Fundamental Observations on the Production of Compensatory Polycythemias in a Case of Patent Ductus Arteriosus With Reversed Blood Flow

Rudi Schmid and A. S. Gilbertsen

It is generally recognized that in chronic anoxemia, erythropoiesis is often stimulated to such a degree as to produce compensatory polycythemia, as occurs for example in high altitude, in certain pulmonary and congenital heart diseases, and under experimental conditions. The exact mechanism leading to the increase in circulating red cell mass is not yet understood, but Miescher¹ and later Minot and Castle² have suggested that in these conditions, erythropoiesis is stimulated directly by anoxia of the bone marrow.

Based on morphological examinations, it has been postulated that even in polycythemia vera, anoxia of the bone marrow may be a decisive factor in the pathogenesis of this disease³. However, the studies by Berk, Burchenal, Wood, and Castle⁴ and by Schwartz and Stats⁵ have demonstrated normal marrow oxygen saturation in their cases. In secondary polycythemia due to anoxemia, the same investigators have found that the marrow oxygen saturation was reduced to the same extent as that of the corresponding arterial blood. Grant and Root⁶ have clearly shown that blood regeneration in posthemorrhagic anemia is not related to marrow anoxia. Using bone marrow cultures, Rosin and Rachmilewitz⁷ have observed increased rates of maturation and multiplication of the constituent cells if kept under high oxygen tension, whereas "injury to the hemic cells and degeneration of the cultures" occurred under low oxygen tension.

Recently, we had the unusual opportunity to observe a patient with a patent ductus arteriosus, whose marked pulmonary hypertension had led to a permanent reversal of blood flow. Compensatory polycythemia was outspoken. Since the shunt from the pulmonary into the systemic circulation occurred distal to the take-off of the left subclavian artery, the entire upper half of the body was receiving fully oxygenated blood. The blood in the aorta distal to the shunt, however, was only partially saturated. This case presented therefore a unique opportunity for studying the role of anoxia of the bone marrow in stimulating erythropoiesis.

Case Report

M. C., a 41 year old unmarried white female complained of exertional dyspnea dating back to childhood. Growth and development had been slightly retarded. Mild cyanosis on exertion had been noted since the age of 31. At 37, she developed repeated episodes of hemoptysis and was hospitalized.

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Physical examination revealed a blood pressure of 120/100 and a pulse rate of 100. There was cyanosis of the feet and definite clubbing of the toes, but no cyanosis or clubbing of the upper extremities. The lung fields were clear, and no murmurs were detectable. Right ventricular enlargement and dilatation and calcification of the pulmonary arteries. Vital capacity was 2.9 liters (88 per cent). Cardiac catheterization studies revealed moderate pulmonary hypertension.

Pertinent laboratory data showed a hemoglobin of 20.5 grams, a red blood count of 9,240,000, and a white blood count of 5,750 with a normal differential count.

During the two years following her discharge, the patient developed progressive dyspnea and orthopnea. She was digitalized and put on a salt-free diet. On readmission on December 30, 1953, the cyanosis and clubbing of the lower extremities were more pronounced than before, whereas the upper extremities and face appeared normal. The blood pressure was 100/60, the pulse rate 84. The lung fields were clear, but the heart was slightly enlarged to the right. The apex impulse was located along the left sternal border in the fourth intercostal space, and a grade 2 diastolic murmur was present in that area. P2 was accentuated. The liver edge was palpated 2 centimeters below the right costal margin.

The hemoglobin was 22.4 grams, the red blood count 7,300,000, the hematocrit 75 per cent, and the white blood count 6,500. The oxygen saturation in the femoral artery was 59 per cent as compared to 96 per cent in the brachial artery.

A diagnosis of patent ductus arteriosus with reversal of flow through the shunt was made, and on February 26, 1954, the patient underwent thoracotomy. The preoperative diagnosis was confirmed, but on partial compression of the ductus, the heart went into ventricular fibrillation and the patient expired immediately. At autopsy, a patent ductus arteriosus occurring distal to the take-off of the left subclavian artery, marked right ventricular enlargement, and marked atherosclerosis, and multiple thrombosis of the pulmonary arteries were found.

**Method of Study**

Bone marrow aspirations on the sternum and iliac crest were performed on the same day, several days prior to surgery. Approximately 1 ml. of material was aspirated from each site for morphological examination. Immediately prior to surgery, the patient was placed under light pentothal anesthesia. She was given no oxygen. Almost simultaneously, samples of blood were removed from the brachial and femoral arteries and samples of marrow were aspirated from the sternum and iliac crest for oxygen saturation studies. Using gentle suction, approximately 6 ml. of marrow were aspirated from each site under oil in a heparinized syringe. Oxygen content and capacity were determined by the methods described by Van Slyke and Neill.

