

ERYTHROBLASTIC ANAEMIA WITH BONE CHANGES IN EGYPTIAN CHILDREN

POSSIBLE COOLEY'S TYPE

BY

DR. M. DIWANI, M.R.C.P., D.C.H.

(From the Paediatric Department, Faculty of Medicine, Cairo)

Cooley's anaemia is a disturbance of the haemopoietic system characterized by a constant racial and familial incidence, a typical facial appearance, a progressive anaemia with large numbers of nucleated erythrocytes in the peripheral blood, enlargement of the spleen, distinctive changes in the bones and an invariably fatal termination. It was in 1925 that Cooley presented to the American Pediatric Society his first five cases. Later on, in 1927, he wrote his paper on: 'anaemia in children with splenomegaly and peculiar changes in the bones,' with a report of seven cases. In discussing the question of von Jaksch's anaemia, Cooley thought of giving this name to the disease he described, instead of coining a new name. But in 1928 he pointed out that this term was not suitable and he suggested the name 'erythroblastic anaemia' because of the large number of nucleated erythrocytes in the blood. In fact the cases recorded originally by von Jaksch's differ in many respects from erythroblastic anaemia. In von Jaksch's cases large numbers of circulating nucleated erythrocytes were not a prominent or constant feature. The ultimate prognosis is good whereas erythroblastic anaemia is invariably fatal. No mention was made of any Mediterranean ancestry, characteristic facial or skeletal changes either in the original description of von Jaksch or in any subsequent accounts. It is possible, however, that many cases of erythroblastic anaemia had been labelled as von Jaksch's or splenic anaemia, and so lost for future reference.

Although most of the reported cases occurred in children of Mediterranean stock, Cooley and Lee (1932) believe that no great stress should be laid on the limitation of this or any other similar disease to a particular race. Cases have been reported in an English child by Bywaters (1938), in a Chinese girl by Foster (1940), and in a Hindu child by Mukherji (1938). Many cases had a history of brothers or sisters affected. Two cases in identical male twins have been recorded by Whipple and Bradford (1932) and in twin sisters by Baty, Blackfan, and Diamond (1932).

Certain clinical characteristics at once attract attention:

1. The face is mongoloid. This is partly due to a thickening of the malar bones and partly to a muddy yellowish discoloration of the skin.

2. The head is large and irregularly shaped with prominent frontal and parietal bosses.

3. The abdomen is prominent. This results chiefly from the increase in size of the spleen and liver.

4. The heart is enlarged in many instances, a point to which Nemet and Gross (1936) have drawn particular attention.

In most instances the skiagrams of the bones present a typical appearance. The long bones and small bones of the hands and feet are porous looking with sharp trabeculations and thinning of the cortex. When the process is more advanced and the cortex is exceedingly thin, pathological fractures may occur. Baty, Blackfan, and Diamond (1932) have reported pathological fractures in two cases. The cranial vault, in the early stages or in the mild cases, shows only thickening due to increased width of the *diplöe* and thinning of the outer and inner tables. In the advanced cases the profile view of the skull gives the appearance of a surface studded with small radiating spicules, which is sometimes likened to 'hair standing on end.' Somewhat similar changes have been reported in sickle-celled anaemia, in acholuric jaundice, and in erythroblastic anaemia associated with idiopathic steatorrhoea.

Examination of the blood reveals a severe hypochromic anaemia. The haemoglobin may be as low as 10 per cent. and the red cell count one million, or less. The red cells show a marked degree of hypochromia associated with an extreme variation in the size and shape of the cells. The predominating cell is very large with a markedly uneven distribution of haemoglobin. Cooley looks on these irregularly stained erythrocytes as characteristic of erythroblastic anaemia. The only other anaemia of childhood presenting a similar picture is sickle-cell anaemia. Erythroblasts and normoblasts in large numbers are present, but true megaloblasts are not found. Reticulocytes may number from 10 to as high as 30 per cent. There is usually a persistent leucocytosis of from 13,000 to 30,000 per c.mm. Caffey (1937) records the smallest number (4100) and

Whipple and Bradford (1932) the largest (116,000). Cooley believes the most striking feature is the frequent change from granulocytosis to lymphocytosis in the same case at short intervals.

