caught between the NIH policy and the policies of journals in which they seek to publish their work, and journals and publishers may be caught between their support for the public health mission of the NIH and their own self-interest.

The NIH initiative may also encourage other governments and private funding organizations to consider public-access policies. For example, the Wellcome Trust and the National Library of Medicine are discussing the establishment of a counterpart to PubMed Central in the United Kingdom.[5] Such a repository would mirror the data held in PubMed Central and also provide the flexibility to add additional publications and content.

As the public-access policy takes effect, there are high expectations for quick movement toward timely availability of all publications from NIH-supported research. PubMed Central, however, could soon receive 5000 papers a month, or only a few hundred. It should rapidly become obvious whether the policy is working as the NIH — and Congress — intended.

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Orchestration of Iron Homeostasis

Robert E. Fleming, M.D., and Bruce R. Bacon, M.D.

The number of newly identified genes participating in the regulation of iron homeostasis has increased at a remarkable pace. The characterization of these genes has led investigators to challenge previous models of the regulation of iron homeostasis in health and its dysregulation in disease. There is now substantial evidence that the liver plays a central role in determining how much iron is absorbed from the gut and in influencing the release of iron from sites of storage. The discovery of the iron regulatory hormone hepcidin has provided a cohesive theory to explain the pathophysiology of such common disorders as hereditary hemochromatosis and the anemia of inflammation (also known as the anemia of chronic disease). The most important cellular targets for hepcidin appear to be the villus enterocyte, the reticuloendothelial macrophage, and the hepatocyte (see diagram).
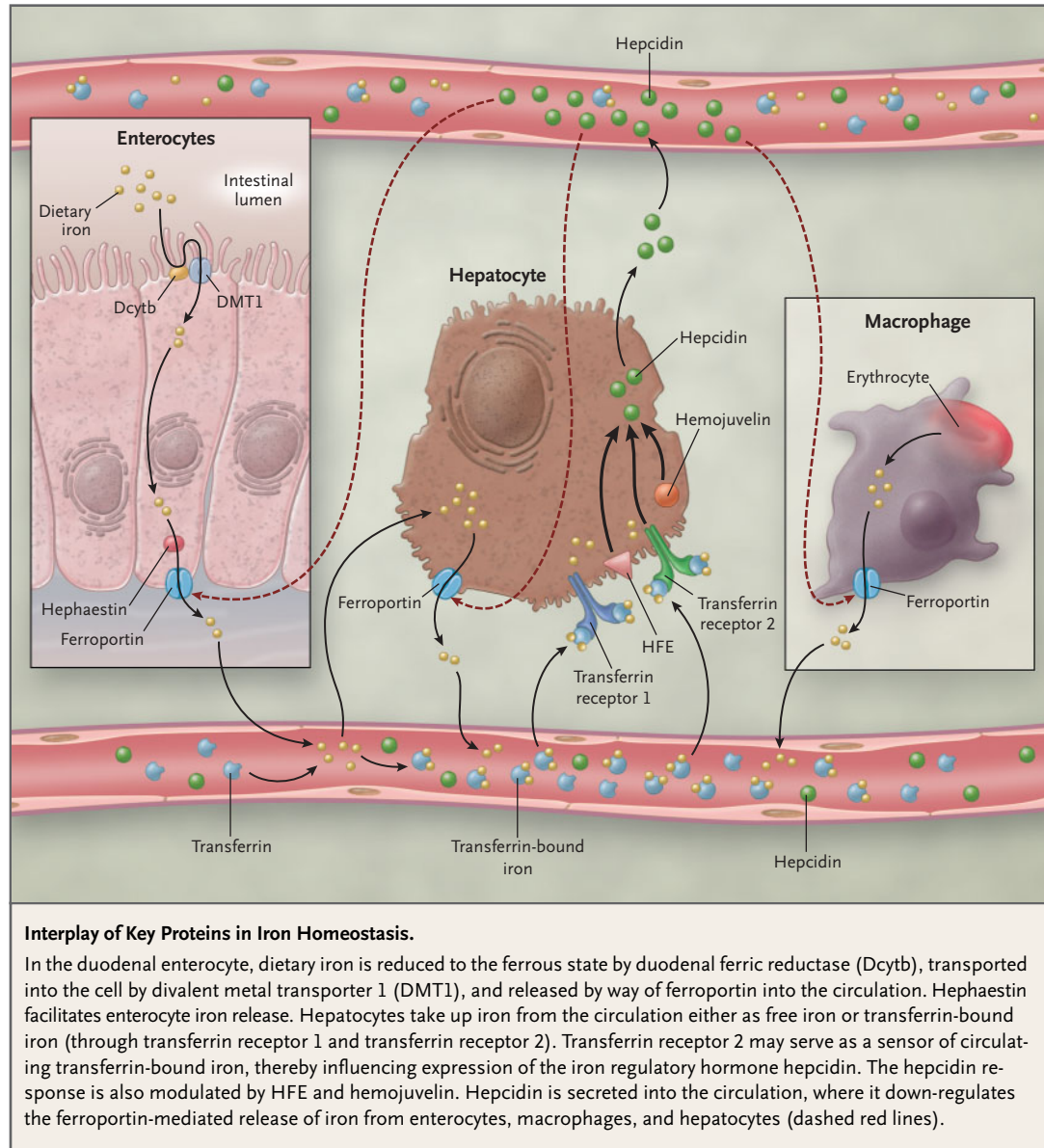
There are no substantial physiologic mechanisms that regulate iron loss. Accordingly, iron homeostasis is dependent on regulatory feedback between body iron needs and intestinal iron absorption. Several factors have been found to influence the rate of iron absorption, including the body's iron stores, the level of erythropoietic activity in bone marrow, the blood hemoglobin concentration, the blood oxygen content, and the presence or absence of inflammatory cytokines.[1] More than one of these factors may act simultaneously, and some are interrelated. Intestinal iron absorption increases with decreased iron stores, increased erythropoietic activity, anemia, or hypoxemia. Conversely, intestinal iron absorption decreases in the presence of inflammation — a process that contributes to the anemia of inflammation. Excess iron absorption relative to body iron stores is the hallmark of hereditary hemochromatosis.[2]

