Constitutional Anemia (Fanconi’s Syndrome) and Leukemia in Two Brothers

By R. H. Cowdell, P. J. R. Phizackerley and D. A. Pyke

In some congenital blood disorders, such as erythroblastosis fetalis and hemophilia, a great deal is known about the mode of hereditary transmission. The syndrome described by Fanconi of bone marrow hypoplasia with congenital defects is a less common condition which has been postulated but not proved to be due to a recessive gene. Leukemia is a disease, the etiology of which, despite recent advances, remains unknown. There are, however, sufficient reports of multiple cases within a family to suggest the possibility of some hereditary predisposition.

Fanconi’s syndrome may be considered for the moment in its two separate parts. The first of these is bone marrow hypoplasia with resultant anemia, thrombocytopenia and often leukopenia. The second part consists of other congenital defects which are not absolutely uniform from case to case but presents a fairly well-defined pattern usually including certain features such as microcephaly and genital hypoplasia. The present paper records the history of two brothers who had similar although not identical congenital defects, the type of which was such that had both suffered from hypoplastic anemia no doubt could have been cast on the diagnosis of Fanconi’s syndrome. Only one of them developed anemia of this kind; the other died of acute leukemia. Two previous reports have been found of Fanconi’s syndrome and leukemia occurring within one family, but in both instances the relationship was that of cousin and the leukemic cousins were without congenital defects.

Case Reports

Case 1 (R. I. 119884)

A. M. was born prematurely, with a birth weight of 31/2 lbs. Apart from an unexplained hematemesis at the age of 11 his progress was not remarkable. He lived an active life, working as a builder’s assistant and playing soccer. In January 1950, at the age of 22, he became pale, tired and breathless on exertion. In February 1950 he was admitted as an emergency case under the care of Professor L. J. Witts, with ten days’ history of pneumonia unresponsive to chemotherapy. His pneumonia proved to be of virus type and gradually subsided during auromycin treatment.

He was a small man, 61 inches (155 cm.) in height, weighing 98 lb. (44.5 Kg.). He was obviously profoundly anemic. There was no peripheral lymphadenopa-
thy, the liver and spleen were not clinically enlarged, and there were no cutaneous petechial hemorrhages. He was not jaundiced, the tongue was well papillated and there was no koilonychia. The skin of the neck and axillae showed a light brown pigmentation, and scattered throughout the pigmented area were numerous small oval areas of unpigmented skin. The thumbs were deformed, especially the left owing to congenital hypoplasia of the phalanges (fig. 1). The feet were normal. No cardiovascular abnormality was found apart from a rough systolic murmur, maximal in the pulmonary area, and large fundal hemorrhages to the lateral side of both discs which had not caused visual loss. On abdominal palpation the right kidney was thought to be enlarged; the left kidney could not be felt. In addition to his small stature there was other evidence of endocrine dysfunction. Although the growth of the beard was good, the axillary hair was scanty and the pubic hair of feminine distribution. The penis was small and the testes atrophic.

The following investigations were carried out:

*Peripheral blood:* Hemoglobin 3.9 Gm. per 100 ml. (26 per cent Haldane). Red cells 1.3 million per cu. mm. MCV 107 c. μ. MCH 30 γγ MCC 28 per cent. Hematocrit 14 per cent. Aniso-poikilo-macrocytosis. Mean cell diameter 8.09 μ. Leukocytes 800 per cu. mm.; neutrophils 96, lymphocytes 640, monocytes 64. Platelets 5000 per cu. mm. Bleeding time (Duke) 15 min. Coagulation time (Lee and White) 8 min. Prothrombin index 90 per cent. Sedimentation rate (Wintrobe) 80 mm. in 1 hour. The Coombs' test and the Wassermann and Kahn reactions were negative. The cold agglutinin titer was 1:64.
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Sternal marrow: This was obtained with great difficulty and contained extremely few cells—

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<td>Cells in mitosis</td>
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<td>Unidentified cells</td>
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Other investigations: A radiograph of the skull showed a very small pituitary fossa, the size of that in a newborn child. In the abdomen, there was a large right and very small left kidney shadow. The hands showed congenital brachydactyly and abnormal metacarpal bones, with no evidence of delay in epiphyseal fusion and no osteoporosis.