The fragility of the red cells is not increased. On the other hand there may be an increased resistance of the red cells to hypotonic saline solutions. This serves to differentiate Cooley's anaemia from haemolytic (acholuric) jaundice in which the resistance is diminished.

The indirect van den Bergh reaction is positive, the icterus index is raised and the urobilinogen in the urine and stools is increased. The haemolysis, however, is not as marked as in congenital haemolytic jaundice or sickle-cell anaemia.

As regards etiology Cooley originally believed that the disease was haemolytic in nature and that the congenital characters placed it in the same class as acholuric jaundice and sickle-cell anaemia. Cooley and Lee do not now consider the disease as primarily haemolytic but rather that it is a dyshaemopoiesis due to a metabolic fault, congenital or racial, which also affects bone formation. The apparent relationship is nearer to pernicious anaemia, i.e. a defect of maturation exists and the immature cells which can be utilized only to a limited extent tend to accumulate at the site of production. If this

thesis be correct Cooley's anaemia might be classified under the deficiency anaemias.

The bone marrow of these cases is said to be indistinguishable from that of pernicious anaemia, i.e. megaloblastic. Sternal marrow puncture performed on two of the author's cases revealed an erythroblastic reaction. Fawdry, of the Cyprus Medical Service, in a personal communication showed the author films of the sternal marrow of the twenty cases that he investigated in Cyprus and in all of them the reaction was erythroblastic.

The course of the disease is slow and progressively downhill. The shortest duration is seventeen months. The majority die before nine years, but some cases survive into adult life. Death usually results from infection.

Treatment is entirely symptomatic. Large doses of iron and liver proved useless. Splenectomy is not followed by improvement. A normoblastic crisis occurs after the operation. Wollstein and Kreidel (1930) described cases in which, after splenectomy the nucleated red cells numbered twenty times as many as before operation, and this state was still present four years after operation. Blood transfusion produces only a transient relief of symptoms. Nittis (1937) has lately reported good results with quinine therapy.

Case reports

FIRST CASE IN A GREEK CHILD

V. P., a female Greek, aged four and a half years, had been noticeably pale since two years, and two weeks before admission she had become progressively paler with bleeding from nose and had a mild pyrexia at the same time. The mother gave a history of two sons dying of severe anaemia at an early age. When examined it was obvious that the child was severely anaemic. The spleen and liver were definitely enlarged. There was oedema of feet and face. Examination of the blood revealed the following:

Hb., 20 per cent.; red cells, 870,000 per c.mm. The red cells showed polychromasia ++, poikilocytosis +++ and anisocytosis ++++. The erythrocytes showed the typically irregular distribution of the Hb. (fig. 1). Leucocytes 7800 per c.mm. Differential count: neutrophil segmented, 41 per cent.; lymphocytes, 48 per cent.; monocytes, 6 per cent.; neutrophil myelocytes, 4 per cent.; myeloblasts, 1 per cent.; normoblasts, 25 per cent., and erythroblasts, 9 per 100 leucocytes. Reticulocytes were 5 per cent. Fragility test was normal. Van den Bergh reaction showed a delayed direct result. The icterus index was 10 units. Radiographic examination of the bones presented a typical porous looking appearance of the long, small and flat bones, with sharp trabeculations and thinning of the cortex (fig. 2). The skull,

