DRUG-INDUCED REMISSION IN HYPOPLASTIC ANAEMIA (FANCONI TYPE)

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True hypoplastic or aplastic anaemia in children is fortunately uncommon, but when it occurs it brings with it a feeling of helplessness on the doctor's part and great strain on the parents; until recently it has always been a death sentence to the child. Some hope of improvement can now be given as the result of a publication by Shahidi and Diamond from Boston.[1] The following report, which confirms their findings, is intended to make this form of treatment more widely known and to encourage further therapeutic trials in such cases. The treatment is not always successful and sometimes requires modification, but it does give reason for a somewhat more hopeful approach to what has hitherto seemed a situation of despair.

Fanconi[2] first described hypoplastic anaemia in association with congenital defects in 1927, and there have been a number of publications on the subject since then, including one from this department which described 5 cases seen in the children's wards at Groote Schuur Hospital, Cape Town.[3]

The congenital defects in reported cases have involved the skin, and the renal, central nervous and cardiovascular systems, but the lesions which usually draw attention to the condition are the musculoskeletal ones. These defects invariably involve the radial side of the forearm and the thumb; the least marked being defective development of the thenar muscles. More often there is, in addition, incomplete formation of the first metacarpal, the thumb being joined to the hand by soft tissue alone. In the most extreme forms, besides the above-mentioned defects, part or all of the radius may be absent. In one of our patients the radial pulses could not be felt, and in another they were of very poor quality. This association of vascular and musculoskeletal defects is probably more than coincidental.

Anaemia usually becomes apparent in the middle years of childhood. While repeated blood transfusions will keep these children in relatively good health for a time, before 1959 there was no known treatment which would bring about regeneration of marrow activity. All blood elements are affected by the marrow dysplasia and the disease has usually proved fatal within a few years of the onset of anaemia, either from massive haemorrhage or overwhelming sepsis.

Shahidi and Diamond[1] reported that reactivation of the bone marrow had occurred in 5 cases of aplastic anaemia in children under treatment with a combination of testosterone and a corticosteroid. One case was of the Fanconi type. It was already known that in many of these cases corticosteroids alone are ineffective, and these authors found that testosterone by itself was not able to maintain adequate haemoglobin levels. It seemed necessary to give both drugs to achieve this.

Two of our patients, a brother and sister, were still living when the report of Shahidi and Diamond appeared. They were started on full doses of methyl testosterone, 2 mg. per kg. per day, and prednisone, 10 mg. per day, in January 1960. Within 3 months there were signs of marrow response and a preliminary report concerning this was published during that year.[4]

When the present paper was submitted for publication, the children had been under treatment for nearly 2 years. The case reports which follow indicate their state of health during that time.

CASE REPORTS

Case 1

Ju.W., the elder child, was 11 years old when the new treatment was started in January 1960. The graph (Fig. 1) indicates her haemoglobin levels during the next 22 months. Two-and-a-half months after commencing treatment there was a rise in the haemoglobin level and this was well maintained. After 7 months, drug therapy was stopped in the hope that the marrow activity might persist. It was soon evident that this was a vain hope, since the haemoglobin level fell progressively during the 2½ months which followed. The drugs were then recommenced and again there was a satisfactory response. In order to arrive at the minimum effective dose, both preparations were gradually reduced; 25 mg. of testosterone and 5 mg. of prednisone daily appeared to be satisfactory. Testosterone was later dropped to 12·5 mg. daily, but there was a slight fall in the haemoglobin level on this dose.

