CONGENITAL HYPOPLASTIC ANAEMIA

REPORT OF TWO CASES

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The prognosis for children suffering from aplastic anaemia, congenital or acquired, has been considerably improved by the introduction by Shahidi and Diamond (1959, 1961) of combined testosterone and corticosteroid treatment. In order to reduce side-effects, anabolic steroids have been tried in place of testosterone, favourable results being obtained by Seip (1961) in two cases treated with methandrostenolone and prednisone, and by Khalil and Ibrahim (1962) in one of two cases treated with fluoxymesterone and dexamethasone.

The present report describes two siblings suffering from hypoplastic anaemia associated with congenital defects, one of these cases being treated initially with β -methazone and testosterone and, later, with β -methazone and methandrostenolone ('dianabol')*.

Case Reports

Case 1. At the age of 9 years she was admitted to the Royal Aberdeen Hospital for Sick Children. Apart from Perthes' epiphysitis of her hip four years previously, she had been well until about three weeks before admission when she complained of tiredness, aching pains in her thighs and breathlessness on exertion. She had been noted to be pale and had been bruising readily. She had suffered no obvious blood loss, had not been jaundiced and had taken no drugs. Her parents, her brother aged 4 years, and sister aged 12 years, were at that time healthy and there was no family history of blood dyscrasia.

Examination showed a pale girl with numerous purpuric spots and bruises and one small retinal haemorrhage. Her lymph nodes and liver were not enlarged and her spleen tip was just palpable. Her fifth fingers were small and incurved, having a short middle phalanx and resembling those characteristically seen in mongolism. Her haemoglobin level was 4.0 g./100 ml., red blood cells 1.20 million and white blood cells 2,600/c.mm. with 40% neutrophil polymorphs, 44% lymphocytes and 16% monocytes. Platelets numbered 44,000/c.mm. and reticulocytes 1%. Several bone marrow examinations were carried out showing relatively normal

cytology apart from marked infiltration of some specimens with immature plasma cells. Other investigations were as follows: urinalysis, negative; serum calcium, 4.7 mEq/litre; serum bilirubin, <0.2 mg./100 ml.; blood urea, 20 mg./100 ml.; total plasma proteins, 6.21 g./100 ml., with normal paper electrophoretic pattern. Long bones and skull were radiologically normal.

The patient survived 39 weeks from the time of her original admission to hospital. During this period she required blood transfusions with increasing frequency for correction of anaemia, 13 transfusions in all being given. Her total white cell count remained in the 1-3,000 range, the neutrophil polymorphs usually being about 500/c.mm. Thrombocytopenia likewise persisted. Short courses of treatment with cortisone in a dosage of up to 100 mg. per day produced no reticulocytosis or increase in haemoglobin, white cells or platelets. As the bone marrow picture at one time was considered to be suggestive of myelomatosis, a course of stilbamidine was given, also without improvement.

The patient's terminal illness was an acute bronchopneumonia occurring at the time of an influenzal epidemic in the community. Autopsy showed gross haemorrhagic bronchiolitis and bronchopneumonia with intra-alveolar haemorrhage and with Gram-positive cocci more conspicuous than inflammatory cells which were mainly mononuclear. Severe peribronchial congestion and haemorrhage were present at the hilum, and the trachea and bronchi showed intense inflammatory change with denudation of epithelium and formation of a pseudo-membrane. The presence of numerous plasma cells in the bone marrow was confirmed, but no infiltration of other organs was found. The kidneys were situated near the pelvic brim and were joined by their lower poles to give a horseshoe configuration.

Case 2. This boy, brother of Case 1, was in good health during the time of his sister's illness. One year after her death, when he was almost 6 years of age, he developed symptoms similar to those of his sister—pallor, bruising, aching legs and lethargy. Physical examination showed that he resembled his sister closely in facial appearance and had similar small incurved fifth fingers with deficiency of the middle phalanx (Fig. 1). He was moderately pale and had numerous bruises,

* Approved name is methandienone.