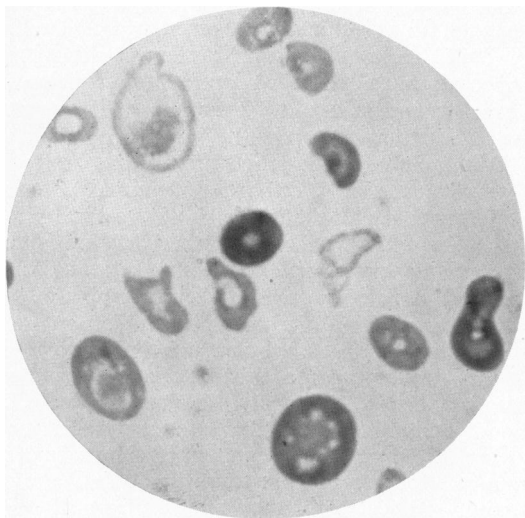


FIG. 1.—V. P. Blood film showing marked anisocytosis and poikilocytosis. Note the irregular distribution of Hb.



FIG. 2.—V. P. Skiagram of the bones of foot showing marked osteoporosis.

though showing medullary thickening and thinning of the tables, did not present the radiating spicules so characteristic of the advanced stage of the disease.

The child died at home two days after the examination and no autopsy was done. I had the opportunity of examining his brother and the blood picture revealed nothing of particular interest.

SECOND CASE IN AN EGYPTIAN CHILD

M. M., a male, genuine Egyptian, aged ten years, admitted to the Children's Hospital for marked pallor. No family history of importance was

obtained. Clinical examination revealed a mongoloid facies; severe pallor; marked enlargement of the spleen which reached as far down as the pelvis; liver was felt four fingers' breadth below the costal margin. Examination of the blood revealed the following: haemoglobin ranged between 20 and 25 per cent. throughout a period of six months in spite of massive doses of iron and liver extracts and repeated blood transfusions. Red cells showed marked anisocytosis, poikilocytosis, punctate basophilia and irregular distribution of the Hb. (fig. 3). Erythroblasts amounted to 25 and normoblasts to

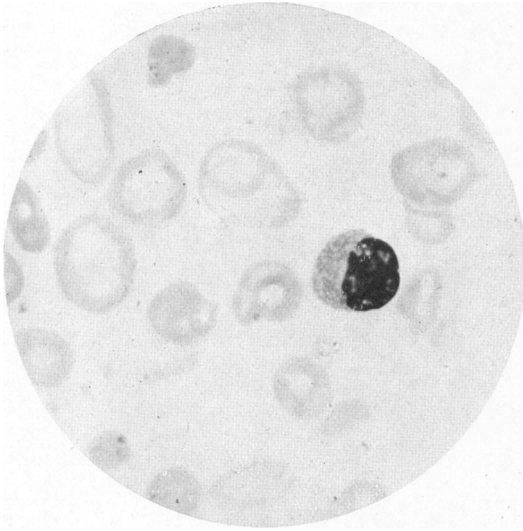


FIG. 3.—M. M. Blood film showing anisocytosis, poikilocytosis, irregular distribution of and Hb. erythroblastaemia.



FIG. 5.—M. M. Skiagram of hand showing osteoporosis of small bones.

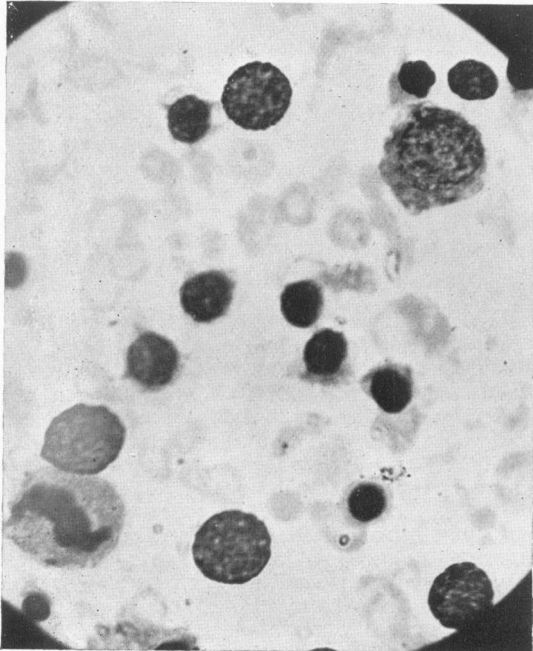


FIG. 4.—M. M. Bone marrow smear showing erythronormoblastic reaction.