**Results**

The results of the morphological studies are shown in table 1, those of the oxygen saturation studies in table 2. From table 1 it is seen that both sternum and iliac marrow in this patient manifested a marked normoblastic hyperplasia. However, as is shown in table 2, the oxygen saturation at these two sites was significantly different. The iliac marrow was only 33 per cent saturated, while the sternal marrow showed 91 per cent saturation. Thus, the sternal marrow with normal oxygen saturation, exhibited the same or even a slightly greater degree of normoblastic hyperplasia than the iliac marrow, in which the oxygen saturation was markedly decreased.
TABLE 1.—Results of Morphological Studies of the Bone Marrow

<table>
<thead>
<tr>
<th></th>
<th>Sternum</th>
<th>Ilium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Patient</td>
</tr>
<tr>
<td>Amount aspirated</td>
<td>1 ml</td>
<td>1.2 ml</td>
</tr>
<tr>
<td>Myeloid-erythroid layer (8)</td>
<td>5-8%</td>
<td>11%</td>
</tr>
<tr>
<td>Normoblasts</td>
<td>18</td>
<td>31.8</td>
</tr>
<tr>
<td>Neutrophils and precursors</td>
<td>65</td>
<td>35.6</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>Basophils</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Lymphoid cells</td>
<td>12</td>
<td>10.6</td>
</tr>
<tr>
<td>Myeloblasts and leucoblasts</td>
<td>3</td>
<td>0.0</td>
</tr>
</tbody>
</table>

TABLE 2.—Results of Simultaneous Oxygen Studies on Bone Marrow and Arterial Blood

<table>
<thead>
<tr>
<th>Specimen</th>
<th>O₂ capacity</th>
<th>O₂ content</th>
<th>O₂ saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial artery blood</td>
<td>25.6</td>
<td>21.4</td>
<td>96</td>
</tr>
<tr>
<td>Sternal bone marrow</td>
<td>26.5</td>
<td>24.1</td>
<td>91</td>
</tr>
<tr>
<td>Femoral artery blood</td>
<td>25.6</td>
<td>14.7</td>
<td>57</td>
</tr>
<tr>
<td>Iliac bone marrow</td>
<td>25.9</td>
<td>13.7</td>
<td>53</td>
</tr>
</tbody>
</table>

DISCUSSION

These data appear to invalidate the concept that bone marrow anoxia is directly responsible for increased erythropoiesis in chronic anoxemia. The normoblastic hyperplasia found in the sternal marrow cannot be explained on the basis of local bone marrow anoxia. It has been suggested that anoxemia of the blood stimulates the production or release of a humoral factor which in turn acts as an erythropoietic stimulus. Support for this latter view has been offered by the experimental studies of Reissmann, Erslev, and Hodgson and Toha, and by the clinical investigation of Oliva, Chiuni, and Tramananta. The results of the present study lend strong support to the concept of a humoral factor.

Since the completion of this study, the authors have seen a recently published abstract by Stohlman, Rath and Rose, reporting a similar case.* As far as can be determined from the abstract, their data are similar to those presently reported, except for the finding of a significant difference between the oxygen saturation in the brachial artery blood and in the sternal bone marrow. This difference may suggest that in their patient, the sternal marrow was supplied with both saturated and partially unsaturated blood. In our patient, on the other hand, the similarity of the oxygen saturation in the brachial artery blood and sternal bone marrow indicates that the sternum was receiving only fully oxygenated blood.

*Since the submission of this paper, Stohlman et al. have reported their study in detail (Blood 9: 721, 1954).

RUDI SCHMID AND A. S. GILBERTSEN
COMPENSATORY POLYCYTHEMIA

SUMMARY

A proved case of patent ductus arteriosus occurring distal to the origin of the left subclavian artery with persistent reversal of flow through the shunt and compensatory polycythemia has been reported. Studies of cellular morphology and oxygen saturation of the bone marrow in the sternum and ilium were performed. The results indicated that the sternal marrow manifested the same marked degree of normoblastic hyperplasia as the iliac marrow, although the oxygen saturation of the iliac marrow was markedly decreased as compared to the normal saturation of the sternal marrow. This demonstrates that anoxia of the bone marrow could not have been the stimulus to the increased erythropoietic activity found in the sternal marrow. The study appears to support the belief that anoxemia of the blood stimulates the production or release of a humoral factor which in turn produces increased erythropoiesis.

SUMMARIO IN INTERLINGUA

Es reportate un demonstrate caso de patente ducto arteriose, distal al origine del sinistre arteria subclavicular, con persistente reversion del fluxo a transverso le derivation e polycythemia compensatori. Esseva executate studios dcl morphologia cellular e del saturation oxygenic del medulla ossee in sterno e ilio. Le resultatos revelava pro le medulla del sterno le mesme marcate grado de hyper-plasia normoblastic que esseva characteristic del medulla del ilio, sed le saturation oxygenic del medulla del ilio esceva marcatemente reducec in comparation con le saturation normal del medulla del sterno. Iste observationes prova que anoxia del medulla ossee non pote haber essite le stimulo del augmentate activitate erythropoietique que esceva trovate in le medulla del sterno. Le studio pare corroborar le opinione que anoxemia stimula le production o le liberation de un factor humoral que de su parte causa le augmentate erythropoiese.

REFERENCES

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