

## REVIEW ARTICLE

### Progress in Understanding the Pathogenesis of the Anemia of Chronic Disease

By Robert T. Means, Jr, and Sanford B. Krantz

**T**HE ANEMIA of chronic disease (ACD) is usually defined as the anemia occurring in chronic infectious, inflammatory disorders, or neoplastic disorders that is not due to marrow replacement by tumor, bleeding, or hemolysis, and that is characterized by hypoferrremia in the presence of adequate iron stores.<sup>1,2</sup> ACD does not include the anemias caused by endocrine, renal, or hepatic insufficiency.<sup>2</sup> Typically, ACD is a mild-to-moderate, normochromic/normocytic anemia, and is characterized by a decreased serum iron and total iron-binding capacity, with normal or increased iron stores demonstrated by serum ferritin or by Prussian blue stain for marrow iron.<sup>2,3</sup> Reticulocytes are not increased appropriately for the degree of anemia, indicating that this is principally an "underproduction" anemia.

Some investigators take issue with the term "ACD,"<sup>4</sup> and it may be cogently argued that it is inappropriate because the syndrome includes anemias associated with diseases that are not always chronic, and may not include anemias associated with diseases that are chronic.<sup>1</sup> More accurate terms, such as "sideropenic anemia with reticuloendothelial siderosis,"<sup>3</sup> never seem to have become common for obvious reasons. However, despite deficiencies in nomenclature, ACD is an easily recognized clinical entity and may be second only to iron deficiency as a common cause of anemia.<sup>2</sup> Cash and Sears<sup>5</sup> reviewed the charts of all anemic patients admitted to the medical service of a metropolitan public hospital over two 2-month periods. Of the 172 anemic patients in whom bleeding, hemolytic disorders, and hematologic malignancies were excluded, 90 (52%) met laboratory criteria for ACD.<sup>5</sup>

Although it is frequently diagnosed, the pathogenesis of ACD has remained unclear. Cartwright<sup>3</sup> postulated that at least three pathologic processes were involved in ACD: shortened erythrocyte survival, failure of the bone marrow to increase red blood cell (RBC) production to compensate for this increased demand, and impaired release of iron from the reticuloendothelial system.<sup>3</sup> However, the origin of these processes and their relative importance in ACD remain topics for debate.

Cartwright also suggested that the supply of erythropoietin (EPO) to the marrow might be the rate-limiting factor in the impaired marrow response to ACD.<sup>3</sup> EPO is the hormone primarily responsible for the regulation of erythropoiesis<sup>6</sup> and, in ACD, it is inversely correlated with the

hemoglobin: as the hemoglobin decreases, the EPO level increases.<sup>7</sup> Because of its primary importance in erythropoiesis, EPO has been a major focus of investigation in ACD.

The anemia associated with rheumatoid arthritis (RA) has often served as a model for ACD, and the initial investigations of EPO levels in ACD were performed in patients with RA. Although these patients increased their serum EPO in response to the development of anemia,<sup>8</sup> the EPO levels attained were lower than those detected in equally anemic patients without RA.<sup>9,10</sup> Baer et al<sup>11</sup> compared the EPO response to anemia of 54 RA patients to that of 41 patients without RA. Both groups of patients showed a linear inverse correlation between the log of the serum EPO level and the hemoglobin concentration, but the line for the RA patients was shifted downward, indicating a blunted EPO response to anemia in RA patients.<sup>11</sup> This finding has been confirmed by other investigators<sup>12</sup> who subsequently demonstrated similar results in patients with cancer<sup>13</sup> and acquired immunodeficiency syndrome (AIDS).<sup>14</sup>

While the decrease in the incremental response of EPO to anemia may contribute to the reduced erythropoiesis in ACD, it cannot be considered the primary cause because EPO levels are still higher than those seen in persons without anemia. The failure of the bone marrow to respond to these increases in EPO must be considered the primary reason for the anemia.

Recently some advances have been made in the understanding of the pathogenesis of ACD, particularly in regard to the role of cytokines as initiators and mediators of this anemia.<sup>15,16</sup> We propose to review these advances here.

---

*From the Hematology Division, Department of Medicine, Vanderbilt University School of Medicine and the Department of Veterans Affairs Medical Center, Nashville, TN.*

*Submitted May 15, 1992; accepted June 9, 1992.*

*Supported by Veterans Health Administration Merit Review grants (R.T.M. and S.B.K.), by Grants DK-15555 and 2 T32-DK07186 from the National Institutes of Health (S.B.K.), and by the Joe C. Davis Hematology Research Fund.*

*Address reprint requests to Robert T. Means, Jr, MD, Hematology Section Room B-201, VA Medical Center, 1310 24th Ave S, Nashville, TN 37215.*

*This is a US government work. There are no restrictions on its use.  
0006-4971/92/8007-0008\$0.00/0*

## INHIBITION OF ERYTHROPOIESIS IN ACD

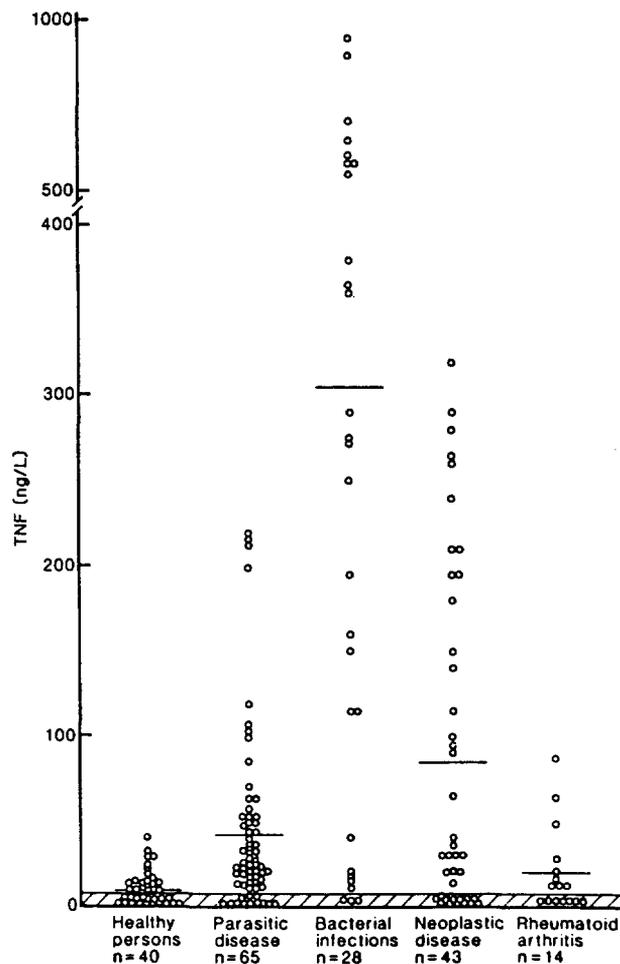
Many investigators have demonstrated cellular or humoral inhibition of erythropoiesis in ACD. Zanjani et al<sup>17</sup> found that erythroid colony formation in vitro in a subset of patients with disseminated histoplasmosis was enhanced by depletion of macrophages, while macrophage depletion of normal marrow did not affect colony formation. Addition of macrophages from these patients to macrophage-depleted normal marrow inhibited colony formation, while macrophages from normal individuals did not inhibit colony formation by patient marrow. This macrophage-dependent inhibition resolved with response of the infection to therapy.<sup>17</sup> Roodman et al<sup>18</sup> reported similar findings in other patients with ACD. In contrast, Reid et al<sup>19</sup> did not find inhibition of erythroid colony formation in vitro by adherent cells from anemic patients with RA, but did report that serum from these patients inhibited colony formation, while serum from nonanemic RA patients or from normals had no inhibitory effect.<sup>19</sup> Dainiak et al<sup>20</sup> also reported an inhibitory effect of serum from patients with RA or systemic lupus erythematosus. Baer et al<sup>21</sup> found suppression of erythroid colony-forming units (CFU-E) in vitro by serum from two of five anemic patients with RA but also by serum from one of four nonanemic RA patients, demonstrating the variability of results that complicates studies requiring addition of whole serum. Cells other than adherent cells also have been implicated as mediators of ACD, because Sugimoto et al<sup>22</sup> reported inhibition of erythroid colony formation by peripheral blood T lymphocytes (but not by serum) from anemic RA patients.

