THE TREATMENT OF HYPOPLASTIC ANAEMIA AFTER CHLORAMPHENICOL

BY

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The first reports of the use of chloramphenicol in human subjects appeared in 1948 (Ley, Smadel and Crocker; Payne, Knaudt and Palacios) and in these patients toxic effects were not observed. In 1950 Volini, Greenspan, Ehrlich, Gonner, Felsenfeld and Schwartz gave chloramphenicol to two patients suffering from typhoid fever and one patient suffering from brucellosis, and they observed a marked fall in the peripheral white cell count, especially affecting the polymorphonuclear leucocytes; the lymphocyte and monocyte counts remained unaffected, and after stopping the drug the white cell count returned to normal. Gill (1950) reported similar changes in the white cell count of two infants aged 4 months and 13 months, and in these patients the haemoglobin level and red cell count remained unaffected. Rich, Ritterhoff and Hoffmann (1950) described the first fatal case of aplastic anaemia in an adult following chloramphenicol therapy, and similar fatal cases in children were reported by Hawkins and Lederer (1952) and Wolman (1952) in this country and by Sturgeon (1952) in America.

Osgood (1953) has reviewed the mortality rates for aplastic anaemia in the United States of America and has claimed that they have not increased since chloramphenicol became available. In spite of this, some writers (Franklin and Garrod, 1953) feel that a potentially toxic drug such as chloramphenicol should not be used, while others recommend its use only in exceptional circumstances. Hodgkinson (1954) has investigated the incidence of blood dyscrasias associated with chloramphenicol in the British Isles, but he did not give details of the treatment received by these patients except to state that three of them were still being maintained by blood transfusion. It might be helpful to clinicians encountering similar cases to record our experience with the treatment of a patient suffering from hypoplastic anaemia after chloramphenicol.

Case Report

A boy aged 6 years was admitted to hospital for investigation of anaemia. He had been well until 17 weeks before admission when he developed acute bronchitis and was treated with chloromycetin palmitate, 2 drachms six-hourly for seven days (total dosage 7 g.). Eight weeks later he developed whooping cough and was again given chloromycetin palmitate, 2 drachms six-hourly for seven days (total dosage 7 g.). Shortly after the drug was discontinued his parents noticed that he was pale. Five weeks later he developed tonsillitis and was treated with oral penicillin. He gave no history of bleeding into the skin or elsewhere, and, apart from increasing pallor and tiredness, there were no abnormal symptoms.

On admission to hospital the temperature, pulse rate and respiration rate were normal and the only abnormal signs were marked pallor and an apical systolic murmur.

A blood count gave Hb 32% (4.7 g.), white cell count 7,000 per c.m.m. (neutrophils 11%, lymphocytes 89%), platelet count 46,000 per c.m.m., reticulocytes less than 1%. Bleeding and clotting times were normal.

Radiographs of the long bones were normal.

Results of sternal marrow puncture were:

<table>
<thead>
<tr>
<th>Type of Cell</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticulum cells</td>
<td>3.2%</td>
</tr>
<tr>
<td>Myeloblasts</td>
<td>0.8%</td>
</tr>
<tr>
<td>Promyelocytes</td>
<td>2.0%</td>
</tr>
<tr>
<td>Neutrophil myelocytes</td>
<td>4.4%</td>
</tr>
<tr>
<td>... metamyelocytes</td>
<td>10.4%</td>
</tr>
<tr>
<td>... polymorphonuclear cells</td>
<td>7.6%</td>
</tr>
<tr>
<td>... band cells</td>
<td>7.2%</td>
</tr>
<tr>
<td>Eosinophil myelocytes</td>
<td>1.2%</td>
</tr>
<tr>
<td>... metamyelocytes</td>
<td>0.8%</td>
</tr>
<tr>
<td>... polymorphonuclear cells</td>
<td>0.4%</td>
</tr>
<tr>
<td>Unclassified cells</td>
<td>1.2%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>40.4%</td>
</tr>
<tr>
<td>Mononuclear cells</td>
<td>0.4%</td>
</tr>
<tr>
<td>Pronormoblasts</td>
<td>0.4%</td>
</tr>
<tr>
<td>Macronormoblasts</td>
<td>0.4%</td>
</tr>
<tr>
<td>Basophilic normoblasts</td>
<td>4.0%</td>
</tr>
<tr>
<td>Polychromic</td>
<td>10.4%</td>
</tr>
<tr>
<td>Orthochromic</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