No abnormality was found in plasma protein or bilirubin level, serum calcium or alkaline phosphatase, or in a histamine test meal or insulin tolerance test. The basal metabolic rate was -20 per cent; serum cholesterol 254 mg. per 100 ml.; and 17-ketosteroid excretion 6 mg. in 24 hours.

A diagnosis of constitutional anemia (Fanconi's syndrome) was made.

Progress: The patient was treated with repeated blood transfusion, receiving 40 pints (21.6 liters) during the period of approximately one year that he survived. In view of the hypogonadism, and in the hope of improving his anemia, a trial was made of testosterone propionate by injection and later of oral methyl testosterone; this was unsuccessful. The leukocyte count gradually fell to 150 per cu. mm. including 50 polymorphs. In February 1951 he died from bronchopneumonia.

Autopsy report: A young man with grayish-brown pigmentation over the neck, axillae, perineum and nipples. In the pigmented areas were scattered small oval white patches. Axillary hair was scanty and pubic hair of female distribution, but the subcutaneous fat was of male distribution. The hands were small and narrow, with bilateral hypoplasia of the thumb phalanges and dorsal displacement of the joints. There was some atrophy of the thenar muscles. Confluent bronchopneumonia was present in the left lower lobe, with less dense involvement of all other lobes and fibrinous pleurisy. The heart was small (180 Gm.) with a soft myocardium and right ventricular dilatation. There was hypoplasia of the entire aorta, with a degree of coarctation which would admit only the tip of the little finger beyond the origin of the innominate artery. Petechial hemor-
rhages were present in the mucosa of the entire intestinal tract. The liver was firm and of uniform golden brown color. The spleen was small, with a dark brown cut surface. The right kidney was enlarged (190 Gm.) and had two renal arteries and two ureters. The lower ureter crossed deep to the other at the pelvic brim to reach the left side of the bladder. There was no left kidney. The testes were of infantile size. There was phimosis with some balanitis. There was almost no red marrow in the skull or femur. That of the vertebrae, ribs and sternum was of pale brown color. The brain was small with slight convolutional atrophy, particularly in the para-sagittal region.

Histology: The bone marrow showed severe orthoplastic hypoplasia with erythrophagocytosis and siderosis (fig. 2a). In the liver there was moderate fatty change, with marked siderosis, which was also present in the spleen (fig. 2b and c). Apart from its small size, the pituitary appeared natural, as did the thyroid. Little lipoid was present in the suprarenal glands. The testes were hypoplastic with no complete spermatogenesis and there was thickening of the lamina propria (fig. 2d). There was a relative but not gross increase of interstitial cells. The cutaneous pigmentation was due to an increase of melanin in the basal layer of the epidermis and numerous melanophores in the superficial dermis. No remarkable features were seen in the kidney, while the lungs showed an acute pneumonic process.

Case 2 (R. I. 16/4950)

G. M., a clerk, aged 27, the brother of A. M., was admitted under the care of Dr. A. M. Cooke in October 1952. He had become pale and noticed breathlessness on slight exertion for two weeks, and there was a brisk epistaxis one week before admission. He bruised abnormally easily. His previous health had been good and he took part in sports, although for some reason unknown to himself he had been rejected for military service. He shaved every second day, and said that his libido was normal.

He was a small but well-built pale man, very like his brother in appearance; 59 inches (150 cm.) in height, weighing 99 lbs. (45 Kg.). The skin was soft and smooth like a child’s, with brown mottling of the neck and axillae and dark pigmentation of the nipples and genitalia (fig. 3a and b). The fingers were long and thin, with very short first metacarpals and wasting of the right thenar eminence. The hair distribution was of male type. The genitalia were very small, the testes being 1 cm. and the penis 2 cms. in length. The temperature was 99.2 F., pulse 110, and blood pressure 140/70.

