A CASE OF FANCONI'S ANAEMIA

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In 1927 Fanconi described under the title 'familial pernicious-like anaemia in children' three brothers with fatal refractory anaemia associated with pigmentation of the skin, testicular atrophy, microcephaly, underdevelopment, squint, and increased tendon jerks. In the same paper he reported a case with muscular dystrophy, pigmentation, testicular hypoplasia, microcephaly, and anaemia of a similar type which remitted spontaneously while the patient was in hospital. The parents of this child were said to be brother and sister. Sporadic and familial cases presenting the triad of severe refractory anaemia, pigmentation, and congenital anomalies have been noted by Uehlinger (1929), Émile-Weil (1938), Hjorth (1940), van Leeuwen (1933), Dacie and Gilpin (1944), Estren, Suess, and Dameshek (1947), and Diamond (1950). A further case showing anaemia, pigmentation, congenital dislocation of the hips, and an anomaly of the left kidney is reported here.

Case Report

M.S., a girl, was born on April 8, 1943. She had always bruised easily but otherwise made normal progress until she began to walk at 2 years of age, when a waddling gait led to the diagnosis of congenital dislocation of both hips. She was admitted to hospital on numerous occasions for treatment of this condition. In December, 1946, she had measles followed by bilateral otorrhoea; she afterwards lost weight, and her general health, which had previously been good, deteriorated. A blood count in May, 1947, during one of her admissions to hospital, showed Hb. 68% (Haldane); red blood cells, 3.3 m. per c.mm.; C.I. 1.0; slight anisocytosis; white blood cells, 5,100 per c.mm. (polymorphs 39%, lymphocytes 59%, monocytes 1%, basophils 1%). A blood transfusion brought the haemoglobin up to 78% (Haldane) and improved the child's general condition.

In April, 1950, at the age of 7 years, she was admitted to Westminster Children's Hospital complaining of fatigue and breathlessness on going uphill. Her legs had always ached a great deal but this aching had become more marked recently. There had been two

<table>
<thead>
<tr>
<th>Date</th>
<th>Hb. (Haldane) (°O)</th>
<th>R.B.C. (m. per c.mm.)</th>
<th>W.B.C. (per c.mm.)</th>
<th>Polymorphs</th>
<th>Lymphocytes</th>
<th>Monocytes</th>
<th>Platelets (per c.mm.)</th>
<th>Reticulocytes (%)</th>
<th>Blood Transfusion</th>
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<tr>
<td>6.4.50</td>
<td>28</td>
<td>1.1</td>
<td>4,400</td>
<td>2,200</td>
<td>2,200</td>
<td>—</td>
<td>40,000</td>
<td>2</td>
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<tr>
<td>12.4.50</td>
<td>45</td>
<td>2.2</td>
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<td>—</td>
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<td>—</td>
<td>72,000</td>
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<td>14.4.50</td>
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<tr>
<td>18.4.50</td>
<td>78</td>
<td>3.6</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>50,000</td>
<td>—</td>
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<tr>
<td>5.5.50</td>
<td>56</td>
<td>—</td>
<td>4,600</td>
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<td>2,300</td>
<td>200</td>
<td>—</td>
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</tr>
<tr>
<td>15.5.50</td>
<td>48</td>
<td>—</td>
<td>3,600</td>
<td>1,200</td>
<td>2,200</td>
<td>200</td>
<td>—</td>
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<tr>
<td>12.6.50</td>
<td>48</td>
<td>—</td>
<td>3,200</td>
<td>1,100</td>
<td>1,900</td>
<td>200</td>
<td>—</td>
<td>18 oz.</td>
<td>—</td>
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<td>13.6.50</td>
<td>66</td>
<td>—</td>
<td>5,000</td>
<td>2,000</td>
<td>2,700</td>
<td>300</td>
<td>98,000</td>
<td>3</td>
<td>—</td>
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<td>20.6.50</td>
<td>58</td>
<td>2.8</td>
<td>3,200</td>
<td>1,200</td>
<td>1,900</td>
<td>100</td>
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violent epistaxes in the past six months and her appetite had been poor in the past few days. The mother had just recently noticed the pallor: she said that the child became very brown in the sun but had not thought the pigmentation to be otherwise remarkable. The patient was backward at school and this was attributed to her deafness. Apart from occasional attacks of bronchitis, and the measles and otorrhoea noted above, there had been no previous illness. The parents and the patient’s brother, aged 4 years, were quite well. The maternal grandmother was said to have had pernicious anaemia and diabetes but otherwise there was no family history of blood disease or congenital deformities. The parents were first cousins, and their blood groups, determined subsequently, were: father group O, Rhesus negative, genotype OO; mother group A, Rhesus positive, genotype A0O or A1A2. The patient was group A1, Rhesus positive, genotype A1O.