Nearly all absorption of dietary iron occurs in the duodenum. Several steps are involved, including the reduction of iron to a ferrous state, apical uptake, intracellular storage or transcellular trafficking, and basolateral release. Molecular participants in each of these processes have been identified[3] (see diagram). The reduction of iron from the ferric to the ferrous state occurs at the enterocyte

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Interplay of Key Proteins in Iron Homeostasis.

In the duodenal enterocyte, dietary iron is reduced to the ferrous state by duodenal ferric reductase (Dcytb), transported into the cell by divalent metal transporter 1 (DMT1), and released by way of ferroportin into the circulation. Hephaestin facilitates enterocyte iron release. Hepatocytes take up iron from the circulation either as free iron or transferrin-bound iron (through transferrin receptor 1 and transferrin receptor 2). Transferrin receptor 2 may serve as a sensor of circulating transferrin-bound iron, thereby influencing expression of the iron regulatory hormone hepcidin. The hepcidin response is also modulated by HFE and hemojuvelin. Hepcidin is secreted into the circulation, where it down-regulates the ferroportin-mediated release of iron from enterocytes, macrophages, and hepatocytes (dashed red lines).

brush border by means of a duodenal ferric reductase (Dcytb). Ferrous iron is then transported across the apical plasma membrane of the enterocyte by divalent metal transporter 1 (DMT1). Iron taken up by the enterocyte may be stored intracellularly as ferritin (and excreted in the feces when the senescent enterocyte is sloughed) or transferred across the basolateral membrane to the plasma. This iron is transferred out of the enterocyte by the basolateral transporter ferroportin — a process that is facilitated by the ferroxidase activity of the ceruloplasmin homologue hephaestin. The expression of each of the genes involved in these steps is subject to

regulation. Changes in the expression of each of the identified molecules that participate in iron absorption have been examined in various conditions. The best characterized of these conditions is anemia caused by dietary iron deficiency, in which the up-regulation of duodenal DMT1, Dcytb, and ferroportin messenger RNA and protein is observed.