*Inhibition of Erythropoiesis by Specific Cytokines*

Improved understanding of the pathogenesis of inflammation has led to the identification of cytokines that are involved in this process, and these cytokines have become available in highly purified or recombinant preparations. Several cytokines involved in the inflammatory response are increased in the diseases associated with ACD, and have been used to develop models for this syndrome. This has allowed more precise delineation of the mechanisms by which erythropoiesis is inhibited in ACD.

**Tumor necrosis factor  $\alpha$  (TNF).** TNF plays a significant role in inflammation and the immune response.<sup>23</sup> TNF levels have been reported to be increased in patients with cancer,<sup>24,25</sup> RA,<sup>25</sup> parasitic and bacterial infections<sup>25,26</sup> (Fig 1), as well as in patients with the AIDS and AIDS-related complex.<sup>27</sup>

Chronic administration of TNF to animals (either by intermittent injection or by implantation of TNF-producing cells) resulted in the development of anemia.<sup>28-31</sup> No significant decreases in platelet or granulocyte counts were noted.<sup>28,29</sup> Like ACD in humans, this anemia was associated with a low serum iron and normal iron stores.<sup>30,31</sup> Mice exposed to TNF as a single intravenous (IV) dose showed suppression of spleen and marrow CFU-E but increased numbers of colonies from erythroid burst-forming units (BFU-E) and granulocyte-macrophage colony-forming units (CFU-GM),<sup>29</sup> while mice into which TNF-producing Chi-



**Fig 1.** TNF concentrations in healthy and diseased persons. Dotted area represents values below the detection limit of the method. Horizontal lines represent mean values of TNF concentrations for each group. Reprinted with permission.<sup>25</sup>

nese hamster ovary cells had been injected showed suppression of BFU-E as well as CFU-E.<sup>30</sup> As discussed below, TNF appears to mediate the interleukin-1 (IL-1)-induced inhibition of erythropoiesis in the in vivo murine model of Johnson et al.<sup>32,33</sup>

Recombinant TNF was administered to patients with metastatic cancer in a phase I trial.<sup>34</sup> They received 1 to 250  $\mu\text{g}/\text{m}^2$  TNF twice weekly for 4 weeks. The 16 patients who completed 4 weeks of therapy became anemic, with the mean hemoglobin decreasing from 118 g/L to 92 g/L, while no significant decreases in granulocytes or platelets were noted.<sup>34</sup> In vitro inhibition of human erythroid colony formation (BFU-E and CFU-E) by TNF has also been demonstrated,<sup>35,36</sup> as has selective inhibition of late erythroid progenitors (CFU-E) relative to late granulocytic progenitors (CFU-G).<sup>37</sup> Roodman et al<sup>35</sup> suggested, based on studies of plucked BFU-E colonies, that TNF directly inhibited these human erythroid progenitors. However, the capacity to generate highly purified human CFU-E from peripheral blood BFU-E<sup>38</sup> allowed Means et al<sup>39</sup> to demonstrate that the inhibitory effect of TNF on CFU-E colony

formation was indirect and mediated by a soluble factor released from marrow stromal cells. This factor has recently been identified as  $\beta$  interferon ( $\beta$ IFN),<sup>40</sup> which is produced by marrow stromal cells in response to superinduction with poly I-poly C<sup>41</sup> and, presumably, in response to other inducers of the immune response. These studies indicate that while TNF may act directly on BFU-E, its effect on CFU-E colony formation is indirect and is mediated by  $\beta$ IFN released from marrow stroma in response to TNF.

**IL-1.** IL-1 is a polypeptide that has a wide variety of actions in inflammation and immunity<sup>42</sup> and shares many of the properties of TNF.<sup>43</sup> Levels of IL-1 are elevated in patients with RA (as well as other ACD-associated conditions,<sup>44,45</sup> and this elevation correlates with markers of disease activity, such as anemia.<sup>46,47</sup>

IL-1 has also been shown to inhibit murine erythropoiesis in vitro<sup>48</sup> and in vivo.<sup>32</sup> Johnson et al<sup>32</sup> treated mice with single or repeated intraperitoneal injections of recombinant human IL-1 $\alpha$ .<sup>32</sup> At 6 hours postinjection, significant suppression of mature erythroid progenitors (CFU-E) occurred, reaching a maximum at 24 hours. This coincided with suppression of the peripheral blood reticulocyte count to 25% of the pretreatment value.<sup>32</sup> Less mature erythroid progenitors (BFU-E), as well as granulocytic, monocytic, and megakaryocytic progenitors, were stimulated by IL-1 $\alpha$ , with the maximum effect seen at 48 hours. After repeated injections of IL-1 $\alpha$ , the mice became anemic. In a subsequent study using the same murine model, Furmanski and Johnson<sup>33</sup> reported that the inhibitory effect of IL-1 $\alpha$  is mediated by TNF $\alpha$ .

IL-1 has also been implicated in ACD in humans. Maury et al<sup>46</sup> have reported that IL-1 $\beta$  levels are slightly elevated in RA patients relative to controls, and are significantly elevated in anemic RA patients relative to RA patients who are not anemic (Fig 2). Other investigators<sup>47</sup> have shown that the decrease in the hemoglobin levels of RA patients is directly correlated with the IL-1 level. Maury et al<sup>46</sup> also showed that recombinant human IL-1 ( $\alpha$  and  $\beta$ ) inhibited in vitro colony formation by BFU-E and CFU-E from normal human marrow, as well as proliferation by human erythroleukemia cells. In vitro colony formation by marrow granulocyte-macrophage progenitors (CFU-GM) was not inhibited by IL-1.<sup>46</sup>

Means et al<sup>49</sup> investigated the inhibition of human CFU-E colony formation by recombinant human IL-1 $\beta$  (rhIL-1) and found that rhIL-1 inhibited colony formation by unpurified marrow CFU-E but not by highly purified CFU-E, indicating that this inhibitory effect was indirect (Fig 3). Further studies showed that this inhibitory effect required the presence of T lymphocytes, and was mediated by  $\gamma$  interferon ( $\gamma$ IFN). rh $\gamma$ IFN, in turn, directly inhibited CFU-E colony formation (Fig 4).<sup>49</sup> This correlated well with data from other investigators (reviewed below) implicating  $\gamma$ IFN in ACD. Because  $\gamma$ IFN inhibits colony formation by CFU-GM<sup>50,51</sup> as well as by erythroid progenitors, this result would appear initially to be in conflict with the erythroid specificity of inhibition by IL-1 reported by Maury et al.<sup>46</sup> However, IL-1 also leads to the release of granulocyte-macrophage (GM) and granulocyte (G) colony-

