PANCYTOPENIA WITH CONGENITAL DEFECTS (FANCONI'S ANAEMIA)

BY

ROBERT MCDONALD and BASIL GOLDSCHMIDT

From the Department of Child Health, University of Cape Town and Groote Schuur Hospital, Observatory, Cape Town

(RECEIVED FOR PUBLICATION OCTOBER 12, 1959)

Fanconi (1927) drew attention to a syndrome of pancytopenia associated with congenital defects which has since become known as Fanconi’s anaemia. Reports of other cases followed from different parts of the world, including one from South Africa (Kessel and Cohen, 1953), but the condition remains a rare one.

We report here five cases of pancytopenia with accompanying congenital anomalies, seen in Cape Town. Some unusual features are mentioned and it will be shown that the syndrome may not be recognized when the associated defects are inconspicuous.

Case Reports

Case 1. D.G., a white boy, was first admitted to Groote Schuur Hospital in January, 1951, at the age of 6 years.

From the age of 14 months he had had recurrent attacks of bronchitis. He had also undergone tonsillectomy, right inguinal herniotomy and dilatation for anal stenosis. For three months before admission he had been pale, anorexic and irritable.

His parents were in good health. Their first child, a girl, was said to have had unilateral polydactyly on the radial side, persistent patency of the ductus arteriosus and subacute bacterial endocarditis and had died at the age of 6 years.

During the patient's 20 admissions to hospital the following features were recorded: he was pale and underweight for his age, weighing 33 lb. at 6 years, and was judged to be of normal intelligence. Microcephaly—head circumference was 19\(\frac{1}{2}\) in. at 8 years; microphthalmia, absent testes and hyperpigmentation of the skin were noted. Both thumbs were grossly deformed (Fig. 1) and attached to his hands by soft tissue only. Radiographs showed maldevelopment of the metacarpals and phalanges of the thumbs and retarded ossification of the carpal bones (Fig. 2). The radial pulse was not palpable at either wrist, but the pulsation of the ulnar arteries was forceful. Femoral artery pulsation was normal. A systolic murmur, maximal in the pulmonary area, was heard at each admission. A systolic thrill in the second and third left interspaces and in the neck was occasionally recorded, but radiographs of the chest, screen examination of the heart and electrocardiogram were thought to be within normal limits.

![Figs. 1 and 2.—D.G., aged 7 years. Note abnormality of thumbs and delayed ossification of carpal bones.](http://adc.bmj.com/)

367
The original blood findings were as follows: Haemoglobin was 7-3 g.%: the peripheral blood smear showed anisocytosis and poikilocytosis of the red cells; white cells numbered 12,250/c.mm., of which 80% were lymphocytes, 18% neutrophils, 1% monocytes and 1% eosinophils; his blood group was A Rh positive and his E.S.R. 34 mm. (Westergren) in the first hour. Bone marrow in January, 1953 was normal and a platelet count at the same time was 142,000/c.mm. Reticulocyte counts varied between 0-5 and 5%.

The anaemia was unresponsive to haematinics and was uninfluenced by splenectomy, which was performed in April, 1953. Blood transfusions became necessary at increasingly short intervals. In June, 1955 he was admitted for blood transfusion and shortly afterwards developed pneumococcal meningitis from which he died. The occurrence of petechial cutaneous haemorrhages is first recorded at this time, when a platelet count was 3,000/c.mm. No autopsy was performed.

Case 2. R.W., a white girl, was first admitted to Groote Schuur Hospital in July, 1953 at the age of 6 years.

It was not made known to us at the time that a super-numerary thumb had been amputated when she was 18 months old. Since the age of 3 her parents had noticed that she bruised very easily and she had had recurrent respiratory infections, each temporarily responsive to sulphadiazine, of which her father, a farmer, kept a stock primarily intended for veterinary use. Increasing pallor, fatigue and weight loss had been noticed for two months.

Both her parents and three younger siblings were reported to be well, although it was recalled that her mother had been anaemic in her youth.

On examination the child was judged to be of normal intelligence. She was pale and thin, weighing 40 lb. and petechial haemorrhages were noted in skin, mucous membrane of pharynx and ocular fundi. The Hess test for capillary fragility was positive. A soft systolic murmur, maximal at the cardiac apex, was constantly heard throughout her subsequent admissions. A mid-diastolic murmur, described as blowing in character, was recorded at her first admission and again six months later, but on no other occasion.

