was slaty blue, firm in consistency, and the cut surface was dark red and dry. The sternal marrow was brown and the femoral marrow was red in the mid-shaft. The erythrocytes sickled and the electrophoretic pattern of the haemoglobin was SC.

A female baby weighing 1,868 g. was removed from the uterus. An occasional sickled cell was seen in the baby's blood and the electrophoretic pattern of the haemoglobin was almost entirely F with a faint shadow in the S position. Post-mortem examination of the baby revealed that the liver and spleen were congested, and histological examination showed many areas of medullary erythropoiesis in the liver. No erythrophagocytosis was noted, however, nor did the histopathology of the spleen suggest the presence of an abnormal haemoglobin disease.

Histological Examination.—All sections were fixed in formol saline. In the liver there was marked erythrophagocytosis, almost every Kupffer cell containing numerous sickled cells. There were areas of extramedullary erythropoiesis in the sinusoids. There was iron pigment in the periportal parenchymal cells and some in the Kupffer cells. A reticulin stain was normal. There was a marked cellular infiltration of the portal tracts and numerous white blood cells in the blood.

The histological appearances of the spleen were similar to those described in the first necropsy, but in addition there were areas of extramedullary erythropoiesis and iron pigment was present in the lining cells of the sinusoids.

The small capillaries of the kidneys were markedly congested, with an occasional cast in the collecting tubules and congestion of the glomeruli. No iron pigment was present.

The smaller capillaries of the lungs were packed with erythrocytes and there were areas of patchy oedema. A small infarct was present.

There were degenerative changes in some of the villi of the placenta with marked congestion. The heart muscle was oedematous. The aorta was normal.

Necropsy No. 3 (375/55).—N.S.L., a Ga woman aged 19 years, complained of severe abdominal pain in the fourth month of her pregnancy. She collapsed and died while being conveyed to hospital.

Necropsy Findings.—The body was that of a reasonably well-nourished young African woman weighing 52 kg. The conjunctivae were slightly jaundiced. There was gross pallor of the internal organs with the exception of the spleen. The lungs were grossly oedematous (965 g.). The heart (250 g.) showed no gross abnormality. The liver (1,455 g.) was pale brown. The spleen was enlarged (427 g.) slaty blue, and the cut surface was dark red but was not as dry as the previous spleens. There were enlarged glands at the porta hepatis but the bile ducts were patent and the gall bladder contained watery bile. The kidneys weighed 245 g. The mid-femoral marrow was red. The mother's haemoglobin on electrophoresis was SC. A 14-week male foetus was removed from the uterus. No sickling was detected in the foetal blood.

Histological Examination.—All sections were fixed in formol saline. In the liver there were numerous white and nucleated red cells in the sinusoids and a marked cellular infiltration of the portal tracts. The Kupffer cells were hypertrophied, but erythrophagocytosis was not as marked as in the previous liver sections. There were granules of iron in the periportal parenchymal cells and much iron pigment in the Kupffer cells. A reticulin stain revealed no abnormality. The pulp cords of the spleen were stuffed with red blood cells. There were haemorrhages round the Malpighian corpuscles and iron pigment was present in the cells lining the sinusoids.

The glomeruli of the kidneys were grossly congested and an occasional glomerulus was fibrosed. There was iron pigment in some of the proximal tubules and an occasional cast was present in the collecting tubules.

In the lungs there was congestion of the smaller capillaries and gross oedema was present. A small schistosome nodule was seen.

Some atrophy of the adrenals was noted. In the placenta there were infarcts with a considerable amount of infection. The sternal marrow was cellular but no iron was present.

No gross changes were noted in the aorta, heart muscle, medulla, mid-brain, cortex, pancreas, and pituitary apart from congestion of the smaller vessels which contained numerous white cells.

Two Necropsy Reports of Sickle Cell Anaemia

A girl aged 4 years and a boy aged 3 died suddenly. They were considered to be suffering from sickle cell anaemia and the findings are given briefly below.

Necropsy No. 4 (378/55).—A.K., a Kusasi girl, aged 4 years, was admitted to the Gold Coast Hospital complaining of "fever" and abdominal pains. There were no malarial parasites in the blood film and the temperature was 100° F. The child died shortly after admission.

Necropsy Findings.—The body was that of a thin African girl. The internal organs were pale apart from the spleen. The lungs were congested. The heart (110 g.) was pale. The liver (700 g.) was pale brown and the lobular markings were accentuated. The spleen (120 g.) was slaty blue, firm in consistency, and the cut surface was dry and red. The mesenteric glands were enlarged and the cut surfaces were pink, but no pathogens were isolated on culture. The electrophoretic pattern of the haemoglobin was SS.