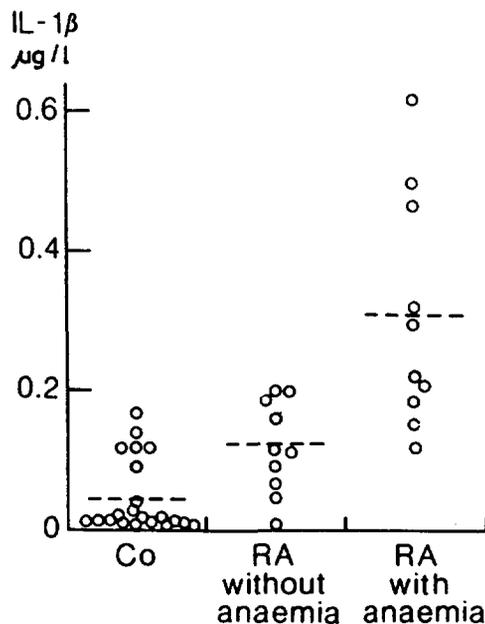


Fig 2. Serum IL-1 $\beta$  concentrations in blood donors (Co) and in patients with rheumatoid arthritis (RA) with and without anemia. The horizontal line indicates the mean concentration. The difference between the anaemic and nonanaemic patients with RA is significant ( $P < .01$ ). Reprinted with permission.<sup>46</sup>

stimulating factors (CSFs),<sup>52</sup> which can overcome the inhibitory effects of  $\gamma$ IFN on myeloid progenitors.<sup>53</sup> CFU-E colony formation, which is not effected by G- or GM-CSF,<sup>54</sup> would not be amenable to "rescue" from inhibition by these growth factors.<sup>49</sup>

**$\gamma$ IFN.**  $\gamma$ IFN is produced mainly by T lymphocytes and is involved in the modulation of immune and inflammatory responses as well as the host defense against microbial challenge.<sup>55,56</sup> Elevated  $\gamma$ IFN levels have been reported in

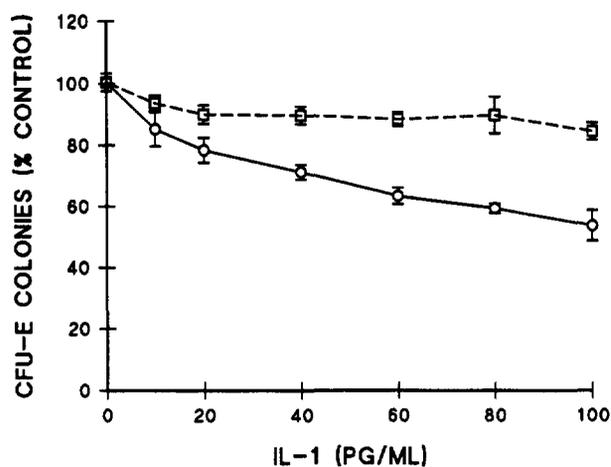
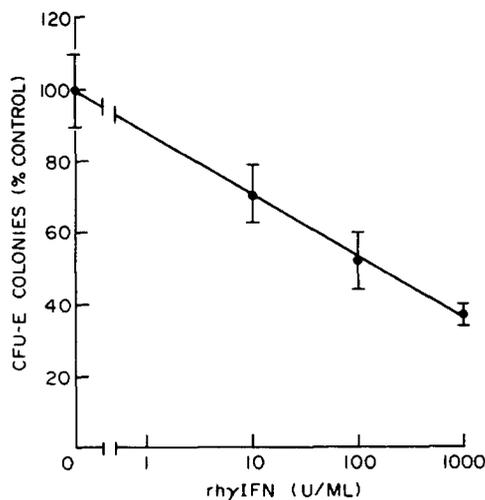


Fig 3. Effect of rhIL-1 on CFU-E colony formation by blood BFU-E derived CFU-E and marrow CFU-E. Growth of highly purified CFU-E colonies from three experiments ( $44.4\% \pm 32.4\%$  CFU-E) ( $\square$ ) and marrow CFU-E colonies from three experiments ( $0.36\% \pm 0.09\%$  CFU-E) ( $\circ$ ). Data from each experiment were normalized to CFU-E colony growth without IL-1. Results are expressed as mean  $\pm$  SE. Reprinted with permission.<sup>49</sup>



**Fig 4. Effects of rh $\gamma$ IFN on highly purified CFU-E colony formation. Results of three experiments with CFU-E purity  $24.0\% \pm 3.7\%$  are combined. Data from each experiment were normalized to CFU-E colony growth without rh $\gamma$ IFN. Results are expressed as mean  $\pm$  SE. Reprinted with permission.<sup>49</sup>**

patients with autoimmune and infectious diseases,<sup>55,57</sup> and cancer patients treated with  $\gamma$ IFN may develop a normochromic/normocytic anemia.<sup>58</sup>  $\gamma$ IFN has also been implicated in the pathogenesis of aplastic anemia.<sup>51,59-61</sup>

A number of investigators have reported inhibition of human erythroid colony formation in vitro by  $\gamma$ IFN.<sup>49,51,62,63</sup> Mamus et al,<sup>62</sup> looking at both BFU-E and CFU-E colony formation, reported that the inhibitory effect of  $\gamma$ IFN was indirect and required accessory cells, while Raefsky et al<sup>63</sup> and Means et al,<sup>49</sup> studying colony formation from purified progenitors, reported that this inhibitory effect was the result of direct action of  $\gamma$ IFN on the CFU-E.

Denz et al<sup>64</sup> have investigated the correlation between anemia and markers of immune activation such as  $\gamma$ IFN and neopterin. Neopterin is a pteridine that indicates activation of macrophages by  $\gamma$ IFN, and the neopterin level is increased in a variety of infectious, inflammatory, and malignant disorders.<sup>16,65,66</sup> Denz et al<sup>64</sup> studied 25 patients with hematologic malignancies, 44% of whom were anemic (hemoglobin  $< 12$  g/dL). Serum neopterin levels showed a significant inverse correlation with hemoglobin. Neopterin and  $\gamma$ IFN levels, in turn, showed a significant direct correlation,<sup>64</sup> demonstrating a relationship between anemia and a marker and mediator of immune activation, as Maury et al<sup>46</sup> and Eastgate et al<sup>47</sup> had previously shown for IL-1.

