The Anemia of Chronic Disorders: Studies of Marrow Regulation and Iron Metabolism

By S. W. Douglas and John W. Adamson

Marrow regulation and iron metabolism were evaluated in 17 patients with mild or moderate anemia associated with chronic disorders. In addition, whole blood P50 and red cell 2,3-diphosphoglycerate (DPG) levels were measured. The study group consisted of seven patients with non-hematologic malignancies, nine with infection or inflammation, and one with idiopathic hypoproliferative anemia. The mean whole blood P50 and DPG levels were elevated to 28.5 ± 1.9 mm Hg and 7.03 ± 0.83 μmole/ml packed RBC, respectively, as compared to normal values of 26.6 ± 0.6 mm Hg and 4.83 ± 0.33 μmole/ml packed RBC. Erythropoietin (ESF) excretion was variable (1.1-28.7 IRP U/day), clearly elevated above normal in only three patients and, within the study group, bore no relation to hematocrit. While nine of the 17 subjects had ESF excretion rates within the 95% limits predicted by hematocrit, the remaining eight had lower than expected values. No significant differences in ferrokinetics, ESF excretion, or hematologic profile were found between patients with malignancy and those with inflammation. Marrow transit times correlated inversely with both serum and urine ESF activity (r = −0.57, p < 0.02; and r = −0.63, p < 0.01, respectively), indicating that the marrow reticulocyte release response to ESF stimulation was unimpaired. Erythroid iron turnovers were unrelated to serum or urinary ESF activity but were significantly correlated with serum iron levels expressed as μg/100 ml whole blood (r = 0.56, p < 0.02). These studies suggest that there is an intraerythrocytic response to the anemia in this group of patients, document that reduced ESF production is not a uniform finding with the anemia of chronic disorders, and provide evidence that the marrow proliferative response to anemia is limited in many patients primarily by the availability of iron.

A NUMBER OF CHRONIC diseases are accompanied by a mild, stable anemia resulting from a modest shortening of red cell lifespan and a lack of compensatory marrow response. This syndrome, known as the anemia of chronic disorders (ACD), is characterized by a low reticulocyte index, marrow erythroid:granulocytic (E:G) ratio of 1:2-3, hypoferremia with low to normal transferrin levels, increased red cell protoporphyrin, and reduced or absent marrow sideroblasts in the presence of reticuloendothelial iron stores.

A number of factors may contribute to the ACD syndrome, including a reduction in ESF production, impaired marrow response to ESF stimulation, and an inadequate iron supply for erythropoiesis. While the relative contributions of these factors have not been clearly defined, the role of ESF has received
considerable attention recently.\textsuperscript{2-5} Data concerning the role of altered ESF production in subjects with ACD appear inconclusive, however, with both appropriate\textsuperscript{2} and decreased\textsuperscript{3-5} levels having been reported. In addition, parameters of the intraerythrocytic adaptation to the ACD have not been established, and thus the anemia could conceivably represent an adaptive response to reduced oxygen demand.

The purposes of this study were to further determine the relative roles of ESF and iron supply in the regulation of erythropoiesis in this syndrome and to examine certain parameters of intraerythrocytic adaptation to the ACD.

\textbf{MATERIALS AND METHODS}

\textbf{Subjects and Hematology}

Patients with chronic illnesses of at least 1 mo duration were selected for study according to the criteria of Cartwright\textsuperscript{4} as follows: (1) mild to moderate, stable anemia (for this study defined as hematocrit $28\% - 38\%$ for males, $26\% - 36\%$ for females); (2) reticulocyte index less than $2.0\%$\textsuperscript{6} with a marrow E:G ratio of 1:2 or less and normal erythroid marrow morphology; (3) serum iron less than 65 $\mu$g/100 ml and transferrin levels less than 350 $\mu$g/100 ml; (4) reduced marrow sideroblasts ($<10\%$) with iron stores present; and (5) absence of renal dysfunction, cytotoxic therapy, external blood loss, or known marrow involvement by tumor. The patients were hospitalized in the Clinical Research Center of the University of Washington or in the Seattle VA Hospital during the period of study.