The marrow smears showed a relatively acellular marrow in which there were very few cells in mitosis. Both leucopoietic and erythropoietic tissue was greatly depressed and the more primitive precursors were scanty. No megakaryocytes could be identified. Many of the erythrocytes showed punctate basophilia.
A diagnosis of hypoplastic anaemia was made and treatment with a number of haematinics was given (Fig. 1). During the period of treatment, lasting 41 weeks, he received ferrous sulphate, 300 mg. daily, and for the first 13 weeks he was given vitamin C, 200 mg. daily. During the initial five weeks of treatment liver extract ('campolon', 2 ml.) was given intramuscularly twice weekly, and for the next eight weeks he was given vitamin B12, 75 mg. daily by mouth. From the thirteenth week to the thirty-sixth week he received 50 mg. of nicotinamide daily by mouth and in addition he was given an intravenous injection of 100 mg. nicotinamide during the thirteenth week. Transfusions of whole blood or packed red cells were given on five occasions during the first three months of treatment. During this period further bone marrow studies were performed and no alteration in the marrow picture was found. The rate of fall of haemoglobin was steady during this period but shortly after nicotinamide was started a reticulocytosis of over 2% was present in the peripheral blood, whereas previously the reticulocyte count had been less than 1%, and a further bone marrow puncture showed evidence of regeneration. The level of haemoglobin, however, continued to fall but, because of the evidence of blood regeneration revealed by the reticulocyte count and bone marrow studies, no further transfusions were given and subsequently the haemoglobin rose steadily and the boy recovered completely. Throughout the early stages of treatment the platelet count varied from 29,000 to 55,000 per c.mm.; it was 73,000 per c.mm. at the twenty-seventh week and 126,000 per c.mm. at the thirty-third week. No haemorrhages occurred into the skin, alimentary tract, or urinary tract.

Discussion

Many substances have been prescribed for patients suffering from anaemias of the hypoplastic or aplastic type. They have included copper, cobalt, manganese, folic acid, thyroxin, insulin, testosterone, stilboestrol, vitamin C, vitamin B12, A.C.T.H., and cortisone. Boon and Walton (1951) concluded from their experience of 25 patients that no drug had yet proved of value and that blood transfusion was the mainstay of treatment. Adams (1951) described 27 cases of aplastic anaemia and came to the same conclusion. Transfusion seemed to prolong life and one of his patients received 217 pints of blood over a period of nine years.

There is experimental evidence that in rabbits (Vasile, 1940) and in dogs (Handler and Featherston, 1943) nicotinamide plays a part in the maturation of red blood cells but there is no direct evidence that this substance is essential for normal erythropoiesis in human beings. Nicotinamide, which is the amide of nicotinic acid and has the advantage of not causing vasodilatation, is thought to act as a coenzyme, and lack of this vitamin results in interference with respiration of the immature red cells. Normal red blood cells contain relatively large amounts of nicotinic acid (Bicknell and Prescott, 1946).

In this patient, recovery from the hypoplastic anaemia began shortly after nicotinamide was started. This response may have been entirely fortuitous and may have coincided with spontaneous regeneration of the bone marrow; or it may have resulted from delayed action of one of the other haematinics which had been prescribed; or nicotinamide may have exerted a beneficial effect on red cell production. Whatever the explanation it would seem to be reasonable to give nicotinamide to patients suffering from this form of anaemia, especially since no other treatment apart from blood transfusion is known to have a beneficial effect on the course of the disease. Many of the fatal cases
HYPOPLASTIC ANAEMIA AFTER CHLORAMPHENICOL

that have been reported died from haemorrhage which was uncontrollable in spite of blood transfusions, but this patient was fortunate in that he did not have any bleeding episodes.

Summary
The clinical findings in a boy of 6 years of age suffering from hypoplastic anaemia after chloramphenicol are reported. The details of treatment are described and it is thought that nicotinamide may have had a beneficial effect on the anaemia.

I am indebted to Dr. B. G. Ockenden for the bone marrow studies and to Professor Norman B. Capon for his advice.

REFERENCES
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