The Erythropoietin/Hematocrit Relationship
in Normal and Polycytemic Man:
Implications of Marrow Regulation

By John W. Adamson

ERYTHROPOIESIS, through the humoral mechanism of erythropoietin regulation, is believed to be controlled primarily by tissue oxygen requirements. Changes in need are met in part by changes in the circulating red cell mass. Accordingly, erythropoietin has been demonstrated in the urine and plasma of patients with anemia or polycythemia of varying origin. However, investigations relating erythropoietin to erythropoiesis in normal individuals have only recently been made possible by improved assay methods. This study was undertaken to clarify the normal erythropoietin response to phlebotomy and to better define the relationship of erythropoietin to erythropoiesis in various polycythemic states.

Materials and Methods

Subjects and Experimental Procedures

In this paper erythrocytosis is defined as any condition in which there is an absolute increase in the measured red cell mass when compared to that predicted by the height (cubed)–body mass formula. Fifteen patients with erythrocytosis and fifteen normal subjects were studied. Most of the patients were admitted to the Clinical Research Center at the University of Washington Hospital. Their initial hematologic evaluation included hematocrit, white blood count, platelet count, basophil count, and leukocyte alkaline phosphatase stain. A routine urinalysis was performed to rule out significant proteinuria. A chest x-ray was performed and, where indicated, intravenous pyelography, with special attention to the early filling phase and rate of washout. In those individuals with suspected erythrocytosis, the red cell mass was determined using 51Cr and plasma volume with Evan's blue dye. In most patients measurements were made of arterial oxygen saturation and partial pressure of oxygen.

After a period of several days' stabilization in the hospital, 24-hour urine collections were begun for erythropoietin assay and continued throughout the duration of the study;
each voiding was frozen immediately. Hematocrits and reticulocyte counts were measured daily. After a baseline period of at least three days, varying amounts of blood (750 to 1500 cc.) were removed acutely from the normal subjects. The volume bled was determined by the measured blood volume and the desired post-phlebotomy hematocrit. Red cell deficits of 10 to 50 per cent were produced by single bleedings in order to relate erythropoietin excretion to a wide range in hematocrit. When possible, patients with erythrocytosis were bled in a similar manner to lower the hematocrit approximately 10 points and the acute phlebotomies were repeated at approximately weekly intervals. In order to achieve stabilization of the hematocrit at the new level, the volume of blood removed from both normals and patients was replaced during phlebotomy by exchange with an appropriate volume expander. In order to ameliorate the effects of volume depletion in the normal subjects, the phlebotomies were carried out by exchanging 500 cc. of whole blood at a time until the total amount desired had been removed. In the polycythemic subjects blood was exchanged in 300–400 cc. volumes in deference to the older age of this group. Initially, human plasma stored for 6 months at room temperature and later 5 per cent albumin solution were used for the purpose of replacement. The exchange phlebotomies were carried out over a period of 1 to 3.5 hours and no adverse reactions or symptoms of hypovolemia were encountered except in patient J.B., who developed mild dizziness upon standing.8

Sham phlebotomies were carried out in three normal subjects by processing them in exactly the same manner as the experimental group. The experiment was designed in such a manner that none of the individuals was aware he had not been phlebotomized until after the study was completed.

In addition, hypertransfusion studies were conducted on two normal volunteers. At the time of phlebotomy, blood was collected in plastic bags containing acid-citrate-dextrose solution and stored at 4°C for three weeks. At the end of the storage period, the blood was cultured and, when found to be free of bacteria, was centrifuged and the red cells harvested. The volunteers were then autotransfused over a period of 2 to 3 hours to hematocrit levels 4 to 6 points above their normal values.

Erythropoietin Measurements

Within a period of two months after collection, the urine specimens were thawed and arranged in 24 hour lots. Because we have observed that erythropoietin recovery decreased with urinary concentrates of 12 or more hours' time, one fourth of each daily pool (equivalent to 6 hours) was concentrated for assay.9 This method of sampling and assay gave values of calculated erythropoietin excretion equivalent to the sum of 6 hour periods in a day's time10 and automatically corrected for the diurnal variation previously reported in erythropoietin excretion.9 In several instances six hour aliquots were run in duplicate, and while considerable variation about the mean existed within each group, the difference of means of response varied by no more than ±25 per cent.10