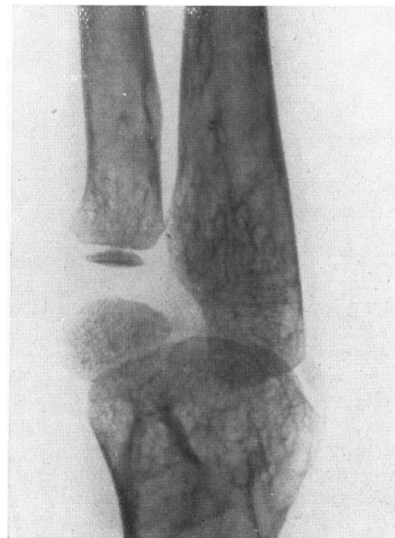


FIG. 6.—M. M. Skiagram of elbow showing osteoporosis at the ends of the bones.

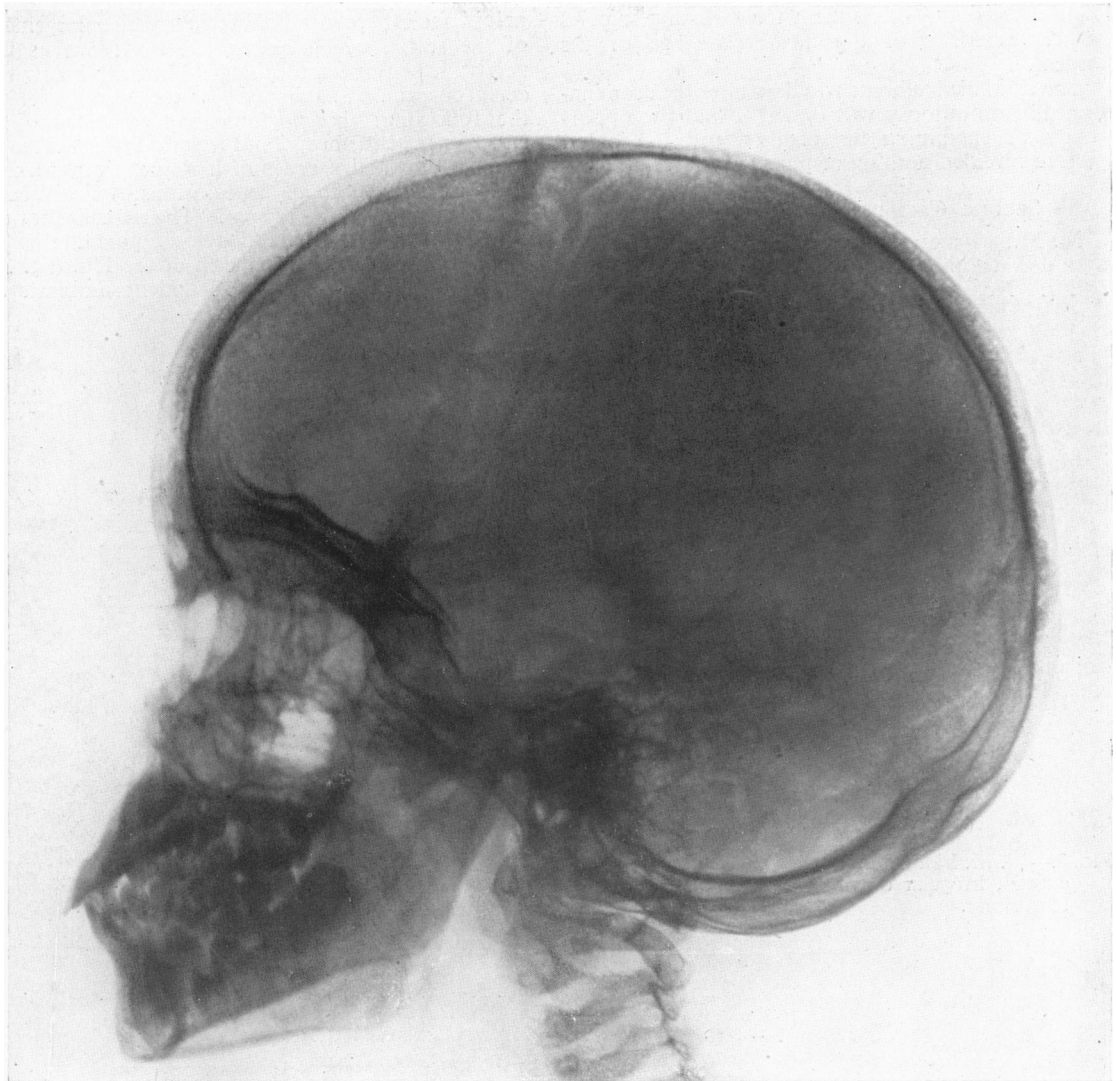


FIG. 7.—M. M. Skiagram of skull showing thickening of diploë and thinning of inner and outer tables.

23 per 100 leucocytes. Leucocytes were 9600 per c.mm. Differential count: myeloblasts, 1 per cent.; premyelocytes, 4 per cent.; myelocytes, 12 per cent.; metamyelocytes, 10 per cent.; band forms (stab cells), 9 per cent.; mature polymorphs, 41 per cent.; eosinophils, 5 per cent.; monocytes, 2 per cent.; lymphocytes, 16 per cent.; reticulocytes were always below 5 per cent. Sternal marrow puncture revealed a marked erythroblastic hyperplasia (fig. 4). Van den Bergh gave a delayed direct reaction. The icterus index was 10 units and on one occasion rose to 50 units. Fragility test: red cells started haemolysis at a concentration of 0.25 (i.e. increased resistance). Blood films were repeatedly negative for malaria. Wassermann reaction negative. Stools repeatedly negative for parasites and ova. X-ray examination of bones revealed marked osteoporosis (fig. 5, 6); the skull showed thickening of the diploë and thinning of the tables (fig. 7). X-ray examination of the heart showed marked dilatation, especially in the transverse diameter (fig. 8).

Nine months have passed since child was first

seen. He is still alive and so far has failed to respond to haematinics and repeated transfusions.

THIRD CASE IN AN EGYPTIAN CHILD

S. S., an Egyptian female, aged six years, was admitted for severe pallor and abdominal distension. Examination revealed a typical mongoloid facies, a markedly enlarged spleen reaching as low down as the pelvic brim and a moderately enlarged liver reaching four to five fingers' breadths below costal margin. Blood examination: Hb., 23 per cent.; red cells, 1,130,000 per c.mm.; leucocytes, 19,200 per c.mm.; myeloblasts, 0 per cent.; premyelocytes, 2 per cent.; myelocytes, 4 per cent.; metamyelocytes, 7 per cent.; staff, 10 per cent.; segmented, 35 per cent.; lymphocytes, 37 per cent.; monocytes, 1 per cent.; eosinophils, 4 per cent. There were 45 nucleated reds (practically all normoblasts) for each 100 leucocytes. Reticulocytes, 5 per cent. Platelets, 56,500 per c.mm. Fragility test: haemolysis started at 0.3 per cent. saline solution, i.e.