The hematocrit, hemoglobin concentration, and red cell indices were measured using an automatic cell counter (Coulter Model S). Reticulocyte counts were determined using standard techniques. Bone marrow aspirations and, in tumor cases, biopsies were obtained from the posterior iliac crest for evaluation of cellularity, E:G ratio, erythroid morphology, and presence of iron stores, sideroblasts, and tumor involvement.

Diagnostic and hematologic characteristics of the 17 patients studied are summarized in Table 1. The group consisted of 14 males and three females, ages 42-83. The mean hematocrit for males was $32.4 \pm 2.5\%$ and $30.7 \pm 2.5\%$ for females. The mean reticulocyte count, corrected for hematocrit, was $1.4 \pm 0.5\%$, for all subjects. On marrow examination, storage iron was present in all patients, but rare sideroblasts were seen in the marrow of only one. No malignant cells were seen in the marrow biopsies of the seven tumor patients (cases 1-7). Serum ferritin levels measured in 13 subjects by the two-site radiometric assay of Lipschitz et al. ranged from 94 to 621 ng/ml, well above the values reported for true iron deficiency.\textsuperscript{7}

\textbf{Whole Blood $P_{50}$ and 2,3-DPG}

The $P_{50}$\textsuperscript{8} of fresh, heparinized whole blood was measured using the mixing technique of Lenfant et al.\textsuperscript{8} and was corrected for the simultaneously measured base excess.\textsuperscript{9} Red cell DPG levels were measured using a modification\textsuperscript{10} of the phosphate partition method of Bartlett.\textsuperscript{11} Control values relating $P_{50}$ and DPG to hemoglobin were taken from the study of Torrance et al.\textsuperscript{10} The hemoglobin concentrations of the anemic controls in that study ranged from 4 to 13 g/100 ml, and the group was made up of patients with iron deficiency, blood loss, aplasia, liver disease, and other forms of hypoproliferative anemia.

\textbf{Erythropoietin}

Serial 24-hr urine collections were obtained for 3-5 days to determine mean values of ESF excretion. Five individuals recovering from phlebotomy-induced or iron-deficiency anemia served as controls. Methods of processing and assaying the urine specimens have been described previously.\textsuperscript{12} Serum samples obtained at the beginning of the ferrokinetic studies were also

\textsuperscript{*That partial pressure of oxygen under conditions of standard temperature and pH at which hemoglobin is half saturated.
Table 1. Diagnostic and Hematologic Values of Study Patients With ACD

