CORTISONE THERAPY IN ERYTHROGENESIS IMPERFECTA

BY

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(RECEIVED FOR PUBLICATION FEBRUARY 8, 1956)

A rare but distinctive condition, which may be called erythropoiesis imperfecta (Cathie, 1950) or infantile pure red-cell anaemia, is gaining recognition. The nomenclature is, however, confusing. For example, some cases have been reported in later childhood, rendering inappropriate the word 'infantile'. Again, the varied titles illustrate the confusion of terminology. In the widest sense, i.e., without special reference to the infantile type, this erythropoietic disorder has been denoted by erythrophthisis (Kaznelson, 1922), pure red-cell anaemia (Lescher and Hubble, 1932), congenital hypoplastic anaemia (Diamond and Blackfan, 1938), chronic congenital regenerative anaemia (Smith, 1949), chronic idiopathic erythroblastopenia (Gasser, 1949), erythropoiesis imperfecta (Cathie, 1950) and anerythrocytogenic anaemia (Loeb, 1951).

Over 30 cases of infantile type (referred to here as erythropoiesis imperfecta) are on record (Josephs, 1936; Diamond and Blackfan, 1938; Kohlbry, 1941; Hoyer, 1942; Rubell, 1942; Robson and Sweeney, 1948; Smith, 1949; Cathie, 1950; Lelong, Josephs, Desmonts and Colin, 1951; Anderson, 1952; Donelly, 1953; Aldridge and Kidd, 1953; Kass and Sundal, 1953; Verger and Léger, 1953; Fisher and Allen, 1953; Burgert, Kennedy and Pease, 1954; Bernard, 1954). These descriptions monotonously reiterate that hitherto the only treatment capable of prolonging life was regular, and usually frequent, blood transfusion.

The case which we refer to here has been fully described (Robson and Sweeney, 1948) from the clinical and haematological aspects. The ineffectiveness of iron and liver preparations was then emphasized, while the life-prolonging effect of frequent blood transfusions was graphically illustrated. More recently, Coles (1955) reported on the failure of cobaltous chloride to produce a haematological remission in this child. A dose of 50 mg. daily was used for a fortnight and followed immediately by 100 mg. daily for a similar period. During this treatment the haemoglobin level continued to fall and there was no increase in the reticulocyte count. Our recent preliminary results with oral cortisone in this patient have been unexpectedly gratifying and are described and discussed here.

Case Review

Before Cortisone Treatment. D.S., now aged 10 years, had since 18 months of age (September, 1946) received regular blood transfusions at approximately three-monthly intervals for eight years, up to the start of cortisone therapy. His two lowest recorded haemoglobin values (Sahli) were 20\%, (concurrent erythrocyte count, 1,230,000 per c.mm.) in September, 1946, and 14\% in February, 1951. Reticulocyte counts varied between 0 and 0.3\%, and leucocyte counts between 6,100 and 16,800 per c.mm. with normal differential counts. Platelet counts ranged from 200,000 to 250,000 per c.mm. Myelograms (Table 1) showed very few red cell precursors as the only consistent abnormality. Leucopoiesis and megakaryopoiesis were always normal. Hypopcellularity of marrow, previously present, was not apparent in 1952, while a high percentage of lymphocytes, some of which were in retrospect erythrocytes, was almost a constant feature. An early bone-marrow biopsy (September, 1947) was examined by Dr. R. G. Macfarlane, who considered that it exhibited an erythroblastic hypoplasia, almost amounting to aplasia. Unfortunately, a myelogram was omitted just before cortisone treatment.

Cortisone Therapy. By 1954 the patient had become so scarred from the incisions for blood transfusions that sites for successful transfusion required increasing deliberation. As there had been no response to cobalt therapy in 1951 (Coles, 1955), a brief trial of cortisone treatment, although empirical, seemed justified.

In early September, 1954, when about due for a transfusion, as his haemoglobin value had fallen to 34\%, treatment with cortisone (50 mg., orally, daily) was begun (Fig. 1). During the next six months this dosage was maintained. His haemoglobin level rose steadily to 90\% in three months and remained so for a similar period, unaided by blood transfusion or other treatment. Indeed, no further resort to transfusion has been necessary. As we were anxious to ascertain whether

* The late Dr. T. Robson.
there had been a cortisone-induced or spontaneous remission he was now admitted for more detailed haematological investigation while on and off cortisone therapy.