**Other cytokines.** Many cytokines involved in the inflammatory and immune response inhibit erythroid colony formation in vitro or are associated with development of anemia, including  $\alpha$  and  $\beta$ IFNs,<sup>40,63,67</sup> IL-6,<sup>68</sup> transforming growth factor- $\beta$  (TGF $\beta$ ),<sup>69,70</sup> and may merit investigation for a role in the pathogenesis of ACD. Recent data from two groups suggests that  $\alpha$ IFN, though a direct inhibitor of BFU-E, acts indirectly through accessory cells to inhibit CFU-E colony formation.<sup>71,72</sup>  $\beta$ IFN appears to directly inhibit CFU-E colony formation.<sup>40</sup>

IL-6 is an attractive candidate as a mediator of ACD

because its production is increased in inflammatory arthritides such as RA,<sup>73</sup> and its administration to primates results in anemia.<sup>68</sup> Vreugdenhil et al<sup>74</sup> demonstrated elevated serum IL-6 levels in RA patients with ACD relative to nonanemic RA patients, and showed that these levels correlated with markers of disease activity such as the sedimentation rate. However, the addition of IL-6 to bone marrow erythroid progenitors in vitro did not inhibit erythroid colony formation. In fact, the addition of anti-IL-6 impaired in vitro erythropoiesis, suggesting that the effect of IL-6 was stimulatory rather than inhibitory. The investigators concluded that IL-6 was a marker of RA activity, but played no role in ACD.<sup>74</sup>

TGF $\beta$  produces anemia when injected into mice<sup>75</sup> and inhibits colony formation by IL-3-dependent progenitors such as BFU-E,<sup>70</sup> but does not inhibit colony formation by CFU-E.<sup>76</sup>

**Synergy between cytokines.** In addition to their own effects, cytokines implicated in the pathogenesis of ACD can exhibit synergy. Synergistic inhibition of erythroid progenitors in vitro by  $\alpha$ IFN and  $\gamma$ IFN has been reported by Raefsky et al<sup>63</sup> and by Means and Krantz.<sup>71</sup>  $\gamma$ IFN also shows synergy with TNF in its inhibitory effect on hematopoiesis in vitro.<sup>77</sup> In addition, various cytokines involved in the inflammatory response have amplification pathways. TNF and IL-1 each induce expression of the other cytokine, and also increase their own expression.<sup>23,42,44,78</sup>

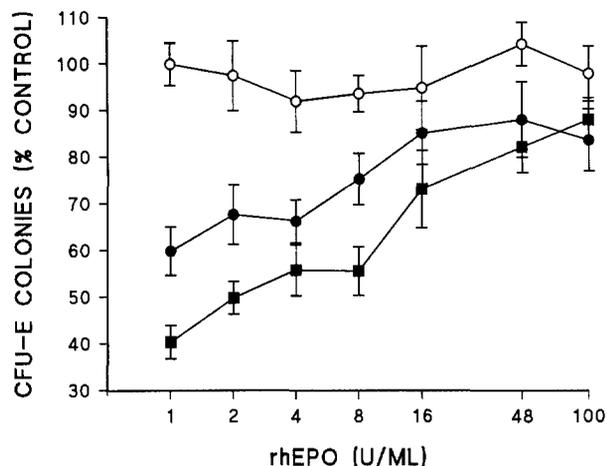
#### CYTOKINE INHIBITION OF EPO PRODUCTION AND EPO ACTION

##### *Mechanism of Impaired EPO Response To Anemia*

As noted above, the EPO response to anemia is blunted in ACD, and this relative EPO deficiency, while not the primary mechanism for decreased erythropoiesis, may contribute to the development of ACD. Recent investigations have suggested a role for cytokines in the impaired EPO response associated with RA. Faquin et al<sup>79</sup> reported that IL-1 ( $\alpha$  or  $\beta$ ), TNF $\alpha$ , and TGF $\beta$  inhibited production of EPO from the hepatoma cell line Hep3B. This effect appeared to occur at the level of the EPO mRNA.<sup>79</sup> Jelkmann et al,<sup>80</sup> using the HepG2 line, reported similar results for IL-1 and TNF, but noted no inhibition by TGF $\beta$ . In addition, they reported that IL-1 $\beta$  inhibited EPO production in isolated serum-free perfused rat kidneys.<sup>80</sup> So by inhibiting EPO production as well as marrow erythropoiesis, cytokines such as IL-1 and TNF may amplify their contributions to the development of ACD.

##### *Cytokines and Impaired EPO Action*

The relative deficiency in the EPO response in ACD led to consideration of the use of EPO as treatment for this condition. Gutnisky and Van Dyke<sup>81</sup> showed that the anemia induced in rats by turpentine abscesses could be corrected by injection of human urinary EPO, indicating that ACD could respond to EPO. The anemia associated with adjuvant-induced arthritis in rats also responded to EPO.<sup>82</sup> When rhEPO became available, studies were performed which demonstrated that pharmacologic concentra-



**Fig 5. Effect of varying EPO concentrations on CFU-E colony formation by mononuclear marrow cells in the presence of recombinant human  $\gamma$ IFN ([○],  $\gamma$ IFN 0 U/ML; [●],  $\gamma$ IFN 100 U/ML; [■],  $\gamma$ IFN 1,000 U/ML). 100% control is defined as CFU-E colony formation in the presence of 1 U/mL recombinant human EPO (rhEPO) and 0 U/mL  $\gamma$ IFN. Each point represents data from three separate experiments with  $290 \pm 30$  CFU-E/ $10^5$  cells. Modified with permission.<sup>93</sup>**

tions of EPO corrected the anemia in patients with RA,<sup>83-86</sup> cancer,<sup>87-89</sup> and AIDS.<sup>90</sup> Sixteen anemic patients with RA were treated with EPO in a multicenter trial.<sup>84</sup> Twelve responded with an increase in hematocrit of 6 points, and 11 of these patients normalized their hematocrits.<sup>84</sup>

EPO can also correct the inhibition of erythropoiesis in some of the cytokine-based models of ACD discussed above. Administration of EPO corrects the suppression of CFU-E seen in mice injected with IL-1,<sup>32</sup> as well as the anemia and reduction in CFU-E numbers reported in mice treated with single injections of TNF.<sup>91</sup> However, it does not correct the anemia or reduction in erythroid progenitors in mice exposed continuously to TNF *in vivo*, which may reflect the relatively higher concentrations of TNF in these animals.<sup>92</sup>

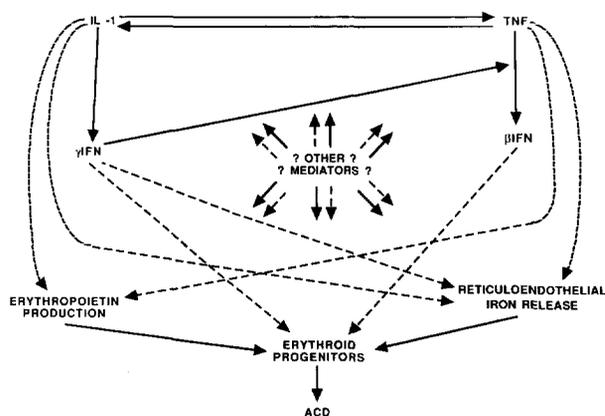
The inhibition of *in vitro* colony formation by either highly purified human CFU-E generated from peripheral blood BFU-E or by human marrow CFU-E induced by  $\gamma$ IFN was also corrected by exposure to very high, pharmacologic, concentrations of EPO.<sup>93</sup> Normally, CFU-E colony formation is not increased by EPO levels higher than 1 U/mL,<sup>38</sup> which saturates the 1,000 EPO receptors present on each CFU-E.<sup>94</sup> However, in the presence of  $\gamma$ IFN concentrations from 100 to 1,000 U/mL, 16 to 64 U/mL EPO was necessary to restore CFU-E colony formation to baseline levels<sup>93</sup> (Fig 5). The amount of EPO required to overcome the inhibitory effect depended on the amount of  $\gamma$ IFN present, suggesting that cases of ACD not responsive to EPO may have extremely high levels of cytokine inhibitors of erythropoiesis (such as  $\gamma$ IFN or TNF) that would require EPO levels higher than can be pharmacologically attained for improvement of erythropoiesis. Whether  $\gamma$ IFN might be decreasing the binding of EPO to its receptors, or the reverse, has not yet been determined, but the means are now available to determine the precise mechanism by which

a cytokine such as  $\gamma$ IFN inhibits the action of EPO on erythroid progenitor cells.