<table>
<thead>
<tr>
<th>Patient/Sex</th>
<th>Diagnosis</th>
<th>Hct</th>
<th>Red Cell Indices</th>
<th>Reticulocytes*</th>
<th>Iron Stores</th>
<th>Serums Ferritin</th>
<th>MCV</th>
<th>MCH</th>
<th>MCHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M Calung</td>
<td></td>
<td>34.0</td>
<td>88</td>
<td>28</td>
<td>32</td>
<td>1.4</td>
<td>1+</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>2/M Caoropharynx</td>
<td></td>
<td>31.6</td>
<td>93</td>
<td>33</td>
<td>32</td>
<td>1.9</td>
<td>2+</td>
<td>334</td>
<td></td>
</tr>
<tr>
<td>3/M Ca esophagus</td>
<td></td>
<td>30.6</td>
<td>91</td>
<td>30</td>
<td>33</td>
<td>1.7</td>
<td>1 +</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>4/M Ca lung</td>
<td></td>
<td>32.0</td>
<td>83</td>
<td>28</td>
<td>35</td>
<td>1.1</td>
<td>2+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/M Ca lung</td>
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<td>31.0</td>
<td>91</td>
<td>28</td>
<td>31</td>
<td>1.1</td>
<td>2+</td>
<td>420</td>
<td></td>
</tr>
<tr>
<td>6/M Ca colon</td>
<td></td>
<td>29.0</td>
<td>90</td>
<td>30</td>
<td>34</td>
<td>0.9</td>
<td>2+</td>
<td></td>
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</tr>
<tr>
<td>7/M Calung; cirrhosis</td>
<td></td>
<td>31.9</td>
<td>105</td>
<td>36</td>
<td>30</td>
<td>1.5</td>
<td>2+</td>
<td>448</td>
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<tr>
<td>8/M Suppurative pancreatitis</td>
<td></td>
<td>37.2</td>
<td>92</td>
<td>32</td>
<td>34</td>
<td>1.3</td>
<td>3+</td>
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</tr>
<tr>
<td>9/M Infected leg burns</td>
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<td>34.7</td>
<td>90</td>
<td>31</td>
<td>33</td>
<td>0.6</td>
<td>2+</td>
<td>621</td>
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</tr>
<tr>
<td>10/M Septic bursitis</td>
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<td>81</td>
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<td>33</td>
<td>1.1</td>
<td>2+</td>
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<td>11/M Psoriasis, cellulitis</td>
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<td>31.3</td>
<td>83</td>
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<td>32</td>
<td>0.9</td>
<td>1 +</td>
<td></td>
<td></td>
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<tr>
<td>12/F Rheumatoid arthritis</td>
<td></td>
<td>32.1</td>
<td>89</td>
<td>28</td>
<td>32</td>
<td>2.6</td>
<td>1+</td>
<td>98</td>
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<tr>
<td>13/M Rheumatoid arthritis</td>
<td></td>
<td>28.5</td>
<td>78</td>
<td>24</td>
<td>31</td>
<td>1.6</td>
<td>3+</td>
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<td>34.4</td>
<td>79</td>
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<td>1 +</td>
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<td>32</td>
<td>1.3</td>
<td>1 +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16/F Polymyalgia rheumatica</td>
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<td>77</td>
<td>25</td>
<td>33</td>
<td>1.2</td>
<td>3+</td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>17/F Idiopathic</td>
<td></td>
<td>33.9</td>
<td>83</td>
<td>29</td>
<td>34</td>
<td>2.0</td>
<td>2+</td>
<td>95</td>
<td></td>
</tr>
</tbody>
</table>

Mean 32.1 ± 2.8 ±7.5 ±3.3 ±1.4 ±0.5

*The number of reticulocytes per 100 red cells corrected for hematocrit by the (observed hct)/(normal hct).

†Graded on a scale of 0-4+.

§Geometric mean.

1. **Ferrokinetic Studies**

Serum iron and total iron-binding capacity were measured using recently recommended techniques. Ferrokinetic studies were performed using the methods of Finch et al. and included measurements of plasma iron turnover (PIT), erythroid iron turnover (EIT), and marrow transit time (MTT). All studies were begun between 9 and 11 am.

2. **Statistical Analysis**

Analysis of regression and its significance was established for the various relationships using standard methods. Confidence limits calculated to predictably include 95% of all new individual observations were determined by the method of Snedecor and Cochran.

3. **Whole Blood P and 2,3-DPG**

As shown in Table 2, the mean red cell 2,3-DPG level was 7.03 (SD ±0.83) jzmole/ml packed RBC compared to a value of 4.83 ±0.33 (nonsmokers) and 5.14 ±0.59 (smokers) for normal nonanemic subjects at sea level. The DPG values for the study patients did not correlate significantly with hemoglobin.
levels and were, in general, higher than that predicted for the degree of anemia (Fig. 1). While the group mean for whole blood $P_{50}$ was significantly above that for nonanemic subjects (28.5 versus 26.6 mm Hg), the range of values was quite wide. Although there was no correlation between hemoglobin concentration and $P_{50}$ in the study group, 14 of 17 values fell within the predicted range of observations (95% limits) determined from 56 nonuremic anemic subjects.