FIG. 1.—Case 2, showing defect of fifth finger.

although no purpuric spots. His liver, spleen and lymph nodes were not enlarged and no other abnormalities were detected on examination. Blood count at that time was: haemoglobin 10.5 g./100 ml., white blood cells 4,400/c.mm. with 41% neutrophil polymorphs, 50% lymphocytes, 5% monocytes and 4% smear cells. His platelets numbered 75,000/c.mm. and reticulocytes 2.4%. Bone marrow was of normal cellularity and the differential count was within normal limits. Other laboratory investigations, as in Case 1, gave normal results. Intravenous pyelography showed no congenital anomaly of the urinary tract. Urine chromatography carried out at a time when the patient

was on steroid therapy showed a moderate amino-aciduria.

Over the ensuing 12 months his blood count gradually deteriorated to reach haemoglobin 4.7 g./100 ml., white blood cells 3,000/c.mm., of which 16% were neutrophil polymorphs, and platelets 23,000/c.mm. At this point he was given a transfusion of blood, and two months later he was started on an eight-week course of combined cortisone and methyl testosterone therapy (Fig. 2), the former in a dosage of 100 mg. a day initially, decreasing to a maintenance dose of 50 mg. per day, and the latter in a dosage of 30 mg. a day. During this time his haemoglobin level fell slowly, although his reticulocyte count increased from the previous level of 1.3% to 3.5%. There was no improvement in his neutrophil polymorph or platelet count. In retrospect it became clear that this course of treatment was neither sufficiently intense nor sufficiently prolonged. Splenectomy was carried out one month after the steroid therapy was discontinued. Again this produced no improvement in the haematological picture and the patient thereafter required increasingly frequent transfusions (Fig. 2). Treatment with combined corticosteroids and testosterone was recommenced using β -methazone 1.0 mg. per day and methyl testosterone 30 mg. per day. Fig. 3 shows that a satisfactory response was obtained with increase in haemoglobin, neutrophil polymorphs and platelets. After he had been on this therapy for four and a half months he showed considerable side-effects, in particular hirsutism and acne. Because of this, methandrostenolone 5 mg. per day was substituted for the methyl testosterone, but, as seen in Fig. 3, this dosage proved to be insufficient and was later increased to 10 mg. per day. His most recent blood count, after two months on the increased therapy, shows haemoglobin 12.1 g./100 ml., white blood cells 4,300/c.mm. (neutrophil polymorphs 36%, lymphocytes 51%, monocytes 7%, smear cells 6%), platelets 114,000/c.mm., reticulocytes 2.9%. The red cells show anisocytosis and macrocytosis and some Howell-Jolly bodies. The reticulocyte count on the combined therapy has shown considerable variation, remaining above the

FIG. 2.—Case 2, chart showing haemoglobin levels over 41-month period of observation. (T = blood transfusion.)

Fig. 3.—Case 2, chart showing detailed haematological response to corticosteroid therapy (β -methazone 1.0 mg. per day) combined initially with methyl testosterone and later with methandrostrenolone.

pretreatment level of 1.3% but ranging from 2.9–5.2%. At the time of the most recent blood count, estimations were made of the amount of alkali resistant haemoglobin in the blood of the patient and his parents. Using the method of Singer, Chernoff and Singer (1951), it was found that the patient's blood contained 7.7% of alkali resistant haemoglobin, and that of both parents contained less than 1%.

Discussion

The anaemia in the two siblings described above was of the familial type of Fanconi's (1927) aplastic anaemia associated with congenital abnormalities. Both children had abnormalities of the fifth fingers, and the elder sister had a horseshoe type of kidney as has been reported in this syndrome by Dacie and Gilpin (1944). Neither child had pigmentation of the skin which is the most common anomaly found in Fanconi's anaemia (McDonald and Goldschmidt, 1960).