On March 7, 1955, he was admitted to hospital. For the next week the dose of cortisone was reduced to 25 mg. daily (Fig. 2) without any fall in the haemoglobin value. Treatment was now suspended and at the end of the next fortnight the haemoglobin level had dropped to 69%. Cortisone treatment was then resumed, using a dose of 75 mg. daily for the next two days. His haemoglobin value had now risen to 84%, where it was maintained for a further five days while receiving 50 mg. of cortisone daily.

Treatment was now stopped a second time and the haemoglobin value again fell. There was a steady decline to 62% by the end of a fortnight. Recom mencement of cortisone therapy (50 mg. daily) was followed by a slow rise in the haemoglobin level to 70% by the end of three weeks. A week later it had reached 80% when he was discharged from hospital (May 17, 1955).

For the next three months at home he continued to take 50 mg. cortisone daily. At the end of the first month the haemoglobin level reached 88%. There was little further change till two months later (August 18) when it was 83%. The concurrent blood urea value, undetermined since early childhood, was unexpectedly found to be 60 mg. per 100 ml. This and subsequent results from blood were obtained by finger-prick as there were no accessible veins. Urine microscopy was normal and there was no albuminuria. The cause of this mild azotaemia, whether cortisone, transfusions, or the earlier anaemia of the disease, was obscure.

To decide if cortisone was responsible the dose was promptly reduced to 37.5 mg. daily. Six weeks later (October 3) the blood urea level, checked weekly, had dropped to 46 mg. per 100 ml. The dose of cortisone was now further reduced to 25 mg. daily. After almost two months on this dose (November 25) the blood urea value had fallen to 38 mg. per 100 ml with no associated undue drop in the haemoglobin value (77%).

At the time of writing (December, 1955) a further reduction in the dose of cortisone is under consideration.

Two other notable haematological features were observed during the administration of cortisone. These were an impressive reticulocytosis and a sustained hyperchromic macrocytosis. Both were studied in greater detail during the final restoration of treatment.

The pattern of the reticulocyte response at this stage was difficult to explain as there were two very distinct spikes (Fig. 2). The first of these appeared on the twelfth day, following a steady rise from 0.6 to 7.9% and succeeded by a steady drop to 1.4% over the next week. The second peak (9.5%) occurred exactly one week later. After a further fortnight the reticulocyte count had steadily declined to 1%. Subsequent values have varied from 0.5 to 2%.

The development of hyperchromasia during treatment was striking (Table 2). The colour index before cortisone administration was invariably close to unity. Values of 1.3 and above first appeared about six months after the initial administration of cortisone but persisted in the two phases, each lasting a fortnight, off treatment, and also during later maintenance of treatment.

Since macrocytosis, as judged by the blood-films, seemed to accompany this hyperchromasia, it was decided to determine the discrete blood values. The results during 'full' control with cortisone (July 11, 1955) were: haematocrit value, 37.5%; mean corpuscular volume, 120 cμ; mean corpuscular haemoglobin concentration,
CORTISONE IN ERYTHROGENESIS IMPERFECTA

CORTISONE

IN

ER

YTHROGENESIS

IMPERFECTA

BLOOD

TRANSFUSIONS

1953' 1954'

0

50

100

36% and mean cell diameter, 7·8 μ, accompanied by a haemoglobin level of 85%, erythrocyte count of 3·11 millions per c.mm., colour index of 1·37 and a reticulocyte count of 1·5%. The corresponding blood-film showed moderate anisocytosis and slight poikilocytosis. These results are given in detail as they provide further evidence that the haematological improvement was not due to a spontaneous remission. If the latter had occurred then a normocytic, normochromic erythrocyte pattern should have accompanied the return of the haemoglobin level to the normal range.

From these observations, therefore, it was concluded that the administration of 50 mg. of cortisone daily, begun just when the usual blood transfusion was due, had by three months produced a haematological remission, which was maintained on this dosage for the next three months. Then, during two phases of cessation of treatment, each for two weeks, the haemoglobin value fell but rose again on resuming treatment. The second suspension of treatment was included: (1) To verify the repeatability of the observation. (2) To provide the