![Fig. 1. The relationship between red cell 2,3-DPG and hemoglobin concentration in 16 patients with ACD. The regression line and 95% confidence limits are those of 56 nonuremic subjects with anemia.](image)

Table 2. 2,3-DPG, $P_{50}$, ESF, and Ferrokinetic Values of Study Patients With ACD

<table>
<thead>
<tr>
<th>Patient</th>
<th>DPG</th>
<th>$P_{50}$</th>
<th>Serum ESF</th>
<th>Urine ESF</th>
<th>Serum SFe</th>
<th>TIBC</th>
<th>PFT</th>
<th>EIT</th>
<th>MTT</th>
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<td>7.91</td>
<td>26.7</td>
<td>0.10</td>
<td>4.4</td>
<td>19</td>
<td>200</td>
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<td>29.6</td>
<td>0.08</td>
<td>1.8</td>
<td>53</td>
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<td>6.2</td>
<td>57</td>
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<td>0.82</td>
<td>0.76</td>
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<td>3.8</td>
<td>50</td>
<td>237</td>
<td>1.58</td>
<td>1.53</td>
<td>3.20</td>
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<td>5</td>
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<td>26.0</td>
<td>0.10</td>
<td>4.9</td>
<td>25</td>
<td>224</td>
<td>0.50</td>
<td>0.45</td>
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<td>6.70</td>
<td>29.4</td>
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<td>3.7</td>
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<td>28.2</td>
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<td>200</td>
<td>1.08</td>
<td>1.04</td>
<td>3.37</td>
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<td>0.10</td>
<td>3.5</td>
<td>39</td>
<td>291</td>
<td>0.57</td>
<td>0.47</td>
<td>4.04</td>
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<td>9</td>
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<td>24.7</td>
<td>0.08</td>
<td>4.9</td>
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<td>260</td>
<td>0.67</td>
<td>0.65</td>
<td>3.60</td>
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<tr>
<td>10</td>
<td>8.07</td>
<td>27.9</td>
<td>0.14</td>
<td>9.3</td>
<td>44</td>
<td>240</td>
<td>1.10</td>
<td>0.82</td>
<td>2.60</td>
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<td>0.10</td>
<td>4.5</td>
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<td>0.73</td>
<td>0.64</td>
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<td>12</td>
<td>8.30</td>
<td>32.1</td>
<td>0.17</td>
<td>12.1</td>
<td>49</td>
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<td>1.27</td>
<td>1.11</td>
<td>2.31</td>
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<tr>
<td>13</td>
<td>8.05</td>
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<td>0.12</td>
<td>28.7</td>
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<td>1.03</td>
<td>1.00</td>
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<td>14</td>
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<td>0.08</td>
<td>6.0</td>
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<td>0.10</td>
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<td>1.23</td>
<td>1.11</td>
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<td>16</td>
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<td>5.9</td>
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<td>269</td>
<td>0.44</td>
<td>0.44</td>
<td>2.87</td>
</tr>
<tr>
<td>17</td>
<td>5.55</td>
<td>28.6</td>
<td>0.12</td>
<td>1.1</td>
<td>60</td>
<td>346</td>
<td>1.10</td>
<td>1.07</td>
<td>2.40</td>
</tr>
<tr>
<td>Mean</td>
<td>7.03</td>
<td>28.5</td>
<td>0.10</td>
<td>4.0</td>
<td>40.2</td>
<td>255.8</td>
<td>0.90</td>
<td>0.82</td>
<td>2.93</td>
</tr>
</tbody>
</table>

(± SD) ±0.83 ±1.9 ±13.6 ±45.2 ±0.32 ±0.30 ±0.58

*μmole/ml packed RBC.
†Millimeters Hg, corrected for base excess.9
§IRP U/ml.
§§IRP U/day.
¶Serum iron and iron-binding capacity, μg/100 ml serum.
**Milligrams iron/100 ml whole blood/day.
***Days.

* From www.bloodjournal.org by guest on May 30, 2017. For personal use only.
In addition, there was no significant correlation between $P_{50}$ and DPG ($r = 0.35, p > 0.2$).

