**Brief Report**

**Erythropoiesis after Exchange Transfusion in Hemolytic Anemia**

By Allan J. Erslev and Joseph P. McKenna

The control of red cell production is undoubtedly geared toward maintaining the red cell mass at a functionally optimal size. Since the primary function of the red cell mass is to transport oxygen to the tissues, it is generally assumed that the control is triggered by the tissue tension of oxygen. Recent studies indicate that the oxygen tension in one target area, the kidney, is inversely proportional to the production or release of the hormone erythropoietin, and that the rate of red cell production is influenced by the amount or concentration of this hormone in circulating blood. However, it is not known if this system provides the sole control of red cell production.

The red cells do have other functions than that of carrying oxygen. They participate in CO₂ transport and they provide important bulk and viscosity to circulating blood, making it possible that other parameters play a role in the regulation of red cell production.

The possibility of dual or even multiple control mechanisms is usually invoked whenever clinical or experimental observations do not seem to fit the tissue-hypoxia control mechanism. One such observation was reported by Stohlman in 1962 and used to support the hypothesis of a dual control of red cell production. Stohlman in a review mentioned that the rate of red cell production was reduced in a patient with hereditary spherocytosis after a 40 per cent exchange transfusion. Since the hemoglobin concentration was kept constant, he felt that the reduction in red cell production could not be related to a change in tissue tension of oxygen but must have been caused by some other regulatory mechanisms.

The present study was made in order to confirm this interesting observation, using reticulocytes, bone marrow differential and serum iron turnover in patients with hemolytic anemia before and after exchange transfusion.

**Materials and Methods**

Three adult patients with hereditary spherocytosis and splenomegaly, and one adult patient with acquired hemolytic anemia, were admitted to the Clinical Research Center for exchange transfusion. Complete hematologic workup in the patients with hereditary spherocytosis revealed the classical picture of chronic mild anemia, spherocytosis, negative...

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Hereditary Spherocytosis

B. M. E: M. ratio

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<th></th>
<th>1</th>
<th>0.9</th>
<th>1.5</th>
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<th>1.2</th>
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<td>Serum iron turnover mg/100 ml/24 hr</td>
<td>2.4</td>
<td>2.4</td>
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<td>2.6</td>
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<tr>
<td>Retic. %</td>
<td>43%</td>
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<tr>
<td>Hgb. gm</td>
<td>14</td>
<td>12</td>
<td>10</td>
<td>8</td>
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<td>DAYS</td>
<td>0</td>
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Fig. 1.—The effect of exchange transfusion on the hemoglobin reticulocyte count, serum iron turnover and bone marrow erythroid: myeloid ratio in three patients with hereditary spherocytosis. Normal serum iron turnover is 0.6 mg./100 ml./24 hours.

Coombs' test, high MCHC, increased osmotic fragility and significant family history. The patient with acquired hemolytic anemia had a positive direct Coomb's test but negative indirect test. She had had a splenectomy 4 years previously and was now tolerating a compensated hemolytic state without difficulties. Erythrokinetic studies were carried out using the techniques and calculations of Bothwell and associates.

The exchange transfusions were made with fresh compatible blood over a 2-day period. Two to four exchanges were made each day and the calculated exchange ranged from 41 per cent of the blood volume to 61 per cent. The exchange was based on blood volume measurements with Cr51 and was monitored with frequent hemoglobin and hematocrit determinations in order to maintain the hemoglobin concentration as constant as possible. There were no febrile transfusion reactions and no significant mechanical problems were encountered in the exchange procedures.

RESULTS

Figures 1 and 2 give the reticulocyte count, the serum iron turnover and the bone marrow erythroid-myeloid ratio before and after exchange transfusions. The reticulocyte counts tended to decrease right after the exchange transfusions, presumably a reflection of the mechanical removal of reticulocytes. However, the serum iron turnovers were not significantly altered in any one of the four patients. The bone marrows obtained before the exchange transfusions were all hypercellular with erythroid hyperplasia. In only two cases were bone marrow aspirations obtained shortly after the exchange transfusions. Using the crude E/M ratio as a guide in these cases, exchange transfusion did not appear to cause a significant change.
Fig. 2.—The effect of exchange transfusion on red cell production and red cell destruction in a patient with acquired hemolytic anemia.

In the patient with acquired hemolytic anemia the exchange transfusion resulted in an immediate reversal of the positive Coomb's test and a prolongation of red cell life span from a Cr$^{51}$ half-life of 6 days to a half-life of 12 days. Although the Coomb's titer slowly rose in the postexchange period, the red cell life span, as judged from the straight Cr$^{51}$ curve, was not changed initially. On the eighth day the patient developed chills, fever, severe backache and hemoglobinuria. Twenty-four hours later the Cr$^{51}$ cells, labeled at the end of the second day of exchange, disappeared from the circulation. These observations indicate that it took eight days to reach a lytic concentration of antibody on the surface of the transfused red cells.
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DISCUSSION

A simple feedback control mechanism of red cell production based on the tissue tension of oxygen in the kidney and mediated by erythropoietin has explained many, but not all, experimental and clinical observations of erythropoietic activity.\(^3\) The major unexplained observations are (1) the difficulty in demonstrating changes in erythropoietin titer between polycythemic, normal and slightly anemic individuals;\(^4\) (2) the suppressed red cell production in transfusion polycythemia despite slow blood flow and tissue hypoxia;\(^5\) (3) the “consumption” of erythropoietin by the bone marrow which prevents the concentration of hormone in blood to assert a regulating role; (4) the existence of “compensated hemolytic anemia” in which accelerated red cell production exists despite a normal hemoglobin concentration and presumably normal tissue tension of oxygen;\(^3\) and (5) suppressed but definite erythropoietic activity in anephric man and animals.\(^6\) A sixth objection, that of a reduced rate of red cell production in patients with hereditary spherocytosis after exact exchange transfusions,\(^1\) does not appear valid. In the study reported here, red cell production as measured by serum iron turnover, and in some cases by B.M. E/M ratio, did not change significantly in three patients with hereditary spherocytosis and one patient with acquired hemolytic anemia after exchange transfusion. The observation made by Stohlman\(^1\) that exchange transfusion does reduce erythropoietic activity in hereditary spherocytosis was based on his finding that the reticulocyte count decreases after an exchange transfusion. However, the mechanical removal of reticulocytes can easily explain this observation without reflecting at all on the rate of red cell production.

It is of interest that in the patient with acquired hemolytic anemia, the exchange transfusion, tolerated so well for the first seven days, resulted in a serious, acute hemolytic episode when enough lytic antibody had been attached to the red cell surface. This observation indicates the danger of performing an exchange transfusion in such patients before major surgery, since the postoperative period may be complicated by a life-threatening intravascular hemolytic event.

SUMMARY

Exchange transfusion with preservation of a constant hemoglobin concentration in three patients with hereditary spherocytosis, and one patient with acquired hemolytic anemia did not result in any significant change in the rate of red cell production as measured by serum iron turnover and bone marrow examinations. These observations support the hypothesis that tissue hypoxia controls red cell production.

SUMMARIO IN INTERLINGUA

Transfusion de excambio con preservation de un constante concentration de hemoglobina in tres patientes con spherocytosis hereditari e in un pa-
tiente con acquiritie anemia hemolytic non resultava in ulle significative alteration del rapiditate del production de erythrocytos mesurate a base de studios del transition seral del ferro e de examines del medulla ossee. Iste observa-
tiones supporta le these que hypoxia tissular exerce un influentia super le pro-
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