A smaller aliquot of urine was also taken for determination of creatinine concentration in order to detect the day to day variations in the completeness of the collections. Normally, daily values of creatinine excretion vary only slightly for a given individual.11 Therefore, for each of the subjects studied, those creatinine values which varied by no more than ±15 per cent were averaged and the mean value obtained. Calculations of the erythropoietin content of urine collections were adjusted by the following formula:

\[
\frac{\text{observed erythropoietin excretion/day} \times \text{mean creatinine}}{\text{observed creatinine}}
\]

As described in detail elsewhere,9 material to be assayed was injected into hypoxia-induced polycythemic mice maintained on a low protein diet, and the 48 hour utilization of radioactive iron in these animals was determined. Erythropoietin was quantitated by comparing the response to the urine concentrates with a known dose/response curve of erythropoietin Standard B.*

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Table 1.—Normal Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>No. of Days observed</th>
<th>Hematocrit</th>
<th>Average E8F Excretion/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1)* (2) (3)</td>
<td>(1) (2) (3)</td>
<td></td>
</tr>
<tr>
<td>R.S.</td>
<td>23</td>
<td>M</td>
<td>3 3</td>
<td>47.5 43.7</td>
<td>3.2 4.7</td>
</tr>
<tr>
<td>R.M.</td>
<td>23</td>
<td>M</td>
<td>3 3</td>
<td>45.0 40.4</td>
<td>3.1 7.2</td>
</tr>
<tr>
<td>W.H.</td>
<td>23</td>
<td>M</td>
<td>3 3</td>
<td>42.7 40.9</td>
<td>3.5 3.8</td>
</tr>
<tr>
<td>P.A.</td>
<td>23</td>
<td>M</td>
<td>3 3</td>
<td>46.9 40.5</td>
<td>4.6 5.8</td>
</tr>
<tr>
<td>E.H.</td>
<td>23</td>
<td>M</td>
<td>3 3</td>
<td>48.0 43.7</td>
<td>4.8 6.6</td>
</tr>
<tr>
<td>D.H.</td>
<td>24</td>
<td>M</td>
<td>3 3</td>
<td>47.0 42.8</td>
<td>3.8 6.2</td>
</tr>
<tr>
<td>S.R.</td>
<td>23</td>
<td>M</td>
<td>3 3</td>
<td>44.2 38.7</td>
<td>6.1 8.1</td>
</tr>
<tr>
<td>R.L.</td>
<td>36</td>
<td>M</td>
<td>4 6 6</td>
<td>45.0 35.0</td>
<td>27.0 3.1 8.4 16.2</td>
</tr>
<tr>
<td>F.K.</td>
<td>21</td>
<td>M</td>
<td>4 6 6</td>
<td>43.0 35.0</td>
<td>27.0 3.7 6.3 11.0</td>
</tr>
<tr>
<td>J.B.†</td>
<td>29</td>
<td>M</td>
<td>3 5</td>
<td>49.0 19.0</td>
<td>4.1 30.4</td>
</tr>
<tr>
<td>J.P.</td>
<td>24</td>
<td>M</td>
<td>3 5</td>
<td>45.7 34.3</td>
<td>3.9 6.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>42.1 50.1‡</td>
<td>3.5 0.4</td>
<td></td>
</tr>
<tr>
<td>R.M.</td>
<td>24</td>
<td>M</td>
<td>3 5</td>
<td>47.0 36.7</td>
<td>7.5 11.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>42.6 50.5‡</td>
<td>6.6 3.6</td>
<td></td>
</tr>
<tr>
<td>L.G.</td>
<td>25</td>
<td>M</td>
<td>3 3</td>
<td>43.5 42.5§</td>
<td>3.1 2.0</td>
</tr>
<tr>
<td>A.A.</td>
<td>24</td>
<td>M</td>
<td>3 3</td>
<td>44.0 43.2§</td>
<td>5.5 6.1</td>
</tr>
<tr>
<td>H.G.</td>
<td>26</td>
<td>M</td>
<td>3 3</td>
<td>45.0 44.8§</td>
<td>2.8 2.5</td>
</tr>
</tbody>
</table>

*Numbers in parentheses represent consecutive periods of study.
†Phlebotomy study carried out by Dr. R. Hamstra, University of Colorado.
‡Transfused with own cells.
§Sham phlebotomy.