On examination she was seen to be a pale child, looking rather older than her 7 years (Fig. 1), with brown pigmentation over the whole body, darkest over the flexures, the neck, the genitalia, and around the eyes, and fading to a brownish-yellow over the face, arms and legs. There was a bruise on the inner side of the right ankle and a few purpuric spots in the right antecubital fossa where blood had been taken an hour earlier. She was thin and undersized, very nervous, and tended to cry easily. Her height was 35-5 in., and her weight 38lb. 8oz. The head circumference was 19-5 in. The temperature was 99-4, pulse 140, and respiration 28. The ear drums were normal. There was no pigmentation in the mouth; the tongue was clean, and there was a small bleeding point on the right tonsil. There were a few carious teeth. There was a loud systolic murmur, maximal at the apex, and also heard posteriorly over the right lung, but no clinical evidence of cardiac enlargement. There was a convergent strabismus; the fundi ocularum were not pigmented and the discs were pale. All tendon jerks were brisk but there was no clonus. The liver and spleen were not palpable and there were no enlarged lymph nodes. There was a sacrococcygeal sinus.

The results of investigations at this stage were as follows.

A blood count gave Hb. 280 (Haldane), R.B.C.s 1·1 m. per c.mm., C.I. 1·3, packed cell volume 11%, mean cell volume 100 c.μ, mean cell haemoglobin concentration 35%, reticulocytes 2%, W.B.C.s 4,400 per c.mm. (polymorphs 51%, lymphocytes 49%), platelets 40,000 per c.mm. There was no blood and no excess urobilinogen in the urine. There was occult blood in the faeces, and 84 mg. % urobilinogen.

A sternal marrow puncture was performed by Dr. J. G. Humble on April 6, 1950, and reported by him as follows:

The total nucleated count was 45,000 per c.mm. A differential count on 500 cells showed myeloblasts 0%, promyelocytes 2%, neutrophil myelocytes 11·8% (4% of these showed mitoses), neutrophil metamyelocytes 10·6%, eosinophil myelocytes 0·8%, neutrophil polymorphs 17·6%, eosinophils 1·4%, lymphocytes 31·8%, plasma cells 1·8%, monocytes 2%, reticulo-endothelial cells 1·2%, no megakaryocytes, haemocytoblasts 0·4%, proerythroblasts 0·2%, normoblasts A 4·6%, normoblasts B 10-8% (6% of these showed mitoses), normoblasts C 3%. There was arrest of maturation of the red and white cell series at the early normoblast and promyelocyte level.

On April 6 the child was given a transfusion of one pint of fresh blood, and a further pint was given on April 14. On April 17 the haemoglobin was 78% (Haldane). From then until June 12, when she was given another 18 oz. of blood, the haemoglobin fell at the rate of about 1% per day. She was discharged home on June 20, to be observed by her own doctor. The haematological course is shown in the accompanying table.