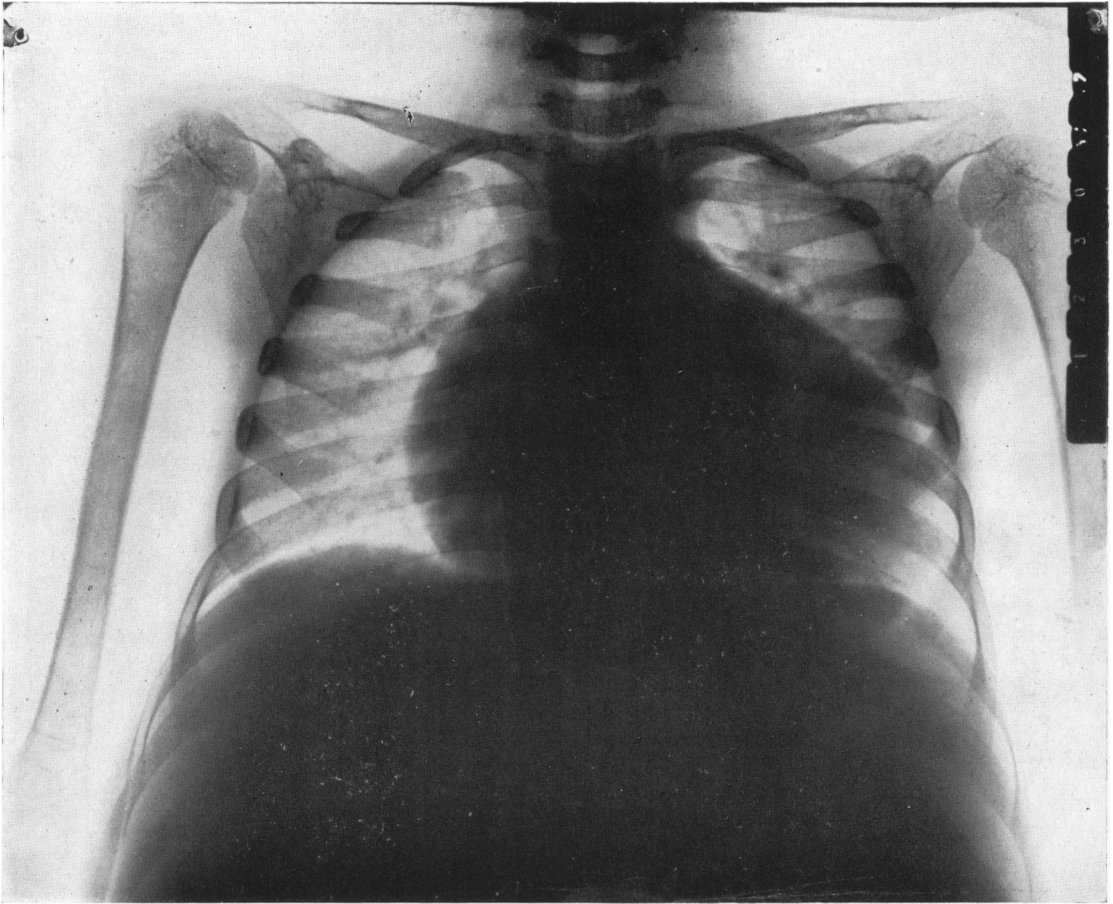


FIG. 8.—M. M. Note marked enlargement of heart, and osteoporosis of humerus, scapula, clavicle, and ribs.

increased resistance. Icterus index was 20 units; Van den Bergh gave an indirect positive result. Bleeding time was 4 minutes, coagulation time 4 minutes. Wassermann reaction negative. Blood

film was negative for malaria. Stools were repeatedly negative for parasites. Bone marrow puncture revealed a definite erythroblastic reaction going to hypoplasia.



FIG. 9.—Case 3. See text.



FIG. 10.—Case 3. See text.