Histological Examination.—There was a cellular infiltration of the portal tracts of the liver and some centrilobular degeneration of the parenchyma. Erythrophagocytosis was present but was not well marked. There were massive iron deposits in the portal tracts and parenchymal and Kupffer cells. A reticulin stain showed patchy areas of fibrosis.

The pulp of the spleen was packed with sickled erythrocytes and the appearance was that of lakes of blood widely separating small Malpighian corpuscles. Haemorrhages and typical siderofibrotic nodules were present.

The glomeruli were markedly congested. Much iron was present in the epithelial cells of the proximal tubules and small amounts in the collecting tubules.

The lungs showed congestion of the smaller capillaries only.

The mesenteric glands showed sinus catarrh.

There was some cortical atrophy in the adrenal.

The pancreas, aorta, and heart showed little of note apart from congestion of the smaller blood vessels.

Necropsy No. 5 (195/55).—K.A., an Ewe boy aged 3 years, complained of abdominal pain at 5 a.m. and died the same morning. The father stated that he had been well the previous evening and had had no serious illness apart from minor attacks of "fever."

Necropsy Findings.—The body was that of a well-nourished boy. There was gross pallor of all the organs with the exception of the spleen. The spleen (400 g.) was dark blue and firm. The cut surface was reddish and the Malpighian corpuscles could not be differentiated. The mesenteric glands were enlarged

and *E. coli* and streptococci were grown on culture. No abnormality was noted in the other organs apart from their pallor. The erythrocytes showed sickling and filamentous forms were present. The electrophoretic pattern of the haemoglobin was SS.

Histological Examination.—There were numerous white cells in the sinusoids, portal tracts, and blood vessels of the liver. Erythrophagocytosis by the Kupffer cells was not as marked as usual and was difficult to distinguish. There was much iron pigment in the Kupffer cells and traces in the parenchymal cells.

The spleen was packed with red blood cells and a little iron pigment was present.

In the kidney an occasional glomerulus was hyalinized. Congestion was not a marked feature. No iron pigment was present.

The lungs showed gross oedema.

The brain, heart muscle, mitral valve, and pancreas showed no specific lesions apart from oedema.

The adrenals showed some atrophy.

Discussion

The prognosis in sickle cell anaemia is generally considered to be poor, few children reaching adult life (Lambotte-Legrand, 1951; Vandepitte, 1955). Little information is available, however, regarding the prognosis in sickle cell haemoglobin C disease. During the last year in Accra 40 patients have been seen suffering from this condition. The ages have varied from 3 to 67 years and the haemo-

globin values from 4.7 to 14.7 g./100 ml. Haematological findings in 14 patients suffering from sickle cell haemoglobin C disease are shown in Table III. The condition appeared to be more severe in children and improved with age, this being borne out by the histories given by the adult patients who, excluding pregnant women, appeared to be little inconvenienced by the disease. The spleen may or may not be palpable. Pregnancy would appear to be a definite hazard and catastrophes are liable to occur, usually in the third trimester. However, some women successfully bear children (see Table III), and why the crisis suddenly occurs in some pregnancies is at present unknown, but infection may well be the precipitating factor.

The pathology of sickle cell haemoglobin C disease in the adult is macroscopically similar to the pathology of sickle cell anaemia in the child. In sickle cell anaemia the spleen is enlarged in childhood, gradually becoming fibrosed as thromboses and haemorrhages occur. Siderofibrotic nodules were present in the girl aged 4 years but none in the boy aged 3, the microscopical appearances in this instance resembling those of sickle cell haemoglobin C disease. However, as the spleen was not palpable in a number of adult patients suffering from sickle cell haemoglobin C disease, it is possible that fibrosis and contraction of the spleen may occur, although this type of spleen has