The peripheral blood showed a haemoglobin of 4-5 g.%: the smear showed anisocytosis and poikilocytosis of the red cells, and the white cells were 1,360/c.mm. (lymphocytes 78%, neutrophils 16%, staff cells 4%, monocytes 1% and eosinophils 1%). The platelet count was 8,000/c.mm., reticulocyte count 1-8%. E.S.R. 95 mm. (Westergren) in the first hour and the blood group A Rh positive. The bone marrow, frequently examined, was thought on one occasion to show megaloblastic hyperplasia, but on all other occasions, apart from the constant observation that platelets were scanty and megakaryocytes absent, it was thought to be normal. Radiographs of chest, pelvis and long bones, screen examination of the heart, electrocardiogram, blood Wasserman reaction, osmotic fragility of red cells, serum bilirubin, direct Coombs test, Paul-Bunnell test, liver function tests, plasma proteins, fractional test meal and intravenous pyelogram all resulted in normal findings.

A diagnosis of anaemia, neutropenia and thrombocytopenia, possibly due to sulphonamide toxicity, was made and during 14 subsequent admissions there was no reason to alter it. In retrospect, however, it should be mentioned that tendon reflexes were noted to be brisk on more than one occasion, that generalized hyperpigmentation of the skin was noted at her 12th admission, and that pyuria was a frequent finding, suggesting that there might have been some slight renal anomaly not demonstrated by intravenous pyelography.

The majority of her admissions were on account of gross anaemia with which epistaxis and infections were often associated. Neutropenia and thrombocytopenia were constant findings. Prolonged courses of A.C.T.H., cortisone, prednisone, vitamin B12, folic acid and iron were without benefit, as was splenectomy, performed at her seventh admission in October, 1954. Blood transfusions and antibiotics were the only effective forms of treatment, and at the last, even these failed. She died of staphylococcal pyaemia with widespread haemorrhagic manifestations, pneumonia and jaundice in August, 1957. No autopsy was performed.

Case 3. Ju.W., younger sister of R.W., was admitted in May, 1959, at the age of 11 years.

For the preceding year increasing pallor and a tendency to bruise easily had been noted by her parents. Six weeks before coming under our care she had been admitted to hospital near her home with a sudden onset of fever accompanied by flitting pains in the knees and ankles. The fever and joint pains were short lived, but her anaemia proved unresponsive to oral and intramuscular iron and to vitamin B12 and she was transferred to Cape Town for further investigation.

Her parents and three younger brothers were reported to be in good health.

On examination she was a well grown and intelligent girl weighing 74 lb. Pallor of mucous membranes, a rather darkly pigmented skin and a short, soft systolic murmur, which was loudest at the lower left sternal border, were the only abnormal physical findings detected.

The haemoglobin was 7-5 g.%: the smear showed marked anisocytosis and poikilocytosis of the red cells; the white cells numbered 7,000/c.mm., of which 94% were lymphocytes and 6% neutrophils. Platelets were scanty, the platelet count being 58,000/c.mm. E.S.R. was 36 mm. (Westergren) in the first hour and her blood group A Rh positive. Two attempts at bone marrow aspiration having failed to produce more than a few marrow cells, a bone biopsy was obtained by trephine from the iliac crest. This specimen was pale, with scanty marrow cells, which appeared to be normal and to be present in normal proportions. Radiographs of chest and long bones and an electrocardiogram showed no abnormality. Blood culture was sterile, the Mantoux test negative and the urine normal.

Folic acid 10 mg. twice daily was given for 10 days without benefit. Two pints of blood were transfused and she was sent home.
PANCYTOPENIA WITH CONGENITAL DEFECTS

It was felt that the occurrence of hypoplastic anaemia, neutropenia and thrombocytopenia in the two sisters must have either a genetic or an environmental cause. Moreover it was suggested by their father in a letter to us that his three sons were beginning to look pale. Their private doctor kindly sent oxalated specimens of blood and examination of these revealed that one, that of Jo.W. (Case 4), was frankly abnormal. In order to search for any possible environmental influence, one of us (B.G.) arranged to visit the farm, 200 miles away, where the family lived in a region of hot springs. The findings were as follows: (1) Scrutiny of the environment with a Geiger counter failed to reveal any source of excessive ionizing radiation. (2) Investigation, including chemical analysis of the farm water, failed to reveal any source of chemical poisoning. (3) Jo.W. was found to have abnormal thumbs incapable of active abduction, adduction or extension and Ju.W. was re-examined and found to have a right thenar eminence smaller than her left and to be incapable of abducting or extending the right thumb. (Fig. 3). (4) It was now learnt that mother and father were distantly related and that R.W. had had a supernumerary thumb amputated at an early age.