Results

Normal Subjects

Basal erythropoietin excretion in the 15 normal subjects studied averaged 4.2 Standard B units per day (± 1.3; 1 std. dev.) and ranged from 2.8 to 7.5 units. In every instance, erythropoietin excretion increased in response to phlebotomy, although only a modest fall in hematocrit was achieved in several individuals. The average hematocrit and amount of erythropoietin excreted before and after phlebotomy are shown in Table 1. In order to minimize the known methodologic variation in the bioassay and the day to day differences in normal erythropoietin excretion reported previously, measurements were made over several days immediately preceding the phlebotomy to establish basal erythropoietin excretion for each individual; these determinations were continued for several days immediately following the phlebotomy in order to incorporate the peak of the erythropoietin response. Two of the subjects (J.P. and R.M.) were subsequently hypertransfused with their own cells and, as indicated in the Table, both responded with an appreciable decrease in erythropoietin output. No consistent alteration in erythropoietin excretion was seen in the three subjects in whom a sham phlebotomy was performed.

Figure 1 indicates the relationship of hematocrit to erythropoietin excretion in response to phlebotomy for the 12 normal subjects. Baseline and post-phlebotomy values are connected by straight lines and erythropoietin excretion expressed on a log scale. With this representation, a similarity between the
slopes of response over widely varying ranges in hematocrits is evident. In addition, the hematocrit/erythropoietin values for R.L. and F.K., the only subjects for whom data at three hematocrit levels were obtained, lie on virtually straight lines.

As determined by the method of least-squares using values of log y, the average slope (β) of the observations, weighted for the degree of change in hematocrit, was −0.03030. The line of regression is shown in Figure 2.

**Hypoxic Erythrocytosis**

Five patients with generalized tissue hypoxia due to chronic pulmonary or cardiac disease were studied (Table 2). The assays of basal erythropoietin excretion showed a wide variation, ranging from a low value of 3.4 to a high of 699.0 units per day. All five subjects had a marked increase in erythropoietin excretion in response to phlebotomy. As shown in Figure 3, the two individuals whose erythropoietin output was initially normal excreted considerably more

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*The "weighted" average slope (β̃w) for the 12 sets of observations was determined by:

\[
\betãw = \frac{(d_1)^2 \beta_1 + (d_2)^2 \beta_2 + \ldots + (d_n)^2 \beta_n}{(d_1)^2 + (d_2)^2 + \ldots + (d_n)^2}
\]

where \((d_1)^2\), etc. equals the square of the change in hematocrit brought about by phlebotomy and \(\beta_1\), etc. represents the respective calculated slope of erythropoietin response in each of the 12 subjects.
erythropoietin after bleeding than did normal subjects at comparable hematocrits.

**Tumor Erythrocytosis**

Three patients were studied who had increased red cell production associated with neoplasms (Table 3); one of these was the subject of a previous communication. In all three, arterial oxygen saturation was normal. Mean levels of erythropoietin excretion at high hematocrits averaged 5.1 Standard B units per day and ranged from 1.6 to 10.5 units. Reduction of the hematocrit of these patients did not significantly alter urinary erythropoietin excretion (Fig. 4).

**Polycythemia Vera**

Seven patients with a diagnosis of polycythemia vera were studied (Table 4); all but three of these (H.C., J.G., and W.K.) patients had been therapeutically bledd in the past but none within 3 months of the study. No other form of treatment had been used on any of the subjects. Prior to study, the excretion of erythropoietin in these patients was virtually unmeasurable; however, with lowering of the hematocrit, six of the seven subjects had an erythropoietin response. As shown in Figure 5, this response appeared similar in shape but of less magnitude than that of normal subjects.
Table 2.—Hypoxic Erythrocytosis