Iron released into the circulation binds to transferrin and is transported to sites of use and storage. Production of hemoglobin by the erythron accounts for most iron use. High-level expression of transferrin receptor 1 in erythroid precursors ensures the uptake of iron into this compartment. Hemo-

globin iron has substantial turnover, as senescent erythrocytes undergo phagocytosis by reticuloendothelial macrophages. Iron export from macrophages is accomplished primarily by ferroportin, the same iron-export protein expressed in the duodenal enterocyte.

Hepatocytes serve as a storage reservoir for iron, taking up dietary iron from portal blood and, at times of increased demand, releasing iron into the circulation by way of ferroportin. The ferroportin-mediated release of iron from enterocytes, macrophages, and hepatocytes is recognized as an important determinant of iron homeostasis. The discovery of hepcidin revealed the important role of the hepatocyte in sensing the body iron status and modulating the ferroportin-mediated release of cellular iron.

Hepcidin is a 25-amino-acid peptide that was first identified in urine and plasma during a search for novel antimicrobial peptides.[4] However, its role in influencing the systemic iron status has been discovered to be paramount, and hepcidin is now considered to be the principal hormone involved in iron regulation.

Each of the previously mentioned factors regulating intestinal iron absorption (iron stores, erythropoietic activity, hemoglobin, oxygen content, and inflammation) also regulates the expression of hepcidin by the liver. When each of these factors undergoes a change, intestinal iron absorption varies inversely with liver hepcidin expression. Hepcidin decreases the functional activity of ferroportin by directly binding to it and causing it to be internalized from the cell surface and degraded.[5] In the enterocyte, this action would be expected to decrease basolateral iron transfer and thus dietary iron absorption. In the reticuloendothelial macrophage and the hepatocyte, hepcidin would lead to a decrease in iron export and thus an increase in stored iron.

Abnormalities in hepcidin regulation have now been implicated in two important clinical conditions: hereditary hemochromatosis and the anemia of inflammation. The abnormalities of iron homeostasis seen in hereditary hemochromatosis are the converse of those seen in the anemia of inflammation. Hepcidin expression is inappropriately low in patients with the former condition, whereas it is increased in patients with inflammatory conditions. In hereditary hemochromatosis, there is increased dietary iron absorption, relative sparing of iron in reticuloendothelial macrophages, and increased iron saturation of circulating transferrin. Hepatocytes become iron-loaded in this setting, presumably because the uptake of iron from the circulation exceeds their ferroportin-mediated iron export. Conversely, in the anemia of inflammation, iron retention by duodenal enterocytes and reticuloendothelial macrophages leads to markedly low transferrin saturation, iron-restricted erythropoiesis, and mild-to-moderate anemia. Thus, hepcidin offers a unifying explanation for the abnormalities in iron metabolism observed in these two common clinical conditions.

Most patients with hereditary hemochromatosis are homozygous for the C282Y mutation in the *HFE* gene. In this issue of the *Journal*, Adams et al. (pages 1769–1778) report the results of a large population screening study examining the prevalence and consequences of the C282Y mutation in various racial and ethnic groups. The authors found that although most persons who are homozygous for this mutation have elevations of the mean ferritin level and transferrin saturation, individual variability is great. Moreover, the differences observed among racial and ethnic groups in these iron-related variables could not be accounted for by differences in the *HFE* genotype. These data indicate that although the *HFE* mutation is the most important heritable cause of iron overload, basal iron status is significantly influenced by other genetic factors, environmental factors, or both. The contribution of genetic factors is probably substantial, as suggested by data from strains of inbred mice.