A systolic murmur was audible at the apex. There was no clinical evidence of enlargement of liver, spleen or lymph nodes. There was a small ecchymosis on the right elbow and capillary nevi on the medial border of the right foot. No abnormality was detected in the nervous system or optic fundi. There was epiphora of the right eye due to a blocked lacrimal duct.

The following investigations were performed:

Peripheral blood: Hemoglobin 6.3 Gm. per 100 ml. (43 per cent Haldane).
Fig. 2.—(Case 1.) A. Staining method: Hematoxylin and eosin. Section of sternal marrow to show hypoplasia (× 320). B. Staining method: Hematoxylin and eosin. Section of spleen to show hypocellularity of medulla and a small poorly-defined follicle (× 320).
Fig. 2.—C. Staining method: Perl's reaction. Section of spleen showing siderosis (X 320).
D. Staining method: Hematoxylin and eosin. Section of testis showing hypoplasia of seminiferous tubules and thickening of lamina propria (X 200).
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Red cells 2.2 million per cu. mm. (14 per cent nucleated), with marked anisocytosis and poikilocytosis. MCH 32 y.

Leukocytes .......................................................... 4300 per cu.mm.
Neutrophils ......................................................... 730
  Myelocytes ..................................................... 50
  Band form ..................................................... 200
  Segmented ................................................... 500
Lymphocytes ...................................................... 1750
Monocytes ........................................................ 400
Turek cells ....................................................... 50
Blast cells ....................................................... 650
“Monocytoid cells” ........................................... 600

The blast cells had single moderately prominent nucleoli but could not be classified with certainty. The monocytoid cells were variable in character. The entire neutrophil series was abnormal in that granulation was scanty or in some
cases absent. Platelets were scanty and of abnormal morphology (15,000 per cu. mm.). The bleeding time (Duke) exceeded 15 minutes. During a tourniquet test, 12 petechiae appeared in 2 minutes' compression.

_Sternal marrow:_ The marrow (fig. 4a) was hypercellular, with 43 per cent of primitive "blast" cells with irregular morphological features. They had rounded nuclei but were commonly lobed or partially segmented. The chromatin pattern was fine with one or two exceptionally large and well defined nucleoli. The cells appeared to shade into the monocytoid series. Azurophil granules were present in the cytoplasm of many of them. No separable granulocytic series could be identified and the metamyelocytes and neutrophil polymorphs seen were frequently gigantic and bizarre in form. Erythropoiesis was distorted with disturbance of nuclear division as shown by multinucleate cells and nuclear irregularity in the more differentiated forms. Basophilic stippling was common. Few megakaryoblasts and no mature megakaryocytes were seen.

It was concluded that while the blast cells in the peripheral blood were suggestive of monocytoid type, the marrow findings were in favor of a granulocytic origin for this leukemic process.

_Other investigations:_ A radiograph of the skull showed the pituitary fossa to be small. No abnormality was seen in the chest, and a radiograph of the abdomen showed both kidneys to be present and of normal size. In the wrists, all epiphyses were fused, and no bone abnormality was seen.

The serum proteins, thymol turbidity, colloidal gold test, sodium, potassium and alkaline phosphatase and the blood urea were all within normal limits. The fasting blood sugar was 92 mg. per 100 ml., and the urinary output of 17-ketosteroids was 4.8 mg. in 24 hours. A radioactive iodine tracer test was consistent with normal thyroid function. Output of follicle-stimulating hormone (assayed
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Fig. 4.—(Case 2.) A. Staining method: Giemsa. Sternal marrow smear (X 580). B. Staining method: Hematoxylin and eosin. Section of liver showing fatty change and small groups of leukemic cells in sinusoids (X 320).
by Dr. I. C. Gilliland) was between twice and four times the upper limit of normal.