TABLE 2
RISE IN THE COLOUR INDEX DURING CORTISONE THERAPY*

<table>
<thead>
<tr>
<th>Date</th>
<th>Hb. (%)</th>
<th>R.B.C. (m./c.mm.)</th>
<th>Colour Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Cortisone Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sept., 1946</td>
<td>20</td>
<td>1·23</td>
<td>0·81</td>
</tr>
<tr>
<td>Aug., 1947</td>
<td>29</td>
<td>1·44</td>
<td>1·04</td>
</tr>
<tr>
<td>Nov., 1948</td>
<td>19</td>
<td>1·1</td>
<td>0·86</td>
</tr>
<tr>
<td>Sept., 1949</td>
<td>20</td>
<td>1·23</td>
<td>0·81</td>
</tr>
<tr>
<td>Dec., 1950</td>
<td>29</td>
<td>1·53</td>
<td>0·97</td>
</tr>
<tr>
<td>Nov., 1951</td>
<td>42</td>
<td>2·08</td>
<td>1·01</td>
</tr>
<tr>
<td>Nov., 1952</td>
<td>40</td>
<td>2·02</td>
<td>0·99</td>
</tr>
<tr>
<td>Feb., 1953</td>
<td>46</td>
<td>2·22</td>
<td>1·04</td>
</tr>
<tr>
<td>During Cortisone Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sept., 1954</td>
<td>68</td>
<td>3·21</td>
<td>1·06</td>
</tr>
<tr>
<td>Oct., 1954</td>
<td>76</td>
<td>3·52</td>
<td>1·08</td>
</tr>
<tr>
<td>Feb. 19, 1955</td>
<td>87</td>
<td>3·91</td>
<td>1·12</td>
</tr>
<tr>
<td>March 15, 1955</td>
<td>88</td>
<td>3·24</td>
<td>1·37</td>
</tr>
<tr>
<td>April 15, 1955</td>
<td>75</td>
<td>2·82</td>
<td>1·34</td>
</tr>
<tr>
<td>May 6, 1955</td>
<td>74</td>
<td>2·69</td>
<td>1·37</td>
</tr>
<tr>
<td>June 21, 1955</td>
<td>83</td>
<td>3·10</td>
<td>1·36</td>
</tr>
</tbody>
</table>

* For simplicity, only a few results are recorded.

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opportunity for a bone-marrow study when cortisone therapy had been stopped for a clear two weeks. The difference between this myelogram (April, 1955) and that obtained during ‘full’ haematological recovery (June, 1955) permitted a partial assessment of the bone-marrow changes produced by cortisone (Table 1). The salient change in erythropoiesis was a marked increase (2·0 to 13·2%) in the orthochromatric normoblasts but only slight in the macronormoblasts along with a moderate inverse trend for the more primitive erythroid cells (pro-erythroblasts and basophilic normoblasts), although the polychromatric normoblasts were scarcely altered numerically. Erythroid mitosis had increased from 0·5 to 1·5%, while the myeloid-erythroid ratio was reduced from 3·6 to 1·8 and the leuco-erythroid ratio from 1·4 to 1·04. Although inspection of the earlier serial myelograms (Table 1) shows a trend towards normality of both erythropoiesis and cellularity of the marrow even before cortisone treatment was begun, there was no corresponding reduction in the volume and frequency of blood transfusions required.

During the administration of cortisone we have detected no adverse effects, apart from the mild azotaemia mentioned. Neither hypertension, cardiac enlargement radiographically, persistent glycosuria, nor the facies of Cushing’s syndrome has appeared after more than one year on cortisone therapy. The results of detailed liver function tests were normal.

Discussion

We do not claim that cortisone has ‘cured’ or even corrected the basic disorder, partly because of our short-term study and partly since we have not produced a normocytic, normochromic, erythrocyte status. It can, however, be reasonably concluded that oral cortisone therapy has provided a convenient, superior and apparently safe alternative to blood transfusion. The disadvantages of the latter are the need for frequent short phases of treatment in hospital, the cosmetic scarring of the limbs from frequent cut-down procedures, the increasing technical difficulty, the unphysiological fluctuations in the haemoglobin level, the periodic invalidism just before the need for transfusion, and such hazards as transfusion reactions, cardio-respiratory stresses and acquired haemochromatosis. While the last-mentioned complication is considered to be inevitable, it is not clinically apparent in our patient, although the bone-marrow microscopy shows heavy deposits of stainable iron.

Until recently the only reliable treatment of erythrogenesis imperfecta was palliative repeated blood transfusion. This view remains unaltered despite the trial of numerous alternatives. Briefly, the list of ineffective treatments includes the conventional haemopoietic agents, various vitamins and hormones, and also short-wave diathermy to the long bones (Cathie, 1952). Splenectomy may have aided the remission in one patient, although the authors (Blackfan and Diamond, 1944) do not make this claim, while Cathie (1952) was unimpressed with the results of this operation. Spontaneous remission has been recorded (Blackfan and Diamond 1944; Burgert et al., 1954). Although the oral administration of cobaltous chloride has been twice reported (Seaman and Koler, 1953; Fountain and Dales, 1955) as apparently effective in the adult type of pure red-cell anaemia, this treatment was ineffective (Coles, 1955) in our patient.