Genes other than *HFE* have been identified that, when mutated, lead to decreased hepcidin expression and clinical hereditary hemochromatosis. One of these genes (*TFR2*) encodes transferrin receptor 2, a homologue of the classic transferrin receptor that is highly expressed by hepatocytes. It has been postulated that transferrin receptor 2 may act as a "sensor" of circulating iron and thereby influence hepcidin expression. Another such gene is hemojuvelin (*HJV*), which is mutated in most persons with juvenile hereditary hemochromatosis. These observations suggest that *HFE*, *TFR2*, and *HJV* participate in a pathway that regulates hepcidin expression. Polymorphisms in these genes might contribute to the observed variation in basal iron status.

Although much has been learned regarding the regulation of iron homeostasis, many important questions remain. The molecular mechanisms by which *HFE*, *TFR2*, and *HJV* influence hepcidin expression are unknown. *HFE* expression in cell types

other than hepatocytes (e.g., reticuloendothelial cells or duodenal crypt cells) may also influence iron homeostasis. Moreover, additional gene products involved in iron metabolism — for instance, the dietary heme transporter and proteins that participate in intracellular iron trafficking — have yet to be identified. There may be therapeutic potential for hepcidin antagonists in the treatment of the anemia of inflammation, or for exogenous hepcidin in the treatment of hemochromatosis. Investigations focused on these unanswered questions will continue to expand our understanding of how iron ab-

sorption and distribution are regulated in health and dysregulated in certain diseases.

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A Unifying Mutation in Chronic Myeloproliferative Disorders

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In 1892, Louis Vaquez of Paris described a patient with cyanotic polycythemia; the autopsy disclosed massive enlargement of the spleen and liver. In 1903, William Osler, then at Johns Hopkins Hospital, reported on four patients with polycythemia, two of whom had splenomegaly. He gave credit to Vaquez for the earlier description, and the disorder was later named Osler–Vaquez disease, though today it is usually referred to as polycythemia vera.

In 1951, William Dameshek drew attention to the relationships among polycythemia vera, idiopathic myelofibrosis, and essential thrombocythemia and proposed that these diseases, as well as chronic myeloid leukemia and erythroleukemia, should be grouped together in the general category of myeloproliferative syndromes. This proposal may have been regarded as suspect at the time, but this year it seems to have been fully vindicated by four research groups that independently discovered that most patients with polycythemia vera and some with myelofibrosis and essential thrombocythemia have an identical acquired point mutation in the Janus kinase 2 (*JAK2*) gene.

The four members of the Janus kinase (JAK) family, Janus kinases 1, 2, and 3 and tyrosine kinase 2 (JAK1, JAK2, JAK3, and TYK2), have slight-

ly different functions.[1] Each has a kinase domain (JAK homology 1, or JH1) and a catalytically inactive pseudokinase domain with an important regulatory function (JAK homology 2, or JH2). To some, the presence of these two similar domains in the protein, one active and the other inactive, was reminiscent of the Roman god Janus, who looked simultaneously in two directions — hence the name.

The JAK proteins function as intermediates between membrane receptors and signaling molecules. When particular cytokines or growth factors bind to their receptors on the cell surface, JAK proteins, which are kinases associated with the cytoplasmic regions of these receptors, become phosphorylated and thereby activated. This activation creates docking sites for downstream molecules, notably those of the STAT (signal transducer and activator of transcription) family (see diagram, Panel A). Activated STAT molecules enter the nucleus, where they act as transcription factors. JAK2 seems to be activated particularly when receptors bind to hematopoietic growth factors. Mutations in the drosophila homologue of the human *JAK2* gene are known to cause a leukemia-like phenotype in affected flies, and rare cases of leukemia in humans are associated with *TEL–JAK2* fusion genes.

In this issue of the *Journal*, Kralovics and colleagues in Basel, Switzerland, and Pavia, Italy (pages 1779–1790), report that 83 of 128 patients with polycythemia vera (65 percent) had a guanine-

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