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Fanconi's Anaemia in an African

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From a family of five children Fanconi in 1927 (as reported by Reinhold *et al.* in 1952) diagnosed three to be suffering with aplastic anaemia and multiple skeletal defects. These defects included hyperpigmentation, microcephaly, retarded growth, convergent squint, testicular hypoplasia and increased deep tendon reflexes.

The blood pictures were those of anaemia, thrombocytopaenia and leukopaenia. The red cells demonstrated macrocytosis. The bone marrows were pale and jelly-like with severe hypoplasia of all elements.

This syndrome of aplastic anaemia associated with multiple skeletal defects has come to be known as Fanconi's anaemia and many cases have subsequently been described. However, a perusal of available literature failed to reveal a specific reference to this disease occurring in an African. This is despite Dawson's statement in 1955 that there is no racial preponderance. The purpose of this article is to report the occurrence of Fanconi's anaemia in an African and to present a review of literature.

Case Report

Joyce, a five-year-old African child, was first diagnosed as being anaemic when she sought medical advice concerning acute abdominal pain in August, 1969. She had been previously asymptomatic and the pain was considered to be coincidental.

In March, 1970, she presented with a history of bleeding gums of three days' duration, having been previously well. The only other abnormal feature elicited in Joyce's past history was the emphasis her mother placed on the smallness of Joyce at birth and in her subsequent years. There was no family history of consanguinity, bleeding disorders including leukaemia, nor of obvious physical abnormalities. She denied any contact with known bone marrow depressant chemicals and drugs.

On initial examination she was very severely anaemic with hypertropheid/bluish bleeding gums. There was no bleeding from other sites and there was neither purpura nor petechiae present. There was no lymphadenopathy, hepatomegaly or splenomegaly and her sternum was not tender. She showed slight cardiac decompensation.

Her skeletal system revealed many abnormalities. Her total length was 38 in., weight 23 lb., head circumference 18 in. (Fig. 1).

Her left thumb was quite abnormal, being thin and fingerlike in appearance, with very limited movement at the interphalangeal joint, but with a strikingly wide range of movement at the metacarpophalangeal joint. Nevertheless, thumb to finger apposition was poor. The associated thenar eminence was absent and this gave a tapered elongated appearance to the radial side of that hand. The radial pulse was absent, but there was a prominent left ulnar pulsation. Both little fingers were small and incurving (Fig. 2).

The carrying angles of her arms were noticeably increased and she was knock-kneed with an intermalleolar distance of three fingers breadth.

She was not inordinately pigmented. Mentally she seemed normal and her nervous system was likewise normal, except for her tendon reflexes, which were always at least brisk, but which to some examiners appeared exaggerated. She showed no evidence of protein-calorie malnutrition if one discounts her stunted growth.

Investigations

Haemoglobin was 9 per cent. or 1.4 grm. per cent. PCV, 4 per cent. MCHC, 35 per cent. Total white cell count, 3,300 per c.mm. (neutrophils 396, lymphocytes 2,871). ESR was 187 mm./2 hours. Platelet count was less than 20,000 c.mm. FILM: Anisocytosis moderate. Poikilocytosis moderate. Macrocytes ++. Occasional atypical mononuclear cells were present. No blood parasites were seen and a sickling test was negative. Serum iron 284 and iron binding capacity 375 mic./gm. per cent. Bilirubin 0.4 mgm. per cent. Haemoglobin binding capacity 176 mg./dl. Coombs' test negative. Prothrombin index 88 per