After a further 8 months the drugs were once again discontinued, but in 6 weeks there was a further slight fall in the haemoglobin level and it was decided not to wait and see if this fall would continue but to recommence treatment. She was given testosterone, 25 mg., and prednisone, 10 mg., daily, each being given in 2 daily doses. Later events showed this to have been wise policy, since there was a further drop over the next few weeks before the drugs again began to

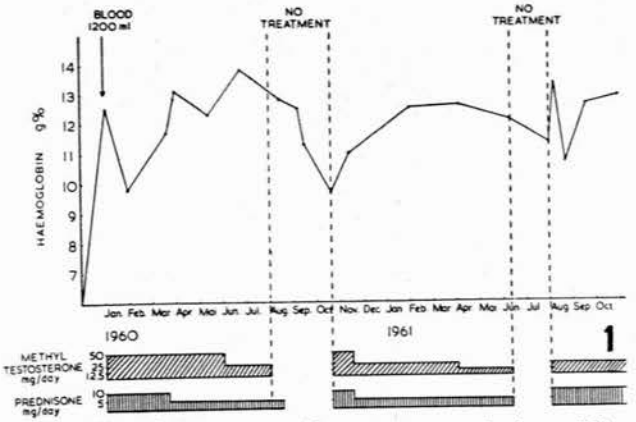

Fig. 1. Effect of testosterone-prednisone treatment on the haemoglobin level in case 1 (Ju. W., 13 years old in 1961).

show their haematopoietic effect. Since that time (August 1961), the haemoglobin has been well maintained. The patient has not required blood transfusion since December 1959.

Despite satisfactory haemoglobin levels and increased marrow activity, no real reticulocyte response has ever been seen. This was surprising, but since the children live some 200 miles from Cape Town and are only seen periodically and never for more than a few days at a time, it is possible that a reticulocytosis has been missed.

Case 2

Jo.W., a brother of the other patient, was 7 years old when first seen. His haemoglobin chart is shown in Fig 2 and treatment was similar to that given to his sister. During the first period, a good haemoglobin level was achieved and maintained, but when the drugs were stopped after 7 months this fell just as had happened with his sister. Since then the haemoglobin has never reached its previous levels and it is probable that the testosterone was reduced too much. In June 1961 the figure was 7·9 G. per 100 ml. The boy was suffering from pertussis at the time, and this may have affected the haemoglobin figures. In spite of this, treatment was stopped since his sister's treatment was being discontinued at that time.

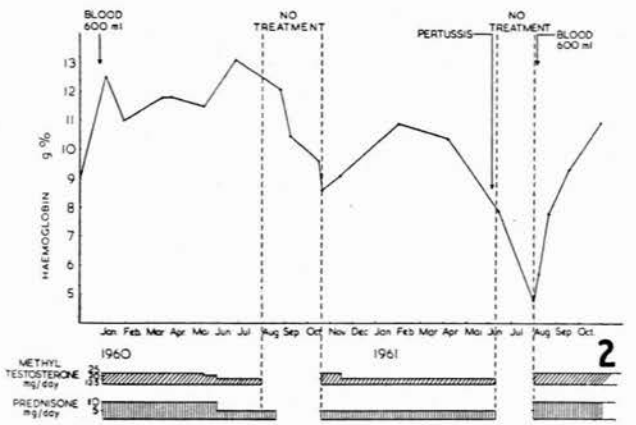

Fig. 2. Effect of testosterone-prednisone treatment on the haemoglobin level in case 2 (Jo. W., 9 years old in 1961).

When he was next seen the haemoglobin had fallen to the rather alarmingly low level of 4·8 G. per 100 ml. He was re-admitted to hospital and restarted on 25 mg. of testosterone and 10 mg. of prednisone daily.

After one week his parents wished to take him home to the country, and although there had been a slight rise of haemoglobin to 5·7 G. per 100 ml., it was thought unwise to release him from close medical supervision without doing something more; he therefore received one pint of blood before leaving hospital. Had he remained he might well have attained a sufficient haemoglobin rise to have made the transfusion unnecessary. One month later the haemoglobin figure stood at only 7·8 G. per 100 ml., but in the next month it rose to 9·3 G. per 100 ml., and 6 weeks later (the final figure on the chart) it was 10·9 G. per 100 ml. This illustrates well the latent period, mentioned by Shahidi and Diamond, which occurs before the effects of treatment are seen. As with his sister, no good reticulocyte response has ever been observed in this boy.