#### CYTOKINES AND ALTERED IRON METABOLISM IN ACD

The distinctive feature of ACD is a low serum iron in the presence of adequate reticuloendothelial (RE) iron stores.<sup>3</sup> This has prompted extensive investigation of iron metabolism in ACD. Early studies demonstrated a block in release of RE iron, and implied that ACD involved a "functional" iron deficiency.<sup>95,96</sup> However, other investigators, using lower doses of radiolabeled iron, found no block in iron reutilization or mobilization, suggesting that the normal RE iron stores with hypoferrremia is a secondary phenomenon caused by decreased erythropoiesis.<sup>97-100</sup>

Recent studies of the role of cytokines in ACD suggest that both impaired iron metabolism and impaired erythropoiesis are involved in ACD. Impairment of erythropoiesis, either by inhibition of progenitors or reduction of EPO increment, has been reviewed above. Moldawer et al<sup>31</sup> and Alvarez-Hernandez et al<sup>101</sup> injected rats and mice, respectively, with recombinant TNF and induced anemia and hypoferrremia. The hypoferrremia was associated with abnormalities of iron release from the RE system and incorporation into RBCs.<sup>31,101</sup> In addition, Denz et al<sup>102</sup> have reported a correlation between neopterin (a marker of immune activation associated with anemia in ACD patients and with  $\gamma$ IFN production<sup>64-66</sup> and ferritin levels in patients with malignancies, suggesting a role for immune activation in altered iron metabolism. Finally, Rogers et al<sup>103</sup> have recently reported that IL-1 increases ferritin production, and suggested that this additional ferritin could act as a trap for iron that might otherwise be available for erythropoiesis. While impairment of iron metabolism and erythropoiesis are each present in ACD, several reasons exist for believing that the latter is the most important contributor to the anemia. First, EPO can correct anemia in ACD (reviewed above) but cannot overcome the anemia of iron deficiency.<sup>104,105</sup> If relative iron deficiency was the primary cause of ACD, treatment with EPO would not correct this anemia. Secondly, in a multicenter trial of EPO in anemic



**Fig 6. Schematic diagram representing effects of inflammatory cytokines on processes involved in the impairment of erythropoiesis in ACD. Positive regulatory effects are indicated by solid lines and negative effects by broken lines.**

RA patients, administration of oral iron to eight iron-deficient RA patients increased serum ferritin levels but did not significantly increase their hematocrits, while EPO normalized the hematocrits of 11 of 12 patients (who also received concomitant iron).<sup>84</sup> Finally, serum levels of transferrin receptor are increased in 15 of 17 patients with iron deficiency, but are only increased in 4 of 41 patients with ACD.<sup>106</sup>

#### SUMMARY

Improved understanding of the inflammatory response and the identification and characterization of the specific cytokines involved, as well as improved understanding of erythropoiesis, and the availability of recombinant human growth factors such as EPO, have greatly enhanced our appreciation of the pathogenesis of ACD by allowing

development of a number of informative models for studying this syndrome. It appears that a variety of cytokines are involved in all aspects of the pathogenesis of ACD, from the inhibition of erythroid progenitors and EPO production to impairment of iron release. A schematic of the contributions of some of these cytokines to the development of ACD is shown in Fig 6. The exact biochemical mechanisms by which these effects occur is still to be determined.

The progress outlined in this report has allowed us to develop a more precise understanding of the pathogenesis of this common and important clinical syndrome. In 1983, Hansen<sup>1</sup> subtitled a review of ACD "A Bag of Unsolved Questions." Although this description is still accurate, our understanding of ACD has now developed to the point where we can offer a more defined subtitle: "A Bag of Cytokines."

#### REFERENCES

- Hansen NE: The anaemia of chronic disorders: A bag of unsolved questions. *Scand J Haematol* 31:397, 1983
- Lee GR: The anemia of chronic disease. *Semin Hematol* 20:61, 1983
- Cartwright GE: The anemia of chronic disorders. *Semin Hematol* 3:351, 1966
- Schilling RF: Anemia of chronic disease: A misnomer. *Ann Intern Med* 115:572, 1991
- Cash JM, Sears DA: The anemia of chronic disease: Spectrum of associated diseases in a series of unselected hospitalized patients. *Am J Med* 87:639, 1989
- Graber SE, Krantz SB: Erythropoietin: Biology and clinical use. *Hematol/Oncol Clin North Am* 3:369, 1989
- Erslev AJ, Caro J, Miller O, Silver R: Plasma erythropoietin in health and disease. *Ann Lab Clin Sci* 10:250, 1980
- Birgeard G, Hallgren R, Caro J: Serum erythropoietin in rheumatoid arthritis and other inflammatory arthritides: Relationship to anaemia and the effect of anti-inflammatory treatment. *Br J Haematol* 65:479, 1987
- Ward HP, Gordon B, Pickett JC: Serum levels of erythropoietin in rheumatoid arthritis. *J Lab Clin Med* 74:93, 1969
- Pavlovic-Kentera V, Ruvodic R, Milenkovic P, Marinkovic D: Erythropoietin in patients with anaemia in rheumatoid arthritis. *Scand J Haematol* 23:141, 1979
- Baer AN, Dessypris EN, Goldwasser E, Krantz SB: Blunted erythropoietin response to anaemia in rheumatoid arthritis. *Br J Haematol* 66:559, 1987
- Hochberg MC, Arnold CM, Hogans BB, Spivak JL: Serum immunoreactive erythropoietin in rheumatoid arthritis: Impaired response to anemia. *Arthritis Rheum* 31:1318, 1988
- Miller CM, Jones RJ, Piantadosi S, Abeloff MD, Spivak JL: Decreased erythropoietin response in patients with the anemia of cancer. *N Engl J Med* 322:1689, 1990
- Spivak JL, Barnes DC, Fuchs E, Quinn TC: Serum immunoreactive erythropoietin in HIV-infected patients. *JAMA* 261:3104, 1989
- Maury CPJ: Anaemia in rheumatoid arthritis: role of cytokines. *Scand J Rheumatol* 18:3, 1989
- Fuchs D, Hausen A, Reibnegger G, Werner ER, Werner-Felmayer G, Dierich MP, Wachter H: Immune activation and the anaemia associated with chronic inflammatory disorders. *Eur J Haematol* 46:65, 1991
- Zanjani ED, McGlave PB, Davis SF, Bonisadre M, Kaplan ME, Sarosi GA: In vitro suppression of erythropoiesis by bone marrow adherent cells from some patients with fungal infection. *Br J Haematol* 50:419, 1982
- Roodman GD, Horadam VW, Wright TL: Inhibition of erythroid colony formation by autologous bone marrow adherent cells from patients with the anemia of chronic disease. *Blood* 62:406, 1983
- Reid CDL, Prouse PJ, Baptista LC, Gumpel JM, Chanarin I: The mechanism of the anaemia in rheumatoid arthritis: Effects of bone marrow adherent cells and of serum on in vitro erythropoiesis. *Br J Haematol* 58:607, 1984
- Dainiak N, Hardin J, Floyd V, Callahan M, Hoffmann R: Humoral suppression of erythropoiesis in systemic lupus erythematosus. *Am J Med* 69:537, 1980
- Baer AN, Dessypris EN, Krantz SB: The pathogenesis of anemia in rheumatoid arthritis: A clinical and laboratory analysis. *Semin Arthritis Rheum* 19:209, 1990
- Sugimoto M, Wakabayashi Y, Hirose S-i, Takaku F: Immunological aspects of the anemia of rheumatoid arthritis. *Am J Hematol* 25:1, 1987
- Grunfeld C, Palladino MA: Tumor necrosis factor: Immunologic, antitumor, metabolic, and cardiovascular activities. *Adv Intern Med* 35:45, 1990
- Balkwill F, Burke F, Talbot D, Tavernier J, Osborne R, Naylor S, Durbin H, Fiers W: Evidence for tumor necrosis factor/cachectin production in cancer. *Lancet* 2:1229, 1987
- Teppo A-M, Maury CPJ: Radioimmunoassay of tumor necrosis factor in serum. *Clin Chem* 33:2024, 1987
- Kern P, Hemmer CJ, Van Damme J, Grass HJ, Dietrich M: Elevated tumor necrosis factor  $\alpha$  and interleukin-6 levels as markers for complicated plasmodium falciparum malaria. *Am J Med* 87:139, 1989
- Labdevirta J, Maury CPJ, Teppo A-M, Repo H: Elevated levels of circulating cachectin/tumor necrosis factor in patients with acquired immunodeficiency syndrome. *Am J Med* 85:289, 1988
- Tracey KJ, Wei H, Manogue KR, Fong Y, Hesse DG, Nguyen HT, Kuo GC, Beutler B, Cotran RS, Cerami A, Lowry SF: Cachectin/tumor necrosis factor induces cachexia, anemia, and inflammation. *J Exp Med* 167:1211, 1988
- Johnson CS, Chang M-J, Furmanski P: In vivo hematopoietic effects of tumor necrosis factor- $\alpha$  in normal and leukemic mice: Characterization and therapeutic applications. *Blood* 72:1875, 1988
- Johnson RA, Waddelow TA, Caro J, Oliff A, Roodman GD:

Chronic exposure to tumor necrosis factor in vivo preferentially inhibits erythropoiesis in nude mice. *Blood* 74:130, 1989

31. Moldawer LL, Marano MA, Wei He, Fong Yuman, Silen ML, Kuo G, Manogue KR, Vlassara H, Cohen H, Cerami A, Lowry SF: Cachectin/tumor necrosis factor alters red blood cell kinetics and induces anemia in vivo. *FASEB J* 3:1637, 1989

32. Johnson CS, Keckler DJ, Topper MI, Braunschweiger PG, Furmanski P: In vivo hematopoietic effects of recombinant interleukin-1 $\alpha$  in mice: Stimulation of granulocytic, monocytic, megakaryocytic, and early erythroid progenitors, suppression of late erythroid progenitors, and reversal of erythroid suppression with erythropoietin. *Blood* 73:678, 1989

33. Furmanski P, Johnson CS: Macrophage control of normal and leukemic erythropoiesis. Identification of the macrophage derived erythroid suppressing activity as interleukin-1 and the mediator of its effect as tumor necrosis factor. *Blood* 75:2328, 1990

34. Blick M, Sherwin SA, Rosenblum M, Gutterman J: Phase I study of recombinant tumor necrosis factor in cancer patients. *Cancer Res* 47:2986, 1987

35. Roodman GD, Bird A, Hutzler D, Montgomery W: Tumor necrosis factor-alpha and hematopoietic progenitors: Effects of tumor necrosis factor on the growth of erythroid progenitors CFU-E and BFU-E and the hematopoietic cell lines K562, HL60, and HEL cells. *Exp Hematol* 15:928, 1987

36. Akahane K, Hosoi T, Urabe A, Kawakami M, Takaku F: Effects of recombinant human tumor necrosis factor (rhTNF) on normal human and mouse hemopoietic progenitor cells. *Int J Cell Cloning* 5:16, 1987

37. Abboud SL, Gerson SL, Berger NA: The effect of tumor necrosis factor on normal human hematopoietic progenitors. *Cancer* 60:2965, 1987

38. Sawada K, Krantz SB, Kans JS, Dessypris EN, Sawyer S, Glick AD, Civin CI: Purification of human erythroid colony-forming units and demonstration of specific binding of erythropoietin. *J Clin Invest* 80:357, 1987

39. Means RT, Dessypris EN, Krantz SB: Inhibition of human erythroid colony-forming units by tumor necrosis factor requires accessory cells. *J Clin Invest* 86:538, 1990

40. Means RT, Krantz SB: Inhibition of human erythroid colony-forming units by tumor necrosis factor is mediated by beta interferon. *Clin Res* 40:210a, 1992 (abstr)

41. Shah G, Dexter TM, Lanotte M: Interferon production by human marrow stromal cells. *Br J Haematol* 54:365, 1983

42. Durum SK, Schmidt JA, Oppenheim JJ: Interleukin 1: An immunological perspective. *Annu Rev Immunol* 3:263, 1985

43. Le J, Vilček J: Biology of disease. Tumor necrosis factor and interleukin 1: Cytokines with multiple overlapping biological activities. *Lab Invest* 56:234, 1987

44. Platanius LC, Vogelzang NJ: Interleukin-1: Biology, pathophysiology, and clinical prospects. *Am J Med* 89:621, 1990

45. Fujiwara H, Klienherz ME, Wallis RS, Ellner JJ: Increased interleukin-1 production and monocyte suppressor activity associated with human tuberculosis. *Am Rev Respir Dis* 133:73, 1986

46. Maury CPJ, Andersson LC, Teppo A-M, Partanen S, Juononen E: Mechanism of the anaemia in rheumatoid arthritis: Demonstration of raised interleukin 1 $\beta$  concentrations in anaemic patients and of interleukin 1 mediated suppression of normal erythropoiesis and proliferation of human erythroleukemia (HEL) cells in vitro. *Ann Rheum Dis* 47:972, 1988

47. Eastgate JA, Wood NC, DiGiovine FS, Symons JA, Grinlinton FA, Duff GW: Correlation of plasma interleukin 1 levels with disease activity in rheumatoid arthritis. *Lancet* 2:706, 1988

48. Schooley JC, Kullgren B, Allison AC: Inhibition by interleukin-1 of the action of erythropoietin on erythroid precursors and its

possible role in the pathogenesis of hypoplastic anemias. *Br J Haematol* 67:11, 1987

49. Means RT, Dessypris EN, Krantz SB: Inhibition of human erythroid colony-forming units by interleukin-1 is mediated by gamma interferon. *J Cell Physiol* 150:59, 1992