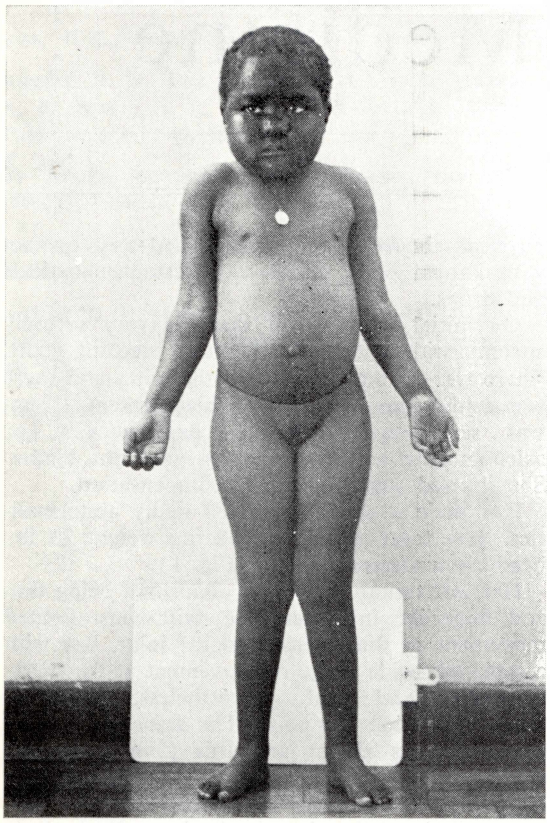

Fig. 1—A five-year-old girl showing an abnormal left thumb, an increased elbow carrying angle, knock knees and a Cushingoid facies.

cent. Stool examination was normal. Urinalysis was clear and there was no aminoaciduria.

The foetal haemoglobin as estimated by the method of Singer *et al.* in 1951 was 12 per cent.

Bone marrow was taken from the anterior ilium. The consistency was normal. The marrow fragments consisted mostly of fat with little haemopoietic tissue. The cell trails were hypocellular. Erythropoiesis was normoblastic and severely depressed. Granulopoiesis was severely depressed, but the lymphocytes were normal. No megakaryocytes, malignant or other abnormal cells or parasites were seen. Iron was present in increased amounts.

The conclusion reached was a diagnosis of aplastic anaemia.

Radiology: The chest X-ray was clear. X-ray of the hands revealed a bone age of only three to four years and a hypoplastic left thumb. An intravenous pyelogram showed normal kidneys. Spinal X-rays were normal.

Chromosomes: The use of Difco kits revealed the presence of chromatid gaps and breaks, including one across a centromere. A complete chromosomal disintegration was seen and the formation of dicentric chromosomes was seen several times.

Treatment and Progress

She was treated initially with blood transfusions which restored her cardiovascular system to apparent normality. However, soon after admission she developed a severe infective illness to which she very nearly succumbed. There was prostration, fever, ascites, an increased bleeding tendency and a vesicular rash which became haemorrhagic. Electron microscopy showed virus particles which were either chicken pox or herpes simplex. During this illness she was started on prednisolone and testosterone. Following recovery from the illness, a rise of her neutrophil count from 500 to 1,300 c.mm. and a rise of her platelet level from less than 10,000 to over 60,000 c.mm. was observed. However, three weeks later concomitant with another infective illness, these figures fell to their prior level from which they did not subsequently vary.

She had repeated severe bleeding episodes usually epistaxes, and her haemoglobin level continually fell, needing restoration every three weeks or so by transfusions. The reticulocyte count was always less than 2 per cent. There was no suggestion of haemolysis at any stage.

She developed severe side effects to her combined hormonal therapy. She became excessively darkly pigmented, gained weight in excess and developed a Cushingoid facies and acne. However the most striking side effect in this five-year-old girl was the development of facial interscapular limb and pubic hair of disturbing severity.

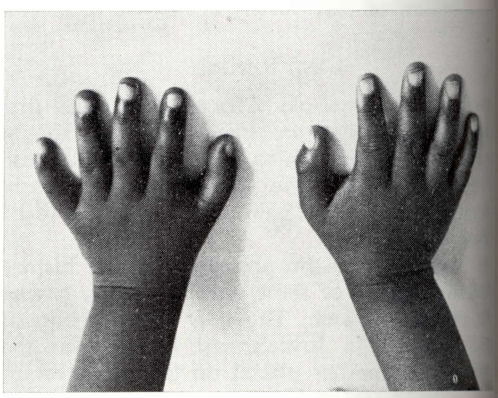

Fig. 2—Note the finger-like hypoplastic left thumb and the incurving little fingers.