White Cells and Platelets

Granulocytes in both these children responded rather more slowly than the haemoglobin, another point emphasized by the Boston workers. Nevertheless, after 4 months' treatment both children had fairly satisfactory polymorph counts of the order of 50%. Subsequently, these fell to rather low levels even while the children were still on treatment. Their most recent figures were a little under 30% in each case.

Platelet counts in the girl have risen from pre-treatment levels of 20 - 50,000 per c.mm. to around 100,000 per c.mm. The boy's platelets also rose to similar levels, but latterly have averaged only about 35,000 per c.mm., although there has been no bleeding tendency. As with his haemoglobin, the lowered platelets may be an indication of inadequate drug dosage.

DISCUSSION

It is clear that these two children cannot manage without continuous drug therapy, and a recent report by Shahidi and Diamond[5] supports this view. Treatment was stopped in 2 of their patients suffering from the congenital type of this condition, and relapse soon followed. In their cases of the 'acquired' type, i.e. from the toxic effect of certain drugs, it was found that treatment could be stopped altogether after a while in those patients who showed a response, the marrow thereafter continuing to function normally.

It would seem that in patients such as ours treatment will have to be continued indefinitely, and one must accordingly be aware of the potential dangers of such long-continued therapy. In our patients hirsuties, acne and cushingoid features have not been much of a problem. There has been some genital enlargement in the boy, but not to a marked degree. The girl has some growth of pubic hair and signs of breast development, but since she is approaching puberty this may not be abnormal. It remains to be seen whether or not the onset of menstruation will be affected.

There has been no X-ray evidence, in either child, of osteoporosis on the one hand or premature epiphyseal fusion on the other. Both are of normal height for their age.

It is hoped that on this regime the simultaneous use of anabolic and catabolic substances may result in a balance being struck as regards bone growth.

On the other hand, the testosterone-prednisone therapy is the only effective one available at present, and there would seem to be no option but to continue it at the minimum effective dosage. It can only be hoped that there may still, at some time, be a spontaneous reactivation of the bone marrow, or that a better method of treatment will become available.

In the near future it is proposed to replace methyl testosterone with a less virilizing anabolic hormone, since the side-effects of testosterone, although not very marked, may make the children the subject of comment by their fellows as they grow older.

Another point of interest in this family is that the mother has become pregnant again. It was explained to her that there was perhaps a 25% chance of the baby being affected, but since there are already 2 normal children in the family, it was decided to let matters take their natural course. The result of this pregnancy is awaited with interest and a little disquiet.

In conclusion it must be pointed out that, although the method of treatment described has been effective in these 2 children, this is not always the case. One child in another part of Southern Africa did not benefit from therapy,[6] and another child, cared for by a paediatrician elsewhere in this country, responded well at first, but died suddenly 5 months after treatment had been started.[7]

SUMMARY

The long-term treatment of 2 patients with Fanconi's anaemia by a combination of testosterone and prednisone is reported. Blood levels rose, and were maintained without the need for blood transfusion as long as adequate dosage of the drugs was given. On 2 occasions cessation of treatment was followed by relapse in each patient.

It would appear, in the light of our present knowledge, that treatment will have to be continued indefinitely. The possible dangers inherent in this policy are appreciated.

Though satisfactory levels have been achieved in our 2 patients, it is clear that this treatment of Fanconi's anaemia is not invariably successful. It is nevertheless felt that this method of treatment should be more widely known, since it is applicable not only to the Fanconi type of anaemia, but to all cases of hypoplastic and aplastic anaemia in children whether the cause is congenital or acquired.

ADDENDUM

In November 1961 'dianabol' was substituted for methyl testosterone in treatment. The girl received 1 mg., and the boy 0·5 mg., twice daily. When last seen in March 1962, both children were maintaining good haemoglobin levels. The new baby, aged 2 months, was also seen at this time, and no physical defects were discovered.

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