Recent attention has been focused on the use of cortisone and A.C.T.H. in erythrogenesis imperfecta. Nevertheless, the rather limited evidence available clearly indicates that this steroid therapy is far from uniformly effective. For instance, Cathie (1952) found it valueless in four cases; Smith (1953) likewise in two cases and Burgert and colleagues (1954) in one patient. Gasser (1951), however, reported the recovery, during cortisone therapy, of an infant with pure red cell anaemia, which followed measles. Two other favourable reports (Kass and Sundal, 1953; Fisher and Allen, 1953) merit more detailed consideration.

Kass and Sundal (1953) described definite haematological improvement from A.C.T.H. therapy in a girl aged 3 with erythrogenesis imperfecta, combined with defective myelopoiesis. They gave two brief courses of A.C.T.H. separated by an interval of 10 weeks. A complete assessment of the contributory effect of A.C.T.H. was, however, masked by a blood transfusion on the sixth day of the first course of 16 days, while the second course for 22 days was begun four days after a blood transfusion. During the second week of treatment, on each occasion, there was a distinct reticulocytosis with a maximal value of 8% in the second course, in contrast to values at all other times which were usually well below 2%. Bone-marrow examination just after the first course of A.C.T.H. showed an active normoblastic erythropoiesis with numerous macroblasts and a brisk myelopoiesis, while the myelogram just before the second course showed an ordinary number of marrow cells, scanty erythroblasts and a striking abundance of lymphocytes, which were the usual features of all the earlier myelograms. Furthermore, after each course of A.C.T.H. the need for blood transfusion was prolonged by several weeks. Although not commented on by the authors, there was, as our study more clearly shows, an increase of the colour index above unity, due presumably to the steroid therapy.

Fisher and Allen (1954) reported their observations on a 3-year-old girl with erythrogenesis imperfecta, which was successfully controlled by
cortisone for at least eight months. Indeed the transient occurrence of polycythaemia left no doubt as to the potent erythropoietic action of cortisone. They begun cortisone therapy (50 mg. daily) about two weeks after a blood transfusion, and when the haemoglobin value had dropped to 87%. After two months of cortisone treatment this value rose to 113% and the administration of the drug was then stopped for one month. During treatment the maximal reticulocyte count (2-5%) was reached at the end of one month. A maintenance dose of 12.5 mg. of cortisone on alternate days sufficed to keep the haemoglobin level just above 80% throughout the next few months. Immediately after the first two months of cortisone therapy the marrow revealed a normal red cell series with maturation of normoblasts. There were 1.5% pro-erythroblasts and 30.5% normoblasts as compared with the myelogram before treatment showing erythroid hypoplasia (pro-erythroblasts, 7-0% and normoblasts, 2-0%).

Any extensive discussion on the possible modes of action of cortisone (and A.C.T.H.) in this condition would be too speculative to be valuable. Nor is there a ready explanation why only some cases, an as yet undetermined proportion, show haematological improvement from this drug. Their initial quantity and qualitative profile of erythroid precursors does not appear to vary significantly from that displayed by some cases which were refractory to cortisone medication.

Summary

A boy, aged 10 years, with erythrogenesis imperfecta, now successfully controlled for over one year by the oral administration of cortisone, is reported. This treatment was instituted just when his regular blood transfusion was indicated and no further resort to transfusion has been necessary. It was verified that the remission was due to cortisone and not spontaneous. After almost one year of cortisone treatment (50 mg. daily) mild azotaemia, but no other complication attributable to cortisone, was detected. Reduction of the dose to 25 mg. daily corrected the azotaemia without the recurrence of any severe degree of anaemia.

Under cortisone therapy an active and apparently normal erythropoiesis was obtained. The corresponding erythrocytic pattern in the peripheral blood, however, was odd, for a normal haemoglobin level was associated with erythrocytic hyperchromasia and macrocytosis. It was concluded that treatment with cortisone, although empirical and effective in some cases of erythrogenesis imperfecta only, provided for our patient a convenient, superior and apparently safe alternative to conventional and obligatory blood transfusions.

It is a pleasure to record our thanks to Dr. R. G. Macfarlane for his report on one of the earlier bone-marrow preparations; to Dr. T. A. J. Wickham for his review of the subsequent myelograms; to Dr. R. V. Facey and his staff for the numerous haematological investigations.

References

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