**Erythropoietin**

Daily ESF excretion in the study patients ranged from 1.1 to 28.7 International Reference Preparation (IRP) U, but was clearly elevated above normal (>6.0 U) in only three subjects (Table 2). No correlation of ESF excretion with hematocrit was seen for the ACD patients (Fig. 3), while a high inverse correlation was found for the control group ($r = -0.79, p < 0.001$). As a group, the ACD subjects had generally lower daily rates of ESF excretion than would be expected on the basis of hematocrit, although observations in nine patients fell within or near the 95% confidence limits of the regression established for control subjects. With the exception of one patient with high serum but virtually undetectable urine ESF activity (case 17), serum and urine ESF levels for the patient group were significantly correlated ($r = 0.59, p < 0.02$) (Fig. 4).
**Ferrokinetic Studies**

The mean and standard deviation of serum iron, total iron-binding capacity, and per cent saturation were 40.2 ± 13.6 μg/100 ml, 255.8 ± 45.2 μg/100 ml, and 16.0% ± 6.0%, respectively. The ranges of values for serum iron and per cent transferrin saturation in this group of patients are similar to those previously reported by Bainton and Finch.\(^{16}\) Total and effective erythropoiesis, as reflected by the PIT and EIT, respectively, ranged from 0.7 to 2.1 times normal, comparable to previously reported values.\(^{14}\) There was no correlation between the PIT or EIT and hemoglobin concentration or ESF activity in the serum or urine. However, a significant correlation was found between the EIT and the serum iron concentration expressed as micrograms of iron per 100 ml whole blood\(^*\) (r = 0.56, p < 0.02, Fig. 5).

Figure 6 compares the hematocrit-MTT relationship of the study patients to that of 50 subjects with varying degrees of phlebotomy-induced or hemolytic

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\(^*\)Serum iron \(\times\) plasmacrit = μg Fe/100 ml whole blood.
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eDerived from In ESF = -0.112 Hct + 5.82 (Fig. 3) and MTT = -0.086 Hct - 0.25 (Fig. 6).

Solving each regression for Hct and equating the results yields MTT = -0.730 In ESF + 3.99.

Fig. 6. The relationship between MTT and hematocrit for the 17 study patients compared to the regression line and 95% confidence limits of 50 subjects with hemolytic and phlebotomy-induced anemia.17

Eight patients had MTTs within the range predicted by hematocrit, while those of the remaining nine were prolonged. The relationship between MTT and serum ESF activity for the study group is shown in Fig. 7 where a significant inverse correlation is seen (r = -0.57, p < 0.02). With patient 17 excluded (vide supra), MTT correlated inversely with ESF excretion (r = -0.63, p < 0.01), and when patient values are compared to the expected relationship,* individual MTT values are seen in Fig. 8 to be near those predicted from the ESF excretion rates.

DISCUSSION

Failure of the erythroid marrow to respond as expected to an apparent anemic stimulus may reflect (1) an adaptation to reduced tissue oxygen requirements, (2) reduced ESF production, (3) a marrow cellular defect, or (4) an inadequate iron supply.

With anemia or hypoxia, there is generally an increase in red cell levels of DPG and a consequent increase in whole blood P. In man, this intraerythrocytic response correlates with the degree of anemia.'± With certain conditions,
however, in which a subnormal red cell mass was associated with panhypopituitarism or growth hormone deficiency, it has recently been shown that there is no increase in DPG and P_{50}.\textsuperscript{18} Such findings imply that the reduced red cell mass in these conditions is adaptive in nature and does not reflect impaired tissue oxygen delivery. In the present study, the elevation of DPG in all patients in whom it was determined and the increased mean P_{50} suggest that the hemoglobin deficit is not a result of reduced oxygen demand. However, arterial or venous pH was not determined simultaneously with DPG and P_{50} in this study, therefore these results do not reflect a detailed analysis of red cell oxygen transport and cannot be related to the recent demonstration that increased DPG and P_{50} reflect the chronic increase in blood pH in anemic patients rather than the hemoglobin deficit.\textsuperscript{19}

