Iron in Hematology: An Historical Perspective

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The pathophysiology of iron deficiency and overload has been reported at ASH meetings for the past 50 years. In 1958, Professor Clem Finch published the first two articles on factors influencing dietary iron absorption in man and was conducting studies of iron kinetics, which eventually led to the development of a ferrokinetic method for evaluating erythroid marrow function in man. Also in 1958, Eugene Goldwasser published in Blood his studies on the effect of cobalt on the production of erythropoietin. For several years researchers had known that cobalt increased red cell production in experiment animals. In the Blood paper, Goldwasser and coworkers showed that cobalt exerts this effect by stimulating the production of erythropoietin. The molecular mechanism of this stimulation was understood 35 years later, when the involvement of hypoxia-inducible factor 1 in transcriptional response to hypoxia was defined.

The notion of preleukemia or myelodysplastic syndromes was unknown in 1958. However, in that year Sir John Dacie and his coworkers wrote a long article on refractory normoblastic anemia that was published in January 1959. This paper not only introduced the concept of refractory anemia with or without ringed sideroblasts, but also showed that ineffective erythropoiesis was a key feature of this condition.

In 1983, when I was a senior fellow at the University of Washington School of Medicine in Seattle working with Clem Finch in iron kinetics, I participated in my first ASH meeting, then in San Francisco. At that time, only three proteins of iron metabolism were known—transferrin, transferrin receptor, and ferritin—and the molecular basis of hereditary hemochromatosis was unknown. Subsequent studies led to the identification of HFE, ferroportin and hemouvelin as novel proteins of iron metabolism. The major breakthrough, however, was the observation that lack of hepcidin gene expression led to severe tissue iron overload in mice. Hepcidin was soon recognized as a key regulator of iron metabolism.

In 1985, the erythropoietin gene was cloned and expressed. This allowed development of recombinant human erythropoietin, the efficacy of which in correcting the anemia of renal failure was quickly demonstrated. Recombinant human erythropoietin was later found to ameliorate the anemia of malignancy. However, recent observations indicate that erythropoiesis-stimulating agents may be associated with serious adverse effects in patients with malignancy.

The first classification of the myelodysplastic syndromes was published in 1982. Almost all patients with these conditions are anemic at diagnosis or develop anemia during the clinical course of the disease, and red cell transfusion represents the mainstay of treatment for most of them. Recent studies indicate that the severity of anemia and transfusion dependency are negative prognostic factors in these patients. Transfusion iron overload may have clinical consequences in a portion of patients with myelodysplastic syndrome, particularly in those with suppressed hepcidin production, and these patients may benefit from iron chelation therapy.

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