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Arterial Oxygen Saturation (%)</th>
<th>WBC (mm$^3$)</th>
<th>Platelet count (mm$^3$)</th>
<th>No. of days observed (1)*</th>
<th>No. of days observed (2)</th>
<th>No. of days observed (3)</th>
<th>Average hematocrit (1)</th>
<th>Average hematocrit (2)</th>
<th>Average hematocrit (3)</th>
<th>Average ESF excretion/day (1)</th>
<th>Average ESF excretion/day (2)</th>
<th>Average ESF excretion/day (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.McL.</td>
<td>45</td>
<td>M</td>
<td>Eisenmenger's complex</td>
<td>87</td>
<td>7,200</td>
<td>4</td>
<td>5</td>
<td>60.0</td>
<td>50.2</td>
<td></td>
<td></td>
<td>50.2</td>
<td>119.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G.A.</td>
<td>59</td>
<td>F</td>
<td>Chronic obstructive pulmonary disease</td>
<td>83</td>
<td>5,600</td>
<td>9</td>
<td>5</td>
<td>51.3</td>
<td>45.3</td>
<td>3.4</td>
<td>13.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L.L.</td>
<td>51</td>
<td>M</td>
<td>Eisenmenger's complex</td>
<td>74</td>
<td>5,100</td>
<td>12</td>
<td>10</td>
<td>5.45</td>
<td>42.5</td>
<td>699.0</td>
<td>980.0</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>S.K.</td>
<td>46</td>
<td>M</td>
<td>Pickwickian syndrome</td>
<td>76</td>
<td>12,800</td>
<td>10</td>
<td>7</td>
<td>55.0</td>
<td>51.5</td>
<td>104.3</td>
<td>209.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.C.</td>
<td>59</td>
<td>F</td>
<td>Chronic obstructive pulmonary disease</td>
<td>84</td>
<td>6,600</td>
<td>5</td>
<td>8</td>
<td>4</td>
<td>54.0</td>
<td>46.5</td>
<td>42.5</td>
<td>5.3</td>
<td>8.1</td>
<td>12.6</td>
<td></td>
</tr>
</tbody>
</table>

*Numbers in parentheses represent consecutive periods of study.
DISCUSSION

The Hematocrit/Erythropoietin Response Curve in Normal Subjects

The ability of erythropoietin to cause proliferation of the erythroid marrow has been clearly demonstrated.\textsuperscript{13-16} Its role in regulating normal erythropoiesis was made plausible by the demonstration of erythropoietin in normal urine.\textsuperscript{9,17,18} Further substantiation of this role is seen in the present studies which indicate that relatively small changes in the hematocrit of healthy subjects, either lowered by phlebotomy or increased by transfusion, lead to definite, predictable changes in the daily excretion of erythropoietin. As shown in Figures 1 and 2 the response appears to be logarithmic. It should be emphasized that this is a response curve, with urinary values of erythropoietin determined over a several day period after exchange phlebotomy. The peak of erythropoietin response usually occurred on the second or third day, but in several subjects no distinguishable peak was observed. While it is recognized that no constant relationship exists between hematocrit and erythropoietin level on a day to day basis after the acute induction of anemia or hypoxia,\textsuperscript{19,20} the period of observation was considered sufficient to embrace the immediate erythropoietin response.

It is not possible at the present time to define all of the factors involved in the erythropoietin/hematocrit relationship. The concept of erythropoietin utilization or inactivation by the marrow\textsuperscript{21} has not been proved.\textsuperscript{22,23} Previous reports comparing serum or urinary erythropoietin to hematocrit in man have not clearly described a logarithmic relationship; however, review of the published data\textsuperscript{24,25} shows no incompatibility with such a relationship.

The Hematocrit/Erythropoietin Response Curve in Polycythemic States

As was predicted ninety years ago\textsuperscript{26} and subsequently demonstrated in individuals with arterial hypoxemia at high altitudes,\textsuperscript{27} an increased need for
Table 3.—*Tumor Erythrocytosis*

<table>
<thead>
<tr>
<th>Subj.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Arterial Oxygen Satura. (%)</th>
<th>WBC (mm³)</th>
<th>Platelet count (mm³)</th>
<th>No. of days observed</th>
<th>Average hematocrit (1)</th>
<th>Average ESF excretion/day (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G.H.</td>
<td>72</td>
<td>M</td>
<td>Hepatoma</td>
<td>96.0</td>
<td>5,000</td>
<td>275,000</td>
<td>8 8</td>
<td>58.5</td>
<td>52.5</td>
</tr>
<tr>
<td>P.V.</td>
<td>45</td>
<td>M</td>
<td>Cerebellar hemangio-</td>
<td>97.0</td>
<td>7,800</td>
<td></td>
<td>3 5 5 5 6</td>
<td>64.0</td>
<td>53.5</td>
</tr>
<tr>
<td>O.P.</td>
<td>72</td>
<td>M</td>
<td>Hypernephroma</td>
<td>96.3</td>
<td>7,500</td>
<td>460,000</td>
<td>7 9 4</td>
<td>62.0</td>
<td>52.7</td>
</tr>
</tbody>
</table>

*Numbers in parentheses represent consecutive periods of study.