A diagnosis of Fanconi’s anaemia could now be made and Ju.W. and Jo.W. were asked to return to us for further investigation.

Ju.W. (Case 3) was readmitted in July, 1959. Her haemoglobin, which was 12 g.% on her discharge six weeks previously, had dropped to 7·5 g.% The cutaneous hyperpigmentation, noted at her first admission, was confirmed by several observers and became more pronounced when her anaemia was again corrected by blood transfusion. There were numerous bruises on her arms and legs and her knee and ankle jerks were very brisk. The significance of slight gynaecomastia was felt to be uncertain in view of her age. Radiographs of her hands showed that the metacarpal and proximal phalanx of her right thumb was of equal length but more slender than that of her left thumb. Intravenous pyelography showed no abnormality.

Case 4. Jo.W., aged 7 years, brother to R.W. and Ju.W., was admitted in July, 1959. Slight pallor and a tendency to bruise readily had been observed for about three months.

On examination there was the striking abnormality of both thumbs already mentioned. He weighed 44 lb. and his intelligence was thought to be normal. Slight hyperpigmentation was confined to the skin of the axillae. There was some bruising on the legs and arms. Radial pulses were not palpable at either wrist, but the ulnar pulsation was forceful. A short, soft systolic murmur, maximal at the apex, was heard but there was no other evidence of heart disease. The tendon reflexes in the legs were accentuated.

The haemoglobin was 10 g.%; the red cells showed anisocytosis and poikilocytosis; white cells numbered 4,000/c.mm., of which lymphocytes comprised 98% and neutrophils 2%. His blood group was AB Rh positive and the E.S.R. was 35 mm. (Westergren) in the first hour. Very few platelets were seen on the peripheral blood smear, the count being 49,000/c.mm. Three attempts at bone marrow aspiration from different sites produced only scanty marrow cells and further measures to obtain a specimen of marrow were not thought justifiable. Radiographs showed spina bifida of the 6th cervical and 3rd thoracic vertebrae in addition to maldevelopment of the metacarpals. Intravenous pyelography was normal.

Case 5. P.v.d.W., a white boy, first came under our care in January, 1957, when he was 6 years old.
At the age of 18 months he had had a bifid uvula repaired. Apart from chicken pox he had been well until the age of 4 years, when excessive bruising and frequent epistaxes commenced. Fatigue and dyspnoea had been noticed for one week prior to admission. His parents and six siblings were said to be healthy.

He was a fair haired boy of average intelligence weighing 41 lb. Numerous bruises were noted, although the Hess test for capillary fragility was negative. His skin was rough and dry and his finger and toe nails were dystrophic. Bilateral epiphora was present due to blockage of both lacrimal ducts. This was improved by probing, but soon recurred and resisted further treatment. A soft, systolic murmur, present at each subsequent admission, was heard at the cardiac apex and lower left sternal border.

His haemoglobin was 5.5 g.%, the red cells showed anisocytosis, poikilocytosis and some polychromasia and the white cells were 4,500/c.mm. Lymphocytes numbered 72%, neutrophils 14%, staff cells 2%, monocytes 7% and eosinophils 5%. Platelets were very scanty, there being only 10,000/c.mm. His blood group was A Rh positive and the E.S.R. 70 mm. (Westergren) in the first hour. Other investigations were: reticuloocyte count 4%; bleeding time eight minutes; coagulation time (Lee and White) seven minutes; prothrombin index 100%; thromboplastin generation test abnormal in a manner consistent with thrombocytopenia and clot retraction normal.

The following additional tests resulted in normal findings: Paul-Bunnell, Widal and brucella agglutination tests, blood Wassermann reaction, blood culture, serum bilirubin, direct Coombs test, osmotic fragility of red cells, plasma proteins and radiograph of chest. Mantoux testing was negative and the urine normal.

Radiographs of long bones showed some widening of the medullary cavities consistent with marrow hyperplasia, which was a constant finding in this case. The bone marrow showed normal erythropoiesis and granulopoiesis apart from some normoblasts suggestive of iron deficiency; platelets were scanty and megakaryocytes were not seen.

Ferrous sulphate 180 mg. was given three times daily and the haemoglobin level rose in three weeks to 10 g.%, reticuloocyte counts remained high and platelet counts low. He was discharged on oral iron and was seen again three months later for review when the findings were unchanged except that the reticuloocyte count had fallen to a normal level and iron deficiency normoblasts had disappeared from the bone marrow.