**Progress:** After admission he ran a low fever. Transfusion of three pints (1.6 liters) of blood was followed by a reaction including mild hemoglobinuria, and a few days later a severe epistaxis occurred. A petechial rash appeared on the arms, and bruises were produced by trivial injury. A second transfusion of 5 pints (2.7 liters), given three weeks after admission, raised the hemoglobin to 12.7 Gm per 100 ml., but after this there was rapid deterioration with hematemesis, hematuria, and development of a hematoma of the tongue, until death after right hemiplegia occurred 4 weeks after he was admitted.

**Autopsy report:** A short young man with plentiful subcutaneous fat, particularly noticeable in the region of the nipples and mons pubis. There was brownish rather mottled pigmentation of the neck and shoulders, while hair distribution was of male type. The hands were small, with short first metacarpals, and hypoplasia of the thenar eminence, much more severe on the right. The tendons of the flexor pollicis brevis and adductor pollicis were present but the muscles were extremely hypoplastic. There was a hematoma of the right side of the tongue, and several patches of interstitial hemorrhage in the lungs. Subpleural and subendocardial petechial hemorrhages were present. The heart was small, with a thin myocardium, but otherwise natural. Many hemorrhagic areas, some associated with acute erosions, were found in the stomach, and there was subperitoneal hemorrhage around the ileo-cecal junction. The liver had a mottled pallor in keeping with fatty change or leukemic infiltration. The spleen was not enlarged (110 Gm.) but the pulp was soft and pink in color. There was a zone of dull red color, apparently due to infiltration, surrounding the mucosa of the renal pelvis and extending to involve the upper third of the ureter. Many petechial hemorrhages were present in the bladder. The testes were very small and firm. The thyroid was small, weighing only 8 Gm., and the hypophysis was very small (100 mg.), while the suprarenals were of natural appearance. The femoral marrow was of reddish-brown color through the whole length of the shaft, with discrete patches of darker red suggestive of hemorrhage. The marrow of the skull, sternum and humerus was of similar appearance.

The brain was very small (1160 Gm.) but edematous, with extensive subarachnoid hemorrhage over the posterior part of the left frontal and anterior part of the left parietal lobe. The left cerebral hemisphere was larger than the right, with flattening of the convolutions and uncinate grooving. Coronal sections showed a large intracerebral hemorrhage in the left frontal and parietal regions, which was undoubtedly the immediate cause of death.

**Histology:** The bone marrow was hypercellular and the cytology was in keeping with the previous biopsy findings. The splenic follicles were small and widely spaced, with diffuse leukemic infiltration and very dense siderosis of the medulla. The liver showed moderate fatty change at the periphery of the lobules, plentiful siderosis of the Kupffer cells, and scanty periportal leukemic infiltration (fig. 4b). The cytology of the pituitary was natural. The thyroid appeared inactive, with increased interstitial fibrous tissue. Little lipoid was present in the adrenal cortex. The testes were hypoplastic, with no complete spermatogenesis. The cutaneous pigmentation was of the same type as in case 1. The kidneys showed
peripelvic hemorrhage and leukemic infiltration, while the lungs were congested with areas of interstitial hemorrhage and early bronchopneumonia.

**DISCUSSION**

Fanconi observed a “familial pernicious-like anemia” in three brothers, each of whom developed anemia and thrombocytopenia, cutaneous pigmentation, microcephaly without mental impairment, retarded growth, testicular hypoplasia, exaggerated deep tendon reflexes and a convergent squint. As a result, the term Fanconi’s Syndrome has come to be used to describe a combination of familial hypoplastic anemia associated with congenital abnormalities. Unfortunately this, like so many eponyms, is liable to cause confusion in view of the probably more widely known Fanconi’s, or de Toni-Debré-Fanconi, syndrome of rickets resistant to vitamin D, low serum inorganic phosphorus, and renal glycosuria. As is stated by Reinhold, Neumark, Lightwood and Carter, Benjamin recorded three cases of severe refractory anemia with underdevelopment of the skeleton, mental backwardness and hypoplasia of the genitalia, and there are grounds for suggesting that he has prior right to eponymous immortality for his description of this condition. Similar anemia may occur in the absence of other congenital anomalies. Eight such cases among children in two families were described by Estren and Dameshek.