Table 4.—*Polycythemia Vera*

<table>
<thead>
<tr>
<th>Subj.</th>
<th>Age</th>
<th>Sex</th>
<th>Arterial Oxygen Satura. (%)</th>
<th>WBC (mm³)</th>
<th>Platelet count (mm³)</th>
<th>Basophil count† (mm³)</th>
<th>LAP* stain</th>
<th>Large spleen</th>
<th>No. of days observed</th>
<th>Average hematocrit (1)</th>
<th>Average ESF excretion/day (1)</th>
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<tr>
<td></td>
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<td></td>
<td>(1)† (2) (3) (4)</td>
<td>(1) (2) (3) (4)</td>
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<tr>
<td>R.M.</td>
<td>66</td>
<td>M</td>
<td>25,800</td>
<td>1,100,000</td>
<td>111</td>
<td>374</td>
<td>Yes</td>
<td>4 7 6</td>
<td>46.6 41.5 38.0</td>
<td>0.0 0.3 0.8</td>
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</tr>
<tr>
<td>R.D.</td>
<td>48</td>
<td>M</td>
<td>13,500</td>
<td>558,000</td>
<td>222</td>
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<td>Yes</td>
<td>3 6 6</td>
<td>48.6 41.2 33.0</td>
<td>0.0 0.6 2.9</td>
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</tr>
<tr>
<td>W.K.</td>
<td>64</td>
<td>M</td>
<td>9,300</td>
<td>191,000</td>
<td>33</td>
<td>113</td>
<td>Yes</td>
<td>3 7 3</td>
<td>64.0 54.4 45.0</td>
<td>0.2 1.3 1.5</td>
<td></td>
</tr>
<tr>
<td>A.F.</td>
<td>55</td>
<td>M</td>
<td>10,800</td>
<td>610,000</td>
<td>110</td>
<td>280</td>
<td>No</td>
<td>3 6 7</td>
<td>49.0 39.4 33.5</td>
<td>0.0 1.7 3.8</td>
<td></td>
</tr>
<tr>
<td>J.G.</td>
<td>60</td>
<td>M</td>
<td>16,100</td>
<td>332,000</td>
<td>25</td>
<td>300</td>
<td>No</td>
<td>5 5</td>
<td>54.5 47.5</td>
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</tr>
<tr>
<td>H.C.</td>
<td>82</td>
<td>M</td>
<td>11,800</td>
<td>239,000</td>
<td>55</td>
<td>348</td>
<td>Yes</td>
<td>6 7 9 6</td>
<td>65.0 55.8 48.1 38.6</td>
<td>0.0 1.2 2.7 4.3</td>
<td></td>
</tr>
<tr>
<td>B.C.</td>
<td>86</td>
<td>F</td>
<td>15,200</td>
<td>662,000</td>
<td>100</td>
<td>257</td>
<td>No</td>
<td>6 5</td>
<td>57.5 51.0</td>
<td>0.0 0.0</td>
<td></td>
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</table>

*Leukocyte alkaline phosphatase; normal range of scores: 68 ± 14.48
†Normal range: up to 80/cu. mm.†
Numbers in parentheses represent consecutive periods of study.
oxygen is met by increasing the oxygen-carrying capacity of the blood. This need for enlargement of the circulating red cell mass is associated with increased erythropoiesis and increased erythropoietin levels. In patients with cardiopulmonary disease compensation may be sufficiently effective so
that hypoxia no longer exists. In such individuals, when equilibration of oxygen supply and demand is reached, urinary erythropoietin might be predicted to be normal possibly as a result of a new balance between erythropoietin production and catabolism. Prior studies have been carried out with methods not sufficiently sensitive to delineate modest changes above and below normal levels.

In the five patients reported here with increased red cell production secondary to chronic hypoxia, basal erythropoietin excretion was increased in three and normal in two. It is possible that the erythropoietin response to hypoxia in the latter two individuals was depressed because of coexistent pulmonary infection. However, these individuals were afebrile at the time of study, had normal peripheral leukocyte counts and when they were bled to a normal hematocrit, both excreted more erythropoietin than did normal subjects at similar hematocrit levels. In addition, the slopes of erythropoietin response to phlebotomy were \(-0.09981\) (patient G.A.) and \(-0.03167\) (patient E.C.), indicating no obvious blunting of the response compared to the normal data. These observations are consistent with a displacement of the erythropoietin response curve to a higher hematocrit as a result of hypoxia.