Nine months later he was readmitted with gross anaemia. Immediate blood transfusion raised the haemoglobin level to 11.5 g.% and prednisone 5 mg. four times daily was then commenced and given for five weeks. This had no effect on the persistently low platelet count, but it was thought possible that a haemolytic aspect of the disease might have been inhibited because, while prednisone was being administered, the haemoglobin level rose steadily to 12.5 g.%. He was discharged again to his home in the country but within a month he was readmitted with extreme pallor. On this occasion he was not transfused. Prednisone was again commenced and after one week oral iron and ascorbic acid were added. Despite the fact that reticuloocyte counts remained slightly above normal and the bone marrow continued to show active erythropoiesis, three weeks of this treatment resulted in no rise of haemoglobin. Splenectomy was now performed and one week post-operatively the platelets numbered 332,000/c.mm.

He now remained well for four months, but then again began to complain of dyspnoea and fatigue on exertion. He was readmitted in February, 1959, grossly anaemic and it was found that thrombocytopenia had recurred. Following blood transfusion, prednisone and iron therapy were again tried but without benefit and he was thereafter readmitted for blood transfusion at intervals of approximately six weeks, neutropenia and thrombocytopenia remaining constant findings. On his final admission to hospital he was bleeding into his gastrointestinal and renal tracts as well as into the skin. Blood transfusion failed to control the bleeding and he died on August 22, 1959.

Discussion and Review of the Literature

The disease may be familial, as in Fanconi's original cases, and is then thought to be inherited as a recessive trait (Reinhold, Neumark, Lightwood and Carter, 1952). It may occur sporadically, for which a gene mutation is believed to be the explanation (Dawson, 1955). We have been able to find full descriptions in the literature of 30 cases occurring in 16 families and of 13 cases occurring sporadically.

The Congenital Abnormalities. A list of the congenital abnormalities more commonly associated with the syndrome is set out in the Table. This includes our own cases and is an amplification of a similar one drawn up by Dawson (1955). Hyperpigmentation of the skin, the commonest abnormality, was found in four of our patients. Deformities of thumbs, and sometimes also of the radii, were frequent findings; the former anomaly

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigmentation</td>
<td>36</td>
</tr>
<tr>
<td>Abnormalities of thumbs</td>
<td>23</td>
</tr>
<tr>
<td>Shortness</td>
<td>22</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>19</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>15</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>13</td>
</tr>
<tr>
<td>Renal abnormalities</td>
<td>13</td>
</tr>
<tr>
<td>Microphthalmia</td>
<td>9</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>9</td>
</tr>
<tr>
<td>Squint</td>
<td>9</td>
</tr>
<tr>
<td>Delayed ossification centres</td>
<td>7</td>
</tr>
<tr>
<td>Ear abnormalities</td>
<td>7</td>
</tr>
<tr>
<td>Heart abnormalities</td>
<td>6</td>
</tr>
</tbody>
</table>
was present in four of our cases. Several authors commented on delay in the appearance of the ossification centres in the carpal bones; this anomaly we found only in our first case. Shortness of stature, hypogonadism and abnormalities of the nervous system, including mental retardation and hyperreflexia, were not infrequently reported as were renal anomalies. The last took the form of a single kidney (Kunz, 1952; Levy, 1952; Reinhold et al., 1952; Kessell and Cohen, 1953; Cowdell, Phizackerley and Pyke, 1955; Dawson, 1955); ectopic position of one kidney (Beautyman, 1951; Francis, Moir and Swift, 1955) and, in one case, a horse-shoe kidney (Dacie and Gilpin, 1944). Congenital cardiac anomalies were occasionally found. All our cases had systolic murmurs, which persisted after transfusion, but further cardiological investigation was not suggestive of any specific abnormality. We are not sure, therefore, whether the murmurs were indicative of some minor cardiac pathology or not. One of our children had a partial spina bifida of a cervical and a thoracic vertebra. This occurred in one of Shaw and Oliver's cases (1959), while Lynch, Sherman and Elliott (1954) stated that they had heard of a child with pancytopenia and this associated anomaly. A feature, found in two of our cases, which we have not seen mentioned elsewhere, was that the fact that the radial pulses could not be felt. If Case 5 (P.v.d.W.) is accepted as belonging to the syndrome, his anomalies are yet others to add to the list.