Reinhold et al. reviewed 21 published cases of Fanconi’s syndrome and reported two more. Their own patients were sisters aged 12 and 10 years with hypoplasia of the bone marrow and various abnormalities, who had three other siblings with congenital abnormalities but without blood changes. Their father, an uncle and two first cousins were microcephalic. Another cousin died at the age of 20 years of monocytic leukemia said to be of the paramyeloblastic type.

The two patients reported in the present paper were the eldest of five children. Interviews with their parents revealed that case 2 (G. M.) was jaundiced at birth for two or three days, while this was not noticed with the others. At 7 years he was given thyroid treatment owing to “failure to thrive,” but his subsequent development was satisfactory. Two younger sisters are well, while the fifth sibling was a boy with a large head and spina bifida who died at 9 months. Both their father and mother, who are not related, are of small stature but otherwise of normal physique, and inquiries have elicited no other known instance of congenital defect or blood disease in the previous two generations.

The types of congenital defect occurring in this syndrome are fairly constant. Thus the hypoplasia of the thumbs present in both A. M. and G. M. was also seen in the case of Emile-Weil and is comparable with the congenital absence of the thumbs in one of Fanconi’s patients, and with the almost complete absence of these digits in the case reported by Estren, Stuess, and Dameshek. Uehlinger reported a rudimentary thumb, and van Leeuwen absence of the first metacarpal bone. Pigmentation and genital hypoplasia were present in nearly all the recorded cases. The pigmentation has usually been generalized, although often with vitiligious patches. It was localized in the cases of Baumann and Reinhold et al. With the exception of Uehlinger who found that the discoloration in his case was due to iron-laden macrophages, other authors who have examined the skin reported that the brown color resulted from an
Microcephaly is a common finding. The present two patients had small heads but this did not reach a pathologic degree. There was no mental defect, as in most of the reported cases, although backwardness was reported by Beautyman and Baumann. The patients of Eehlinger and van Leeuwen, like our patient A. M., had only one kidney, while Dacie and Gilpin found a horseshoe kidney in one case. Retarded growth and obesity are frequent. Of conditions not seen in the present patients, convergent strabismus has been reported several times and a wide variety of skeletal abnormalities may occur.

There is thus a general pattern in the type of defect found, although it is not easy to crystallize this into a series of requirements for diagnosis. Some degree of anterior pituitary insufficiency associated with general and particularly gonadal underdevelopment is sufficiently frequent to be regarded as a diagnostic criterion, while microcephaly and cutaneous pigmentation are usually present. Neither in our cases nor in those previously reported can all the major defects be related to hypopituitarism, and the high output of follicle-stimulating hormone in our second case is an anomalous feature. It is interesting to recall that Burger and Witts found that men with unexplained anemia were often of asthenic habit and looked younger than their age. Snapper, Groen, Hunter and Witts described five cases of histamine-fast achlorhydria with hyperchromic anemia or subacute combined degeneration in patients with pituitary and gonadal insufficiency. These presented later in life than is usual for Fanconi's syndrome, the youngest being 44 years of age, while Fanconi's syndrome is normally apparent in childhood or not later than the beginning of the third decade. In most other reported examples of pituitary deficiency with anemia, except those of the Fanconi type, the anemia was hypochromic and responded to iron.

The anemia in Fanconi's syndrome is always related to profound bone marrow hypoplasia and it is usual to find an associated thrombocytopenia with some times also leukopenia, so that Leitner, Britton and Neumark refer to it as pancytopenic rather than hypoplastic or aplastic. The mean cell diameter is commonly 8 μ or more, and the color index is often high, but anisocytosis and poikilocytosis are usually less severe than in pernicious anemia in relapse. Reinhold et al discuss the possible contributory relationship of hemolysis, and conclude that it is generally absent, with the notable exception of one of the cases of Dacie and Gilpin. In this patient there was in vitro autohemolysis similar to that found in paroxysmal nocturnal hemoglobinuria. It was suggested that the rapid return of anemia after blood transfusion in their other two cases might have been due to hemolysis, and the interval between transfusion became considerably greater after splenectomy. The rate of blood destruction after transfusion in our patient A. M. was slightly in excess of that expected but not sufficiently so to give clear indication of a hemolytic process. The degree of siderosis in the liver, spleen, bone marrow and other organs was severe, but not more than could be accounted for by the quantity of blood transfused.