50. Lu L, Welte K, Gabrilove JL, Hangoc G, Bruno E, Hoffman R, Broxmeyer HE: Effects of recombinant tumor necrosis factor  $\alpha$ , human  $\gamma$ -interferon, and prostaglandin E on colony formation of human hematopoietic progenitor cells stimulated by natural human pluripotent colony stimulating factor, pluripoetin  $\alpha$ , and recombinant erythropoietin in serum-free cultures. *Cancer Res* 46:4357, 1986

51. Zoumbos NC, Djeu JY, Young NS: Interferon is the suppressor of hematopoiesis generated by stimulated lymphocytes. *J Immunol* 133:769, 1984

52. Kauchansky K, Lin N, Adamson JW: Interleukin-1 stimulates fibroblasts to synthesize granulocyte-macrophage and granulocyte colony-stimulating factors. Mechanism for the hematopoietic response to inflammation. *J Clin Invest* 81:92, 1988

53. Zoumbos NC, Baranski B, Young NS: Different hematopoietic growth factors have different capacity in overcoming the in vitro interferon gamma-induced suppression of bone marrow progenitor cells. *Eur J Haematol* 44:282, 1990

54. Sawada K, Krantz SB, Dessypris EN, Koury ST, Sawyer ST: Human colony-forming units-erythroid do not require accessory cells, but do require direct interaction with insulin-like growth factor-I and/or insulin for erythroid development. *J Clin Invest* 83:1701, 1989

55. Murray HW: Interferon-gamma, the activated macrophage, and host defense against microbial challenge. *Ann Intern Med* 108:595, 1988

56. Landolfo S, Garotta G: IFN $\gamma$ , a lymphokine that modulates immunological and inflammatory responses. *J Immunol Res* 3:81, 1991

57. Hooks JJ, Moutsopoulos HM, Geis SA, Stahl NI, Decker JL, Notkins AL: Immune interferon in the circulation of patients with autoimmune disease. *N Engl J Med* 301:5, 1979

58. Vadhan-Raj S, Al-Katib A, Bhulla R, Pelus L, Nathan CF, Sherwin SA, Oettgen HF, Krown SE: Phase I trial of recombinant interferon gamma in cancer patients. *J Clin Oncol* 4:137, 1986

59. Zoumbos NC, Gascon P, Djeu JY, Trost SR, Young NS: Circulating activated suppressor T-lymphocytes in aplastic anemia. *N Engl J Med* 312:257, 1985

60. Young NS, Leonard E, Platanius L: Lymphocytes and lymphokines in aplastic anemia: Pathogenic role and implications for pathogenesis. *Blood Cells* 13:87, 1987

61. Miura A, Endo K, Sugawara T, Kameoka J-I, Watanabe N, Meguro K, Fukuhara O, Sato I, Suzuki C, Yoshinaga K: T cell-mediated inhibition of erythropoiesis in aplastic anaemia: The possible role of IFN- $\gamma$  and TNF- $\alpha$ . *Br J Haematol* 78:442, 1991

62. Mamus SW, Beck-Schroeder S, Zanjani ED: Suppression of normal human erythropoiesis by gamma interferon in vitro: Role of monocytes and T-lymphocytes. *J Clin Invest* 75:1496, 1985

63. Raefsky EL, Platanius LC, Zoumbos NC, Young NS: Studies of interferon as a regulator of hematopoietic cell proliferation. *J Immunol* 135:2507, 1985

64. Denz H, Fuchs D, Huber H, Nachbaur D, Reibnegger G, Thaler J, Werner ER, Wachter H: Correlation between neopterin, interferon-gamma and haemoglobin in patients with haematological disorders. *Eur J Haematol* 44:196, 1990

65. Fuchs D, Hausen A, Reibnegger G, Werner ER, Dierich MP, Wachter H: Neopterin as a marker for activated cell-mediated immunity: Application in HIV infection. *Immunol Today* 9:150, 1988