The Blood Picture. In the protocols consulted, all patients had greatly reduced platelet counts and in most cases there was a leucopenia especially affecting the neutrophils. Variation in size, shape and colour of the red cells was common. Reticulocyte counts varied from less than 1% in many cases to quite high levels in others. In cases in which the sedimentation rate was reported this was nearly always considerably raised, but as there was usually an accompanying anaemia the significance of this finding is uncertain. The bone marrow, sometimes initially described as normal, eventually nearly always showed reduced numbers of all blood forming elements.

Age of Onset and Sex Distribution. The more obvious defects are usually noticed soon after birth though some are not apparent until later. Anaemia is not usually manifest until after 6 years of age, although its onset has been reported both earlier and later than this. There are cases on record where the anaemia only became apparent in adult life (Rohr, 1949; McAlpine, 1954; Cowdell et al., 1955). On the other hand, Emery, Gordon, Rendle-Short, Varadi and Warrack (1957) have reported two infants dying in the neonatal period. Both had haemorrhagic manifestations with scanty platelets and in both cases the radii were absent. They quoted five similar cases from the literature. All were sporadic in origin. Shaw and Oliver (1959) have recently given an account of the same blood and skeletal defects in two siblings in the first months of life. These findings indicate that the anaemia may, on occasion, occur in extreme youth in both the sporadic and familial types of Fanconi's anaemia.

In the cases we have studied or read about, 43 in all, the disease occurred twice as often in boys (29) as in girls (14), but as the numbers are small it is not certain if this is the true sex incidence.

Variants. There appear to be possible variants of the syndrome. Estren and Dameshek (1947) described two families in which three and five members respectively died from hypoplastic anaemia. Though none of these had associated anomalies, their familial nature would seem to link them with Fanconi's anaemia.

In another report Cowdell et al. (1955) tell of two brothers both of whom had typical congenital defects. One of them showed anaemia at the age of 22 years; the bone marrow was hypoplastic and he died one year later. The other brother developed leukaemia when 27 years of age. This suggests another direction in which the disease may show itself.

Treatment and Prognosis. There is no known curative treatment. All types of haematinics have been tried and steroids have been used in some of the cases reported (Kunz, 1952; Kessell and Cohen, 1953; Francis et al., 1955) as well as by ourselves. No real benefit has resulted from any of these forms of treatment. In a few cases it has been claimed that splenectomy has improved matters, particularly when the reticulocyte count has been high, but for the most part the course of the disease has been uninfluenced. There was no improvement in our three patients who had their spleens removed. Repeated blood transfusion is the only means by which definite temporary improvement can be effected. Intervals between transfusions become progressively short and eventually blood has to be given about every two months and sometimes more frequently.

The disease is invariably fatal, with the single exception of Dawson's (1955) case of a girl first seen with anaemia at 10 years of age. At the age of 20 she was reported to be alive, well and married. The usual duration of illness is from a few months
to several years, the average life expectancy being two to four years after the first appearance of anaemic symptoms. In most cases death has been due to infection or massive haemorrhage.

Fanconi's anaemia should be considered in the differential diagnosis of all cases of pancytopenia. A careful examination for congenital defects, however minor, should be made and other members of the family should be investigated for signs of the trait. If this is not done the syndrome may not be recognized, as occurred in the first two members of the family we have described. It was only when the third child was seen that the correct diagnosis was made and the significance of barely noted defects in his sisters was appreciated.

Summary

Four cases of Fanconi's anaemia are presented as well as a fifth case which it is suggested may be another example of this condition.

That the disease may not be recognized if the associated congenital defects are minor ones is exemplified in two out of three cases found in one family.

The literature is reviewed and the congenital defects which commonly occur are listed and discussed including some unusual manifestations in our cases.

Our thanks are due to Professor F. J. Ford for helpful advice, to the Medical Superintendent, Groote Schuur Hospital for permission to publish and to Mr. B. Todt, hospital photographer, for the photographs.

References


Addendum

When this article was submitted the paper by Shahidi and Diamond (1959) on the treatment of aplastic anaemia with a combination of testosterone and steroids had not yet appeared.

Our two surviving children are now being treated in this way and the results will form the subject of a future communication.
Pancytopenia with Congenital Defects (Fanconi's Anaemia)

Robert McDonald and Basil Goldschmidt

*Arch Dis Child* 1960 35: 367-372
doi: 10.1136/adc.35.182.367

Updated information and services can be found at:
http://adc.bmj.com/content/35/182/367.citation

These include:

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/