TABLE III
SUMMARY OF FINDINGS IN 14 PATIENTS SUFFERING FROM SICKLE CELL HAEMOGLOBIN C DISEASE

Patient	Tribe	Age	Sex	No. of Children	Hb (g./100 ml.)	R.B.C.	W.B.C.	P.C.V. (%)	Reticulocytes (%)	Bilirubin (mg./100 ml.)	Thymol Turbidity (%)	Alkaline Phosphatase (%)	Thin Film and Remarks
M.M. ...	Moshie	67	M	4	12.5	4.15	6,400	35	3.0	1.5	1.5	5.7	Target cells, spleen not palpable
S.B.M. ...	Ga	44	M	1	14.0	5.03	8,700	41	0.2	0.6	3.5	7.7	" "
N. ...	Ga	40	M	4	14.2	4.54	9,800	40.5	0.4	0.2	2.5	9.0	Target cells, few poikilocytes, scanty normoblasts
A.A. ...	Ga	34	F	7	4.7	1.35	122,000	12	8.4	4.0	—	—	Died in coma in 32nd week of 8th pregnancy 250 nucleated reds/100 whites
K.O.A. ...	Ga	29	M	1	13.3	4.78	11,800	41	2.4	0.3	5.0	7.5	Few target cells and poikilocytes
A.M.K. ...	?	29	M	—	12.3	4.64	8,280	35	1.3	1.2	—	—	Target cells
C.A. ...	Ga	27	M	—	9.5	3.44	6,200	32	3.0	—	—	—	" "
G.O.O.A. ...	Ga	24	M	—	14.7	4.98	8,000	44	5.0	0.2	2.5	5.0	" "
D.V.O.A. ...	Akan	23	F	—	9.1	4.46	5,700	32	0.8	0.3	—	—	Occasional target cell, spleen not palpable
A.K. ...	Ga	20	F	1	7.8	2.72	22,300	19	6.4	0.3	5.0	20.6	Numerous target cells, 15 nucleated reds/100 whites
C.L. ...	Lokko	16	F	—	13.1	4.37	6,400	40	2.4	0.7	—	—	Target cells
H.S. ...	Ga	9	F	—	11.8	4.2	16,000	33	3.2	0.3	—	18.0	Target cells, occasional poikilocyte. 6 nucleated reds 100 whites. Spleen not palpable
N.N. ...	Ga	8	M	—	7.4	2.07	31,400	24	12.4	—	2.5	—	Target cells. Few poikilocytes — occasional normoblast
J.C.Q.T. ...	Ga	7	M	—	12.1	—	15,900	33	1.6	0.8	—	—	Target cells

not yet been described in this condition. A striking distinction between the pathology of these types of abnormal haemoglobin diseases is the amount of iron pigment present in the organs, heavy deposits usually being present in sickle cell anaemia and minimal deposits in sickle cell haemoglobin C disease, suggesting that in this condition the degree of haemolysis is considerably less. This is also borne out clinically. It should be remembered, however, that the three necropsies reported were performed on pregnant women and the foetus may have utilized some of the iron deposited in the maternal organs. It is possible that heavier deposits of iron pigment may be found in the organs of adult males. The pathology of sickle cell haemoglobin C disease would appear to be similar in many respects to the pathology of sickle cell anaemia, and to depend on three factors: (1) A haemolytic element; (2) segregation of erythrocytes in the spleen; and (3) intravascular agglutination of sickled erythrocytes, the crisis probably being precipitated by infection.

Summary

The necropsy findings are given in three pregnant women dying of sickle cell haemoglobin C disease and two children dying of sickle cell anaemia. The histopathological appearances were similar, but the degree of siderosis was less in sickle cell haemoglobin C disease and siderofibrotic nodules were not seen in the spleen. The possibility of the sickle cell trait being in combination with other inherited blood dyscrasias and causing death in Ghana has been discussed.

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Addendum

Since this paper was submitted for publication post-mortem examinations have been performed on two male Gold Coast Africans whose haemoglobins on electrophoresis exhibited the pattern SC. Brief notes are given below.

Case 1.—A Sissala aged 25 years. Macroscopically at necropsy all the organs were congested. The liver weighed 2,500 g. The spleen was bound down by adhesions and was hard and fibrotic (315 g.). It was gritty on section and the cut surface was dark red and dry. Histological examination revealed that there was marked erythrophagocytosis by the Kupffer cells in the liver. Traces of iron only were present in the Kupffer cells and sternal marrow. Siderofibrotic nodules were present in the spleen, which exhibited the typical congestion of the pulp with haemorrhages surrounding the Malpighian corpuscles. The cause of death was considered to be a sickle cell crisis probably precipitated by infection.

Case 2.—K.F., a male African of the Ewe tribe, aged 50 years, was admitted to the Gold Coast Hospital in a comatose condition. He died shortly after admission. The diagnosis of pneumococcal meningitis was confirmed at necropsy. Histological examination of the liver showed gross congestion with sickled erythrocytes and there was iron pigment in the Kupffer cells only. The spleen (548 g.) showed the macroscopic and microscopic appearances already described; siderofibrotic nodules were, however, present. The iron content of the marrow was slightly increased.

These two necropsies confirm that siderosis is slight in sickle cell haemoglobin C disease and that siderofibrotic nodules may occur in the spleen.