66. Wachter H, Fuchs D, Hausen A, Reibnegger G, Werner ER: Neopterin as a marker for activation of cellular immunity: Immunologic basis and clinical application. *Adv Clin Chem* 27:81, 1989
67. Broxmeyer HE, Lu L, Platzer E, Feit C, Juliano L, Rubin BY: Comparative analysis of the influences of human gamma, alpha, and beta interferons on human multipotential (CFU-GEMM), erythroid (BFU-E), and granulocyte-macrophage (CFU-GM) progenitor cells. *J Immunol* 131:1300, 1983
68. Asano S, Okano A, Ozawa K, Nakahata T, Ishibashi T, Koike K, Kirnura H, Tanioka Y, Shibuya A, Hirano T, Kishimoto T, Takaku F, Akiyama Y: In vivo effects of recombinant human interleukin-6 in primates: Stimulated production of platelets. *Blood* 75:1602, 1990
69. Wilder RL, Lafyatis R, Roberts AB, Case John P, Kumkumian GK, Sano H, Sporn MB, Remmers EF: Transforming growth factor- $\beta$  in rheumatoid arthritis. *Ann NY Acad Sci* 593:197, 1990
70. Keller JR, Sing GK, Ellingsworth LR, Ruscetti SK, Ruscetti FW: Two forms of transforming growth factor- $\beta$  are equally important selective growth inhibitors of early murine hematopoiesis. *Ann NY Acad Sci* 593:172, 1990
71. Means RT, Krantz SB: Inhibition of human erythroid colony-forming units (CFU-E) by interferons (IFNs): Different modes of action for  $\alpha$ ,  $\beta$ , and  $\gamma$  IFNs. *Blood* 78:1215a, (abstr, suppl 1)
72. Tarumi T, Sawada K, Sato N, Ieko I, Sakai N, Koizumi K, Sahurama S, Nakagawa S, Takahashi TA, Sekiguchi S, Yasukouchi T: Recombinant human interferon-alpha (rIFN $\alpha$ ) directly inhibits burst-forming units-erythroid (BFU-E) in early differentiated state. *Br J Haematol* (abstr, suppl) (in press)
73. Houssiau FA, Devogelaer J-P, Van Damme J, Nagant de Deuxchaisnes C, Van Snick J: Interleukin-6 in synovial fluid and serum of patients with rheumatoid arthritis and other inflammatory arthritides. *Arthritis Rheum* 31:784, 1988
74. Vreugdenhil G, Lowenberg B, van Eijk HG, Swaak AJG: Anaemia of chronic disease in rheumatoid arthritis: Raised serum interleukin-6 (IL-6) levels and the effects of IL-6 and anti-IL-6 on in vitro erythropoiesis. *Rheumatol Int* 10:127, 1990
75. Miller KL, Avis P, Waegell W: Modulation of erythropoiesis by treatment of mice with transforming growth factor beta. *Exp Hematol* 18:603, 1990 (abstr)
76. Hino M, Tojo A, Miyazono K, Urabe A, Takaku F: Effects of  $\beta$  transforming growth factors on hematopoietic progenitor cells. *Br J Haematol* 70:143, 1988
77. Broxmeyer HE, Williams DE, Lu L, Anderson SL, Beyer GS, Hoffman R, Rubin BY: The suppressive influences of tumor necrosis factors on bone marrow hematopoietic progenitor cells from normal donors and patients with leukemia: Synergism of tumor necrosis factor and interferon- $\gamma$ . *J Immunol* 136:4487, 1986
78. Phillip R, Epstein LB: Tumor necrosis factor as immunomodulator and mediator of monocyte cytotoxicity induced by itself, gamma interferon, and interleukin-1. *Nature* 323:86, 1986
79. Faquin WC, Schneider TJ, Goldberg MA: Effect of inflammatory cytokines on hypoxia-induced erythropoietin production. *Blood* 79:1987, 1992
80. Jelkmann W, Pagel H, Wolff M, Fandrey J: Monokines inhibiting erythropoietin production in human hepatoma cultures and in isolated perfused rat kidneys. *Life Sci* 50:301, 1991
81. Gutnisky A, Van Dyke D: Normal response to erythropoietin or hypoxia in rats made anemic with turpentine abscess. *Proc Soc Exp Biol Med* 112:75, 1963
82. Asai F, Oshima T: Recombinant human erythropoietin, but not iron supplementation, improves anemia in rats with adjuvant induced arthritis. *Jpn J Pharmacol* 57:291, 1991
83. Means RT, Olsen NJ, Krantz SB, Dessypris EN, Graber SE, Stone WJ, O'Neil VL, Pincus T: Treatment of the anemia of rheumatoid arthritis with recombinant human erythropoietin: Clinical and in vitro studies. *Arthritis Rheum* 32:638, 1989
84. Pincus T, Olsen NJ, Russell IJ, Wolfe F, Harris ER, Schnitzer TJ, Boccagno JA, Krantz SB: Multicenter study of recombinant human erythropoietin in correction of anemia in rheumatoid arthritis. *Am J Med* 89:161, 1990
85. Tauchi T, Ohyashiki JH, Fujieda H, Lin KY, Ohyashiki D, Toyama K: Suppressed erythropoietin response to anemia and the efficacy of recombinant erythropoietin in the anemia of rheumatoid arthritis. *J Rheumatol* 17:885, 1990
86. Biregegard G, Gudbjornsson B, Hallgren R, Wide L: Anemia of chronic inflammatory arthritides: Treatment with recombinant human erythropoietin. *Contrib Nephrol* 88:295, 1991
87. Oster W, Herrmann F, Gamm H, Zeile G, Lindemann A, Muller G, Brune T, Kraemer H-P, Mertelsmann R: Erythropoietin for the treatment of anemia of malignancy associated with bone marrow infiltration. *J Clin Oncol* 8:956, 1990
88. Ludwig H, Fritz E, Kotzmann H, Hocker P, Gisslinger H, Barnas U: Erythropoietin treatment of anemia associated with multiple myeloma. *N Engl J Med* 322:1693, 1990
89. Henry DH, Bennett J, Brooks B, Carey R, Case D, Denton D, Fishkin E, Jacobsen R, Jones S, Keller A, Kugler J, Moore J, Silver R, Storniolo AM, Wampler G, Larholt K, Abels R: Recombinant human erythropoietin (r-HuEPO) for the treatment of the anemia of cancer, final results of multicenter trials. *Blood* 78:152a, 1991 (abstr, suppl 1)
90. Fischl M, Galpin JE, Levine JD, Groopman JE, Henry DH, Kennedy P, Miles S, Robbins W, Starrett B, Zalusky R, Abels RI, Tsai HC, Rudnick SA: Recombinant human erythropoietin for patients with AIDS treated with zidovudine. *N Engl J Med* 322:1488, 1990
91. Johnson CS, Cook CA, Furmanski P: In vivo suppression of erythropoiesis by tumor necrosis factor- $\alpha$ : Reversal with exogenous erythropoietin (EPO). *Exp Hematol* 18:109, 1990
92. Clibon U, Bonewald L, Caro J, Roodman GD: Erythropoietin fails to reverse the anemia in mice continuously exposed to tumor necrosis factor-alpha in vivo. *Exp Hematol* 18:438, 1990
93. Means RT, Krantz SB: Inhibition of human erythroid colony-forming units by  $\gamma$  interferon can be corrected by recombinant human erythropoietin. *Blood* 78:2564, 1991
94. Sawada K, Krantz SB, Sawyer ST, Civin CI: Quantitation of specific binding of erythropoietin to human erythroid colony-forming cells. *J Cell Physiol* 137:337, 1988
95. Bennett RM, Holt PJJ, Lewis SM: Role of the reticuloendothelial system in the anaemia of rheumatoid arthritis: A study using the  $^{59}\text{Fe}$ -labelled dextran model. *Ann Rheum Dis* 33:147, 1974
96. Haurani FI, Burke WM, Martinez EJ: Effective reutilization of iron in the anemia of inflammation. *J Lab Clin Med* 65:560, 1965
97. Williams P, Cavill I, Kanakakorn K: Iron kinetics in the anaemia of rheumatoid arthritis. *Rheumatol Rehab* 13:17, 1974
98. Konijn AM, Hershko C: Ferritin synthesis and inflammation. I. Pathogenesis of impaired iron release. *Br J Haematol* 37:7, 1977
99. Williams RA, Samson D, Tikerpac J, Crowne H, Gumpel JM: *In vitro* studies of ineffective erythropoiesis in rheumatoid arthritis. *Ann Rheum Dis* 41:502, 1982
100. Zarrabi MH, Lysik R, DiStefano J, Zucker S: The anaemia of chronic disorders: Studies of iron reutilization in the anaemia of experimental malignancy and chronic inflammation. *Br J Haematol* 35:647, 1977
101. Alvarez-Hernandez X, Liceaga J, McKay IC, Brock JH: Induction of hypoferrremia and modulation of macrophage iron metabolism by tumor necrosis factor. *Lab Invest* 61:319, 1989

102. Denz H, Fuchs D, Huber P, Landmann R, Ludwig Ch, Obrecht JP, Wachter H: Association between serum neopterin and ferritin in patients with haematological neoplasias. *Pteridines* 2:120, 1990
103. Rogers J, Durmowicz G, Kasschau K, Lacroix L, Bridges K: A motif within the 5' non-coding regions of acute phase mRNAs mediates ferritin translation by IL-1 $\beta$  and may contribute to the anemia of chronic disease. *Blood*:367a, 1991 (abstr, suppl 1)
104. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW: Correction of the anemia of end-stage renal disease with recombinant human erythropoietin: Results of a combined phase I and II clinical trial. *N Engl J Med* 316:73, 1987
105. Masunga H, Murakami A, Goto M, Ueda M: Effects of erythropoietin injection on the anemic rats with different serum erythropoietin titer. *Jpn J Vet Sci* 19:1, 1986
106. Ferguson BJ, Skikine BS, Simpson KM, Baynes RD, Cook JD: Serum transferrin receptor distinguishes the anemia of chronic disease from iron deficiency anemia. *J Lab Clin Med* 19:385, 1992



**blood**<sup>®</sup>

1992 80: 1639-1647

## **Progress in understanding the pathogenesis of the anemia of chronic disease [see comments]**

RT Jr Means and SB Krantz

---

Updated information and services can be found at:  
<http://www.bloodjournal.org/content/80/7/1639.full.html>

Articles on similar topics can be found in the following Blood collections

---

Information about reproducing this article in parts or in its entirety may be found online at:  
[http://www.bloodjournal.org/site/misc/rights.xhtml#repub\\_requests](http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests)

Information about ordering reprints may be found online at:  
<http://www.bloodjournal.org/site/misc/rights.xhtml#reprints>

Information about subscriptions and ASH membership may be found online at:  
<http://www.bloodjournal.org/site/subscriptions/index.xhtml>