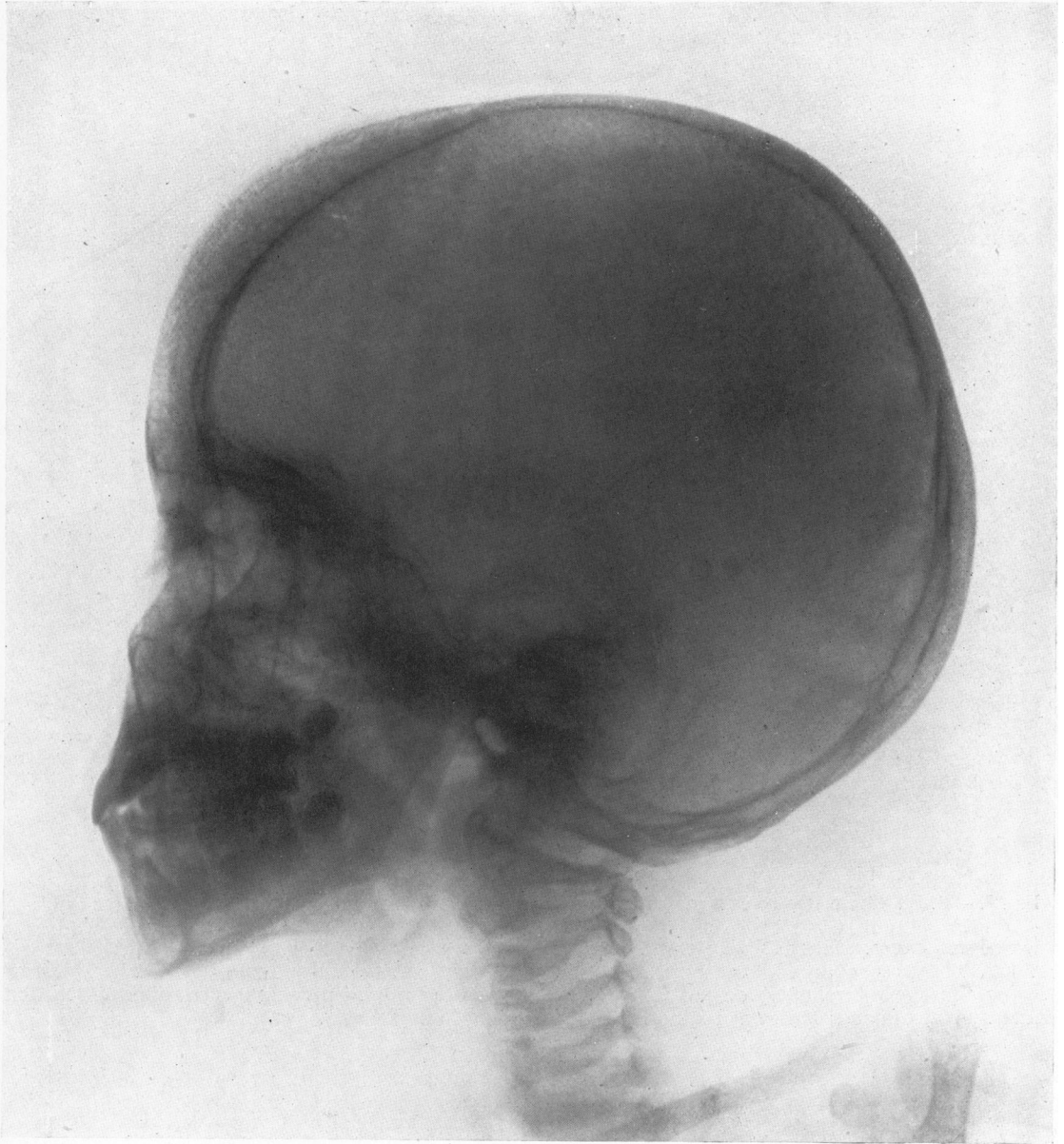


FIG. 11.—Case 3. See text.

X-ray examination of bones showed marked generalized osteoporosis, and the skull showed typical 'hair on end' appearance. The heart showed enlargement of all chambers (fig. 8, 9, 10, 11).

Summary

1. Three cases of Cooley's syndrome are described. Two of them occurred in genuine Egyptian children, the third in a Greek child.
2. Sternal marrow biopsy done in two of the cases revealed a marked erythroblastic hyperplasia.
3. Marked enlargement of the heart was noticed in two of the cases.

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