ALTERED IRON METABOLISM AND THE ANEMIA OF CHRONIC DISEASE: A ROLE OF IMMUNE ACTIVATION

To the Editor:

Recently, Means and Krantz showed that the inhibition of erythroid colony-forming units caused by interferon-γ (IFN-γ) can be corrected in vitro by recombinant human erythropoietin (EPO).1

In vivo, the pathogenetic mechanism of the anemia of chronic disease (ACD) is not yet understood. Because this symptom is very common, many attempts have been made to explore the factors involved and to establish treatment modalities. In vitro results suggest that IFN-γ could be responsible for the development of ACD. We earlier found correlations between the anemia of patients with hematologic disorders and the degree of cellular immune activation, measured by increased serum IFN-γ and neopterin concentrations.2 Similar correlations could be found in various clinical conditions such as chronic pneumonia3 and gynecologic cancer.4

A potential mechanism involved in the development of ACD is the shift of iron towards the storage compartment. Because activated macrophages are able to influence the iron metabolism in vitro, they seem to play a crucial role.5 We recently found a significant correlation between the levels of neopterin and ferritin in patients with malignant disorders.6 A negative correlation, on the other hand, existed between neopterin and the degree of anemia, confirming results described previously.7 Likewise, serum iron was correlated with neopterin in a negative manner. Finally, a significant correlation was found between iron concentrations and the hemoglobin content of the single erythrocyte, pointing to the development of a hypochromic population of erythrocytes. During follow-up, successful treatment of patients was associated with decreasing neopterin and ferritin concentrations and an increase of serum iron and hemoglobin. Thus, the reduction of immune activation seems to improve the changes described above.

From these findings we assume that the ACD is mediated by IFN-γ. The fact that tumor-associated anemia, eg, in multiple myeloma, can be corrected by EPO7 appears to confirm the in vitro results of Means and Krantz.1 The striking similarity of the findings in chronic inflammatory and in malignant disorders8 supports the idea of a common pathogenetic mechanism and underlines the central role of activated macrophages in this puzzling network. It would be interesting to know whether a correlation exists between the degree of immune activation and the responsiveness of tumor-associated anemia to EPO treatment.

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RESPONSE

Drs Denz, Fuchs, and Wachter present interesting data supporting a role for γ interferon (γIFN) in the pathogenesis of the anemia of chronic disease (ACD). Further support for this association is provided by our recently published observation that inhibition of erythroid colony formation by interleukin-1 (IL-1) is also mediated by γIFN.1

The information provided by Denz et al showing an association of cellular immune activation and serum ferritin levels in ACD is of particular interest, because the importance of iron metabolism in ACD has been controversial. Rogers et al have recently presented data indicating that IL-1 increases ferritin production, which might contribute to ACD by trapping iron that would otherwise be available for erythropoiesis.4 However, Asai and Oshima have reported that anemia in an animal model of ACD can be corrected by recombinant erythropoietin, but not by the administration of intravenous iron colloid,5 suggesting that the increase in γIFN may be more important in the pathogenesis of ACD than the changes in iron metabolism.

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Altered iron metabolism and the anemia of chronic disease: a role of immune activation [letter; comment] [see comments]

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