The familial nature of Fanconi's syndrome is implicit in its definition, and Reinhold et al make out a good case for the condition being determined by a recessive gene. There is also no doubt that leukemia may affect more than one member of a family. Guasch, in addition to reviewing the relevant literature, reported on the results of a questionnaire sent to hematologists which revealed
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39 examples of consanguineous leukemia among 8586 leukemic patients, an incidence of 0.45 per cent, but the nature of any hereditary process which may be concerned is unknown. Leukemia occurring in the family of patients with Fanconi's syndrome appears to have been previously reported only twice. In both instances the relationship was that of cousin and neither of the leukemic patients was observed to have congenital abnormalities. As has been noted, one of these cases was a first cousin of the patients described by Reinhold et al.18 This young man, whose history is recorded in detail by Fairburn and Burgen,16 had monocytic leukemia preceded for several months by recurrent furunculosis and he eventually developed extensive nodular and ulcerated leukemic infiltration of one arm. Cutaneous involvement of this type is not known to occur in leukemia of other than the monocytic variety. Baumann2 reported that a cousin of his patient with the Fanconi syndrome developed acute myeloid leukemia.

It is not suggested that there is necessarily any profound significance in this association of leukemia and the familial anemia of Fanconi based on such scanty observations as one instance in brothers and two in cousins, but it does provide a little more evidence bearing on the question of the connection between certain cases of leukemia and aplastic anemia. We have seen several patients who initially had all the features of aplastic anemia, in whom repeated marrow puncture in the early stages of their disease showed uniformly severe hypoplasia so that the possibility of having obtained an unrepresentative sample was virtually eliminated, and who later developed frank leukemia. Three such cases were mentioned by Adams.1 We have no evidence whether these should be regarded as cases of leukemia with an initial phase similar to aplastic anemia, or whether they indicate that true aplastic or hypoplastic anemia may pass on into leukemia, but the association is clearly one deserving consideration.

SUMMARY

Two brothers physically very alike became ill in their third decade, one with severe bone marrow hypoplasia and the other with acute leukemia. Both died and the autopsy findings are described.

The two shared certain congenital defects, notably short stature with small heads, cutaneous pigmentation, pituitary and genital hypoplasia, and deformity of the thumbs. The brother with hypoplastic anemia also had aortic hypoplasia and his left kidney was absent.

No previous report has been discovered of the association of Fanconi's syndrome (of bone marrow hypoplasia with congenital defects) and leukemia with similar congenital defects in brothers. In two reports of leukemia affecting cousins of patients with Fanconi's syndrome, the leukemic cousins were without congenital defects.

SUMMARY IN INTERLINGUA

Duo fratres—physicamentemente muto similis—deveniva malade in lor tertica decaede: le un con sever hypoplasia del medulla ossee, le altere con acute leucemia. Ambes moriva. Le constatationes autopic es describite. Le duo fratres habeva certe defectos congenite in commun. Istos includheva specialmente un curte statura con parve capites, pigmentation cutanea, hypo-
plasia pituitari e genital, e deformitè del pollici. Le fratè con anemia hypoplastic habeva etiam hypoplasia aortic e su ren sinistre esseva absente.

Un examinè del litteratura revelava nulle previe reporto de un par de fratres, del quales le un habeva hypoplasia del medulla ossee con defectos congetite (syndrome de Fanconi) durante que le altere habeva simile defectos congetite associate con acute leucemia. Il existe duo reportos de leucemia in patientes cuje cosinos habeva le syndrome de Fanconi, sed in iste casos le leucemia non esseva associate con defectos congetite.

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