As in acquired aplastic anaemia, the bone marrow in these children may be acellular or hypercellular (Smith, 1960). Case 1 is of particular interest in that a specimen of marrow was so markedly infiltrated with immature plasma cells as to suggest a diagnosis of myelomatosis. Sturgeon (1951), however, mentions abundance of plasma cells in the

marrow as a feature of diagnostic value in differentiating acquired aplastic anaemia and aleukaemic leukaemia, and he states that similar marrow patterns are found in congenital aplastic anaemia associated with deformities. Similar infiltration of the marrow with plasma cells is found in agranulocytosis (Custer, 1935; Darling, Parker and Jackson, 1936).

The response of Case 2 to methyl testosterone and corticosteroid is similar to that obtained by Shahidi and Diamond (1959, 1961). When methandrostrenolone in a dosage of 5 mg. per day was substituted for methyl testosterone deterioration of the blood was evident, improvement again taking place when the dosage was increased. Seip (1961) suggested from his limited experience that approximately 0.25 mg./kg. body weight per day of methandrostrenolone was adequate, but in the present case such a dosage proved insufficient. Because of the effect of anabolic steroids on bone maturation it is advisable that the minimal effective dose is used.

The finding of 7.7% of alkali resistant haemoglobin in the patient is in agreement with Shahidi, Gerald and Diamond's (1962) report that the level remains elevated in patients with congenital aplastic anaemia during treatment, whereas it tends to fall in the acquired variety during remission.

Summary

Two siblings suffering from Fanconi's type of aplastic anaemia are described. One shows satisfactory response to treatment with combined corticosteroid and anabolic steroid therapy.

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REFERENCES

- Custer, R. P. (1935). Studies on the structure and function of bone marrow. IV. Bone marrow in agranulocytosis. *Amer. J. med. Sci.*, **189**, 507.
- Dacie, J. V. and Gilpin, A. (1944). Refractory anaemia (Fanconi type). Its incidence in three members of one family, with in one case a relationship to chronic haemolytic anaemia with nocturnal haemoglobinuria (Marchiafava-Micheli disease or 'nocturnal haemoglobinuria'). *Arch. Dis. Childh.*, **19**, 155.
- Darling, R. C., Parker, F. and Jackson, H. (1936). The pathological changes in the bone marrow in agranulocytosis. *Amer. J. Path.*, **12**, 1.
- Fanconi, G. (1927). Familiäre infantile perniziosaartige Anämie (perniziöses Blutbild und Konstitution). *Jb. Kinderheilk.*, **117**, 257.
- Khalil, M. and Ibrahim, A. H. (1962). The treatment of aplastic anaemia with anabolic steroids. *Acta paediat. (Uppsala)*, **51**, 201.
- McDonald, R. and Goldschmidt, B. (1960). Pancytopenia with congenital defects (Fanconi's anaemia). *Arch. Dis. Childh.*, **35**, 367.
- Seip, M. (1961). Aplastic anemia treated with anabolic steroids and corticosteroids. *Acta paediat. (Uppsala)*, **50**, 561.
- Shahidi, N. T. and Diamond, L. K. (1959). Testosterone-induced remission in aplastic anemia. *A.M.A. J. Dis. Child.*, **98**, 293.
- , — (1961). Testosterone-induced remission in aplastic anemia of both acquired and congenital types. *New Engl. J. Med.*, **264**, 953.
- , Gerald, P. S. and Diamond, L. K. (1962). Alkali-resistant hemoglobin in aplastic anemia of both acquired and congenital types. *ibid.*, **266**, 117.
- Singer, K., Chernoff, A. I. and Singer, L. (1951). Studies on abnormal hemoglobins. I. Their demonstration in sickle cell anemia and other hematologic disorders by means of alkali denaturation. *Blood*, **6**, 413.
- Smith, C. H. (1960). *Blood Diseases of Infancy and Childhood*, p. 200. Mosby, St. Louis.
- Sturgeon, P. (1951). Idiopathic aplastic anemia in children. Its early differentiation from aleukemic leukemia by bone marrow aspiration. *Pediatrics*, **8**, 216.