Family

An examination of her two siblings revealed them both to have short incurving little fingers. Her two-year-old brother, who had the most marked deformity, also showed a haemoglobin level of 76 per cent., i.e., 11.4 gm. per cent., a relative neutropaenia of 1,920 cells and a total count of 12,800 white cells per c.mm. They both had a normal platelet count. Her brother showed fragmentation of a "B" group chromosome.

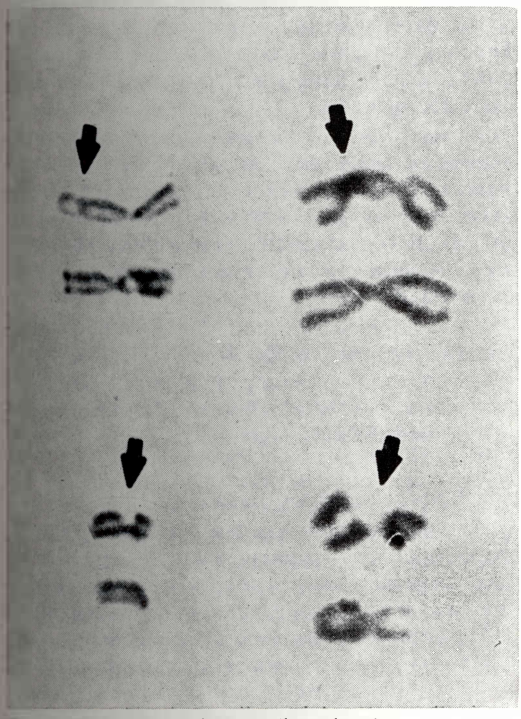

Fig. 3—The arrows point to dicentric chromosomes, a transverse breakage at the centromere and an achromatic gap.

Discussion

Having a peripheral pancytopaenia, a hypoplastic marrow, multiple congenital skeletal abnormalities and characteristic choromosomal changes, this patient is an incontestable example of Fanconi's anaemia.

This syndrome has been reported well over 160 times since 1927, with an ever-lengthening list of associated defects. However, the aetiology remains a mystery. Consanguinity of parents has been reported. More than one sibling has often been affected, either with classical Fanconi's anaemia, or skeletal defects with normal haematology (Perkins *et al.*, 1969), or with an abnormal blood picture ranging from thrombocytopaenia to pancytopaenia, yet with no associated defects (Hirshman *et al.*, 1969), or lastly with a normal picture and no other defects except the characteristic chromosomal changes (Swift *et al.*, 1966).

Althoff in 1953 observed that the different organ systems usually involved all differentiate at a similar embryonic stage (twenty-fifth to thirty-fourth day of life). He suggested that a single early embryonic defect may be responsible for inducing all the later manifestations. A recessive autosomal defect has been suggested (Cowdell *et al.*, 1955), as has a single genetic mutation in the isolated case. Fanconi in 1964, as reported by Paul *et al.* in 1966, suggests the possibility of a reciprocal chromosomal translocation in one of the parents and a duplication deficiency in the affected offspring.

Most cases present in childhood with anaemia or frank bleeding, especially epistaxes. The relative acuteness of Joyce's clinical onset and her presentation with swollen bleeding gums are somewhat unusual. The disease has been seen in the neonate beginning as an amegakaryocytic thrombocytopaenia (Emery *et al.*, 1957), which ultimately has progressed to a pancytopaenia. Fanconi in 1964 observed that most children who develop the classical disease are born underweight and that dwarfism can be recognised early. The history of Joyce's smallness at birth and subsequent years as given by her mother confirms his observation. The disease has also been described as occurring in the third decade (Cowdell *et al.*, 1955).