After the first two transfusions the pyrexia and tachycardia gradually settled down, the child’s general condition improved, and she became more cheerful. Occasional crops of petechiae in the mouth and on the trunk and limbs, and bleeding from the gums and right tonsil were noted during the first month. There was haematuria between April 4 and April 20. She had an epistaxis on April 16, and bleeding from the right ear on April 23, after which there were no haemorrhagic

Fig. 1.—The patient.
manifestations except for slight oozing from the gums. There were a few urticarial spots on the right cheek and left wrist on April 15. Ferrous sulphate, a proteolysed liver extract ("hepamino"), folic acid, and vitamin B12 had no effect on the anaemia or the reticulocytes.

Results of other investigations were as follows:

- Serum bilirubin level 0·0 mg. %; serum sodium level 324 mg. %; bleeding time (Duke) 5 minutes; clotting time (Lee and White) 4 minutes; capillary resistance test (Hess) positive; red cell fragility normal. An adrenaline response test (Benda, 1930) showed the usual immediate increase in circulating leucocytes due to contraction of the spleen after the administration of 13 minims adrenaline subcutaneously. There was no second rise of myeloid cells attributable to bone-marrow stimulation.

A 'hyalase' subcutaneous pyelogram showed a normal kidney and ureter on the right but no dye was excreted on the left. A retrograde pyelogram on the left side outlined an apparently normal but presumably unfunctioning kidney lying in the pelvis. Radiographs of all bones showed no abnormality apart from the dislocated hips and some coarse trabeculation of the bones of the feet. A chest radiograph was normal.

**Discussion**

That this condition is inherited is suggested by its occurrence in siblings (Fanconi, 1927; Émile-Weil, 1938; Hjorth, 1940), in an incestuous brother and sister mating (Fanconi), and in cousin marriages (Dacie and Gilpin, 1944; and this case). In Hjorth's cases the brother had a clubfoot and the sister dislocation of the hip. One maternal cousin had a congenital dislocation of the hip and another had a clubfoot, absent calcaneus, and a dislocated patella. A paternal cousin had absent thumbs and was mentally defective. Estren and Dameshek (1947) consider that the cases of familial hypoplastic anaemia described by them may belong to the same group. There is support for this view in the cases described by Dacie and Gilpin: one brother had anaemia, pigmentation and congenital defects, whereas the other had anaemia only. These authors also mention that a sib of the mother and a sib of the father had married one another and produced a child who died of aplastic anaemia.

Anomalies of thumbs, kidneys, and testes have been frequently reported in these cases. In the four cases previously described in which the blood group has been mentioned it was group A as in this case.

Haemosiderosis of the internal organs is a usual finding at necropsy, but the skin pigment appears to be melanin (Fanconi, 1927; Uehlinger, 1929). Melanosis of the intestine was noted by Hjorth (1940).

This condition must be distinguished from Fanconi's syndrome of rickets, aminoaciduria, and glycosuria (Fanconi, 1936) which is quite a different disease.

The prognosis is bad: all patients previously described showing the full syndrome have died except the case of Estren et al. which was slightly improved during a follow-up period of several months after splenectomy, and Fanconi's case mentioned above where the anaemia appeared to be transient. Splenectomy had no effect in van Leeuwen's case apart from a temporary rise in platelets. The spleen was removed in Dacie and Gilpin's case showing anaemia only and the patient ultimately recovered (Dacie, 1950). Splenectomy was followed by some improvement in one case of familial hypoplastic anaemia described by Estren and Dameshek. In the case described here splenectomy might be considered since the bone-marrow picture and the result of the adrenaline response test are consistent with a splenic haematomata. Repeated blood transfusion to keep the patient alive in the hope of a remission is the only other treatment which offers any prospect of success.

**Summary**

A case of Fanconi anaemia is described showing pigmentation of the skin, congenital dislocation of the hips, an abnormality of the left kidney, convergent strabismus, a sacrococcygeal sinus, under-development, mental backwardness, and anaemia with granulopenia and thrombopenia. The parents were first cousins. The aetiology, prognosis, and treatment are briefly discussed.

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**References**

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