The possibility that reduced ESF stimulation contributes to the ACD has been suggested previously.\textsuperscript{3,5} Although elevated serum levels of ESF were found in 8 of 21 patients (hematocrit  $\geq$ 28\%) with rheumatoid arthritis, chronic infections, and malignancy, the values were less than predicted for the degree of anemia.\textsuperscript{5} In a more recent study, patients with anemia associated with malignancy had significantly higher serum ESF levels than those with inflammation,\textsuperscript{20} but in both groups ESF levels were less than expected when subjects with hemoglobin concentrations of <8 g/100 ml were excluded. In contrast, Alexanian found that urinary ESF excretion was appropriate for the degree of anemia in several patients with "hypoferremia of chronic disease."\textsuperscript{2} In the current study, a wide variation in both urinary and serum ESF activity was found in an otherwise hematologically uniform group of patients. While, as a group, the study patients had lower urinary ESF levels than predicted on the basis of hematocrit, about half (9 of 17) had ESF excretion values which fell within 2 SD of the regression line for the control subjects (Fig. 3). No statistical difference in urine or serum ESF activity was found between patients with infection or inflammation and those with malignancy.

While there is evidence that a number of patients with ACD do have relatively low levels of assayable ESF, the results of this and other studies suggest that lack of ESF stimulation alone is an insufficient explanation for the hypoproliferative marrow response. Recently, it has been reported that in vitro
cultures of marrow from patients with advanced malignancy have a decreased response to ESF compared to marrow from patients with inflammatory disease or from normal controls, implying an impaired proliferative response to ESF in tumor patients rather than a decreased number of precursor cells. These results are of interest but difficult to interpret, since techniques for independently quantitating numbers of ESF-responsive cells are not available and the influence on the in vitro response to ESF of varying numbers of cells cultured is not reported. In the present study, patients with tumor cannot be separated from those with inflammation on the bases of hematologic, ferrokinetic, or ESF data. Therefore, either impaired marrow responsiveness to ESF is common to both groups or erythropoiesis is more significantly limited by other factors.

Results of ferrokinetic studies in these patients define and confirm the hypoproliferative nature of the ACD. In many respects this syndrome resembles simple iron-deficiency anemia—a reduced serum iron and per cent transferrin saturation, rapid clearance of radioiron from the plasma, increased iron utilization, and elevated free erythrocyte protoporphyrin levels. The serum iron concentrations seen in the ACD are sufficient to limit erythropoiesis to little more than twice normal, and a correlation between PIT and serum iron level has been demonstrated previously in a large group of patients with anemia associated with inflammation. A comparable relationship between EIT and serum iron expressed per 100 ml whole blood was found in this study (Fig. 5) and can be derived for cases previously reported for which selection criteria and sufficient ferrokinetic data are available. These results indicate that marrow proliferation in the ACD is as effective as would be expected on the basis of the circulating iron level, a finding previously postulated for the anemia associated with rheumatoid arthritis. Possible indirect evidence of increased erythropoiesis by an improved marrow iron supply was provided by a rise in serum iron and hemoglobin concentration in three patients with rheumatoid arthritis receiving daily desferrioxamine.

Both ESF levels and MTT have independently been shown to correlate with hematocrit in anemias unassociated with ineffective erythropoiesis or marrow stromal damage. On this basis it has been postulated that the MTT, as a measure of marrow reticulocyte release, reflects the degree of ESF stimulation. The correlation between MTT and both serum and urine ESF activity in the current study group supports the above hypothesis, serves to confirm the significance of the elevated ESF levels observed, and suggests that marrow reticulocyte release in response to ESF stimulation is unimpaired in the ACD syndrome.

Of the several possible mechanisms leading to the hypoproliferative marrow response in the ACD syndrome, reduced ESF production of itself is an unlikely explanation, since elevated serum and urinary levels have been observed here and by others. In addition, when rates of red cell production approaching three to four times normal are seen at a near normal hematocrit, ESF levels correlate with the hematocrit and not with the rate of erythropoiesis. Consequently, while confirming the relative reduction in ESF levels in most patients, this study suggests again that the marrow iron supply may be the primary factor limiting erythropoiesis in many subjects. Only by providing a more adequate...
iron supply to the marrow will it be possible to assess the relative roles of reduced ESF production or impaired marrow responsiveness in the ACD syndrome.

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