Anatomical Abnormalities

Many associated congenital defects have been reported (Vowels *et al.*, 1970), and among the commonest are deformities of the radial aspect of the upper limb. The thumb has been aplastic, hypoplastic, dislocated or joined to the hand merely by soft tissue. Absent thenar eminences have been reported, as have been absent or deformed radii, radial metacarpal and carpal bones. The associated radial pulse has occasionally been absent. The deformity of Joyce's hand and wrist is thus classical. Other skeletal abnormalities, including spina bifida, cervical ribs, Sprengel's deformity, congenital dislocated hips, club feet, syndactyly and reduced ossification centres (as demonstrated in the X-ray of Joyce's wrist), have also been seen. The skeletal associations of knock knees and increased carrying angle of the elbows are perhaps unique to Joyce.

Malformations of the urinary tract have been many and varied. They have been reported to be present in 25 per cent. of the cases and they include agenesis, ectopia, horseshoe kidney and abnormalities of the ureter and renal vessels. Aminoaciduria has been reported, but this syndrome is not to be confused with Fanconi's

syndrome of refractory rickets and multiple renal tubular defects.

Congenital cardiovascular abnormalities have been present, e.g., coarctation of the aorta and patent ductus arteriosus. When her red cell mass was improved, Joyce gave no suggestion of organic heart disease.

Associated abnormalities of the external ear and deafness have been described, as have been abnormalities of the eye, e.g., microphthalmia, ptosis, narrowed palpebral fissured, nystagmus and squint.

Many features of the disease that Fanconi first described are among the commonest features still to be seen. Growth and developmental retardation are almost always present and were certainly obvious in Joyce. Hyperpigmentation due to excess melanin deposition is very common. This melanin may be generalised in distribution or occur in the form of cafe au lait spots in sacral, axillary, inguinal and peri-umbilical areas. Of the original features, Joyce also showed microcephaly and perhaps increased deep tendon reflexes.

Chromosomal Abnormalities

Chromosomal changes have been well reviewed (Bloom *et al.*, 1966; Wasserman *et al.*, 1968; Perkins *et al.*, 1969; Hirshman *et al.*, 1969) and it seems that they are very common. Indeed, more than one report (Bloom *et al.*, 1966; Hirshman *et al.*, 1969) suggests their presence may be a criterion for diagnosis. The basic defect is chromatid breakage which may involve one or both chromatids anywhere along their lengths. This defect combined with a "stickiness" of the broken ends results in the formation of bizarre chromosomal figures. Commonly seen is a simple break towards the end of a chromatid with the end piece either absent (perhaps translocated) or angulated. There may be an achromatic gap in the chromatid as evidence of breakage without deformity. Breakage may be seen transversely at the centromere. Complex figures result from the union of broken chromatids, e.g., dicentric figures result from the breakage and re-union of chromatids in adjacent regions. Should both chromatids of two chromosomes break and their "sticky" ends unite, then complex quadriradial figures may be formed. Complete fragmentation of a whole chromosome may occur. Another abnormality commonly seen and perhaps related to "stickiness" is endoreduplication in which chromosome doubling occurs as in the normal divisional process, but there is failure of separation in the individual pairs. When one views the cell at metaphase, 46, double pairs—that is, 46 four-stranded figures—are seen.

It is not difficult to imagine the possibility of chromosomal abnormalities occurring which may produce non-viable cell lines at division, and perhaps the reason for marrow aplasia is akin to this. If so, then why does the disease wait usually six or seven years before it presents? If lymphoid cells provide marrow stem cells (Yoffey 1962) and these lymphoid cells have intermitotic durations measured in years, as suggested by Norman *et al.*, 1965, then perhaps this is the reason. The catastrophic effect of these chromosomal defects on the offspring of a patient with Fanconi's anaemia have yet to be described, as most patients have died in childhood or have been hypogonadal.

Another view of the aetiology is related to the proven susceptibility of the chromosomes in Fanconi's anaemia to breakages caused by viruses (Hirshman *et al.*, 1969). A viral aetiology has thus been considered, but more likely the viruses are just precipitating potential breakage caused by another factor.

It is significant that similar chromosomal changes can be found in leukaemia and it is therefore not surprising that the incidence of leukaemia in affected children and their relatives is very inordinately high.