In tumor-induced erythrocytosis, a fall in hematocrit of as much as 25 points had no measurable effect on the normal to slightly elevated urinary excretion of erythropoietin. For example, in the patient with a cerebellar tumor, the hematocrit was lowered from 64 to 39 without any increase in erythropoietin excretion, even though it was low initially. This type of response is unique to tumors in our experience and may reflect the fact that in many patients with malignant neoplasms a hypoproliferative anemia is seen which is contributed to by depressed erythropoietin production. Although the response to phlebotomy was certainly depressed it is likely that if the hematocrit had been lowered to more anemic levels, there would have been stimulation of erythropoietin production by the kidney. Nevertheless, the patterns of response in these three patients support the concept of unregulated production of erythropoietin by neoplastic tissue.

There have been conflicting reports on the role of erythropoietin in polycythemia vera.\(^{28,29,32-35}\) However, with more sensitive measurements utilizing concentrated urine, erythropoietin excretion has been shown to be greatly reduced.\(^{18,36}\) In six of the seven patients with polycythemia vera reported here, urinary erythropoietin was initially undetectable. Only one patient had demonstrable urinary erythropoietin prior to phlebotomy and this was negligible in amount. When these same patients were challenged by repeated phlebotomies, there was usually a step-wise increase in the excretion of erythropoietin. The physiologic situation in this disease resembles that of continuous autotransfusion where red cell production is independent of oxygen deprivation and erythropoietin stimulation. This interpretation is consistent with the inability of an oxygen rich environment\(^{37,38}\) or hypertransfusion\(^{39}\) to suppress erythropoiesis in this disease. As suggested by others\(^{40,42}\) red cell production is not under the regulation of erythropoietin and must be considered autonomous.
The humoral system regulating erythropoiesis appears to be a complex one with recent evidence that the material assayed is the product of an interaction between a plasma protein and an enzymatically active substance of renal origin. Observations in this study concern only the effective substance, erythropoietin. It has been postulated that both positive and negative controls of erythropoiesis exist, and the presence of an inhibitor in a plasma extract from hypertransfused animals and in patients with untreated polycythemia vera has been reported. Attempts in this laboratory and by others to demonstrate such a substance have been unsuccessful. Thus, the findings reported here indicate a highly sensitive relationship between erythropoietin excretion and circulating hemoglobin or oxygen supply and appear most consistent with the concept that erythropoiesis is regulated by changes in production of the single stimulating factor, erythropoietin.

**SUMMARY**

The relationship between erythropoietin excretion and change in hematocrit has been determined in normal and polycythemic subjects. Erythropoietin was measured by a method involving the assay of urinary concentrates in polycythemic protein-depleted mice. Basal erythropoietin excretion in normal subjects ranged from 2.8 to 7.5 Standard B units per day. Studies in subjects made anemic by bleeding demonstrated an inverse relationship between hematocrit and the log of erythropoietin excretion. Patients with hypoxia-induced erythrocytosis had increased levels of urinary erythropoietin when their hematocrit was reduced to normal levels by phlebotomy. Three patients whose erythrocytosis was associated with tumors had an erythropoietin excretion which remained constant over a wide range in hematocrit. In polycythemia vera, erythropoietin output was absent or markedly decreased at high hematocrit levels, but measurable erythropoietin appeared in the urine when the hematocrit was reduced to normal or anemic levels by bleeding.

**SUMMARIO IN INTERLINGUA**

Le relation inter le excretion de erythropoietina e alterationes in le hematocrite esseva determinate in simbjeetos normal e polycythemic. Le erythropoietina esseva mesurate per medio de un methodo requirente le essayage de concentratos urinari in polycythemic muses a carentia de proteina. Le excretion basal de erythropoietina in subjectos normal variava inter 2,8 e 7,5 unitates standard B per die. Studios in subjectos rendite anemic per sanguination demonstravau un relation inverse inter le hematocrite e le logarithmo del excretion de erythropoietina. Patientes con erythrocytosis inducite per hypoxia habeva augmentate nivellos de erythropoietina urinari quando lor hematocrite esseva reducite a nivellos normal per le effectuation de phlebotomia. Tres patientes in qui le erythrocytosis esseva associate con tumores habeva un excretion de erythropoietina que remaneva constante con extense variationes del hematocrite. In polycythemia ver, le rendimento de erythropoietina esseva absente o marcatemente reducite a alte nivellos hematocritic, sed mensurable quantitates de erythropoietina apparaeva in le urina quando le hematocrite esseva reducite a nivellos normal o anemic per sanguination.

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The Erythropoietin/Hematocrit Relationship in Normal and Polycythemic Man: Implications of Marrow Regulation

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