Haematological Abnormalities

Aplastic anaemia has been defined as a severe depression of haemopoiesis characterised by pancytopaenia and hypocellularity of the bone marrow without evidence of infiltrative disease (O'Gorman-Hughes, 1966). In Fanconi's anaemia there has usually been a progressive and ultimately fatal pancytopaenia, although, rarely, depression of one or two cell lines has dominated (Nilson, 1960).

The red cells are normocytic to macrocytic (as was seen in Joyce's films) and initially there may be a reticulocytosis. This latter may also occur in response to treatment. Depression of all the white cells may occur, but usually just the neutrophils are involved. Platelets may be severely depressed and megakaryocytes may be absent from bone marrow preparations. Enzymatic deficiencies have been reported in white and red cells and in platelets (as reviewed by Swift *et al.*, 1966). The depressive effect on cell lines by infections, especially viral, is well known.

Shahidi *et al.*, 1962, reported the persistence of a raised level of foetal or alkali resistant haemoglobin even up to 15 per cent. Why this should occur is a mystery, but it may be compensatory. It is a biochemical abnormality which

may occur before there is clinical evidence of the disease.

Raised serum levels of iron and increased deposition of iron in tissue are common. This may result from the underproduction of the red cells creating a surplus of unused iron, but is exaggerated by repeated transfusions, each one of which probably adds about 200 mgm. of iron to the body.

Treatment

A haemolytic element is occasionally suspected because of a reticulocytosis, perhaps raised bilirubin and decreased haptoglobin levels and a decreased life span of tagged red cells. Splenectomy has been performed on this basis and also when intractable bleeding has been associated with severe thrombocytopaenia, but the results are debatable. Some authors report favourably concerning splenectomy (Dawson, 1955; Kock, 1967), but the occasional natural remission must be remembered (Dawson, 1955; Wasserman, 1968; McDonald, 1968).

It would seem wise to assess with radioactivity studies—

(1) the life span of the red cells;
(2) the site of any excessive destruction;
(3) the site of blood production. This may theoretically be maximal in the spleen which is under consideration for removal.

Although Joyce required transfusions every few weeks, there was no evidence of haemolysis clinically and biochemically and it seemed that her frequent bleeding episodes were solely responsible for the falling haemoglobin levels.

The treatment, however, is predominantly medical and rests on the prevention and control of haemorrhage, blood transfusions, combined cortisone and testosterone therapy, isolation from infection and antibiotics.

Prevention and Control of Haemorrhages.—The problem is similar to that encountered in haemophilia and depends on parental and if possible the patient's understanding of the illness. Local measures are important, e.g., the prompt treatment of a potentially exsanguinating epistaxis by nasal packing. Steripson gauze has been used with satisfaction in controlling Joyce's epistaxes.

Transfusions.—As well as the usual complications of transfusion there are special ones which may be a problem in this disease.

(1) Haemosiderosis: In the absence of bleeding, repeated transfusions will saturate the tissues with iron and will ultimately impede recovery. Paul *et al.* in 1966 reported a case in which the whole reticulo-endothelial system was black with iron.

(2) Bone marrow depression: This is related to the quantity of cells transfused. In the experience of Shahidi and Diamond (1961) a post-transfusion level of 8 to 9 gm. per cent. of haemoglobin did not appear to depress bone marrow and seemed to be an optimal level.

(3) The development of antibodies to minor groups: Shahidi and Diamond (1961) did not find this a problem, but they stress the importance of an exact cross match even in an emergency.

These transfusions should be given circumspectly and usually on clinical grounds rather than on laboratory figures. Patients may stabilise on surprisingly low haemoglobin values, e.g., 3 to 4 grams per cent., and transfusions should be reserved for patients showing signs of tachycardia, anxiety, irritability, apathy, prostration, etc. The reason for giving blood to the non-bleeding patient is to raise the red cell mass to a level which abolishes the symptoms and signs of anoxia, to prevent an excessive cardiac output and potential failure, and to give a reserve in case of severe bleeding. Packed cells are usually preferred with or without an associated diuretic and/or digitalisation. Exchange transfusions have been given in the critical ill patient with actual or potential cardiac decompensation.

For the treatment of acute bleeding, platelet rich plasma is preferred by Shahidi and Diamond (1961), who are less impressed with the effects of fresh whole blood.

Combined Cortisone and Testosterone Therapy.—Cortisone is used for its presumed effect on capillary fragility and permeability and also in the hope that it will lessen any haemolysis. The results of using cortisone alone are poor and in fact an increase in marrow fat has been noticed on occasions. The recommended initial dosage is 1-2 mg./kg./day.

When cortisone is used in combination with testosterone the results have been promising (Shahidi *et al.*, 1961; Desposito *et al.*, 1964; McDonald *et al.*, 1968). The rationale for using testosterone grew from the observation that it acts as a non-specific marrow stimulant. This was first noticed when women with carcinoma of the breast, treated with testosterone, developed a rising haemoglobin. High levels of haemoglobin were also noticed to be associated with adrenogenital tumours. The effect was confirmed with animal studies and then by clinical trials.

Many reports have subsequently mentioned amelioration of the disease and the production of relatively long remissions using the combined therapy with testosterone in a dosage of 1-2 mg./kg./day. Which preparation is used does not seem to matter, although it is worth changing

the preparation if there is no response. Raising the dosage does not seem to make any difference therapeutically, apart from increasing the side effects.

Therapeutic response is slow and may not be evident for one to six months (Shahidi *et al.*, 1961), during which time the marrow spaces are being repopulated. Reticulocytosis is seen first, followed by a haemoglobin and white cell increase. The platelets usually respond last and unsatisfactorily. Joyce was unusual in these respects if any significance can be attached to her early unsustained rise in white cells and platelets. At no stage did she show reticulocytosis.

With response the dosages should be slowly decreased to a maintenance level. These patients may be dependent on therapy, possibly for life, for cessation of treatment has often been followed by an exacerbation of the disease. Therapy has no effect on the chromosomal abnormalities.

Side Effects.—Hirsutism is particularly a problem, as reported by Swift in 1966, but other stigmata are frequent, e.g., hyperpigmentation, striae, acne, weight gain and Cushinoid features. Bone changes have not been a problem and it is supposed that the anabolic effect of testosterone is antagonised by the catabolic effect of cortisone, with the result that premature epiphyseal closure due to increased bone maturity has not been reported.

Isolation.—The risk of infection in an aplastic child being treated with steroids needs no emphasis. Infections *per se* may be critical, but the depressant effect on the bone marrow of even a mild infection is an added complication. Prophylactic gamma globulin is sometimes given.

Antibiotics.—Bactericidal drugs in large doses are preferred and should be given intravenously for a serious infection, especially when injection haematomata are a problem. The use of chloramphenicol and sulphonamides is not ideal because of their effect on bone marrow.

Prognosis

This disease has mostly been fatal, with death occurring one or two years after the onset. However, several patients having long natural remissions have been described. The use of combined cortisone and testosterone therapy has brought promise to a previously unhappy situation. Clinical and haematological response has been seen and seemingly therapeutic remissions have been described lasting so far for several years. It remains to be seen what the future holds for those patients who have responded to therapy and especially for the majority of patients who are dependent upon it.

Acknowledgments

I gratefully acknowledge the permission gi by Professor Kendall to publish this account his patient. I also appreciate his and Dr. Axt help in the preparation of this text.

Mr. Nigel Lyons obligingly cultured chromosomes and prepared their photographs publication, and for this important help I indebted. I also thank Dr. Lowe and the labo tory staff of Harare hospital for their numer investigations.

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ADDENDUM

Since the submission of this article for publicati June 1970, Joyce has progressed well. She has ha clinical exacerbations and her haemotology has stabi Her haemoglobin level remains at about 9 gm/100 ml her white cell count at about 3,500 cells per cu. mm. a neutrophil count of over 1,000 cells per cu. mm. dosages have been decreased and she is now o prednisolone 2.5 mg. second daily and testosterone 25 second daily. Her cushingoid features are lessening