During the past half century, excessive/misplaced iron has been observed to be a risk factor for an increasing number and diversity of disease conditions. An extensive list of conditions and of the types of iron association were published in early 2008. Within the subsequent year, four additional disorders have been recognized to be enhanced by iron: aging muscle atrophy, viral replication, rosacea and pulmonary alveolar proteinosis. This paper adds new data and emphasis on these disorders as entities associated with increased iron load and toxicity.

A review written early in 2008 contained an extensive list of diseases for which excessive and/or misplaced iron has been reported to be a causative or associated risk factor. The metal is toxic by catalyzing generation of hydroxyl radicals that intensify oxidative stress as well as by serving as a growth-essential nutrient for invading microbial and neoplastic cells.

In the subsequent twelve months following submission of the manuscript, four additional conditions in which iron is toxic have been described: (a) intensification of aging muscle atrophy, (b) increased replication of human immunodeficiency virus (HIV) and hepatitis C virus (HCV), (c) enhancement of rosacea, and (d) augmentation of pulmonary alveolar proteinosis (PAP). In this paper, the previously published tables of iron-related conditions and of the types of iron association are expanded to include these four conditions.

In the report on muscle atrophy, non-heme iron levels in gastrocnemius muscle in male rats increased by 233% between six and thirty months of age. Abundance of mRNA transferrin receptor-1 decreased by 80%. In related research in the same laboratory, non-heme iron and RNA oxidation increased significantly with age in quadriceps-derived subsarcolemma mitochondria. In a third related study, in rats between 29 and 37 months of age, non-heme iron in gastrocnemius muscle increased by 200% with an accompanying significant increase in oxidized RNA. These changes were associated with evidence of sarcopenia; that is, decreased muscle mass and grip.

Although iron is not a component of viruses, infected host cells apparently need the metal to synthesize viral particles. During the past several decades, it has become manifest that one of the dangers of excessive iron is its ability to favor animal viral infections. The importance of iron in HIV infection has received particular attention. The multi-faceted molecular sites of action of iron in synthesis of HIV, as well as of HCV, are now being compiled. Of special interest are indications that viruses can manipulate iron homeostasis so as to ensure their replication in host cells.

Rosacea is a common chronic light-sensitive inflammatory skin disease. In this inquiry, peroxide and antioxidant potential of serum as well as of skin cell ferritin were assayed. Serum peroxide levels were higher and total anti-oxidant potential was lower in patients than in healthy controls (p < 0.05). The number of ferritin positive cells was higher (p < 0.001) in patient samples especially in those with severe disease. Ultraviolet irradiation of skin plus skin cell iron accelerated development of photo-sensitization, photoaging and skin cancer. It will be of interest to directly measure iron deposits in rosacea cells.

In the investigation on PAP, bronchoalveolar lavage samples of 20 patients were compared with those of 20 healthy volunteers. Concentrations of iron, transferrin, transferrin receptor, lactoferrin and ferritin were significantly elevated in PAP relative to healthy persons. In contrast, quantities of ascorbate, glutathione and urate were significantly depressed in PAP patients, indicative of anti-oxidant depletion. The results suggest an iron-catalyzed oxidative stress in the maintenance of PAP.

Similar alterations in pulmonary iron homeostasis have been observed in several other chronic lung diseases.

The list of iron-associated diseases, whose compilation began 25 years ago, continues to grow (Tables 1 and 2). Recognition of the toxicity of iron is stimulating research efforts to develop iron chelator drugs that might be able to remove the metal from specific disease sites.
Iron toxicity

Table 1  Conditions for which excessive/misplaced iron can be a risk factor

| Aging                      | Infectious                              | Ophthalmic               |
|----------------------------|-----------------------------------------|--------------------------|
| muscle atrophy             | bacterial, fungal & protozoan infections| macular degeneration     |
| Cardiovascular             | viral infections: HIV, HCV              |                          |
| atherosclerosis            |                                         |                          |
| cardiomyopathy             |                                         |                          |
| hypertension               |                                         |                          |
| ischemic stroke            |                                         |                          |
| venous leg ulcer           |                                         |                          |
| Dermal                     |                                         |                          |
| porphyria                  |                                         |                          |
| cutanea tarda              |                                         |                          |
| roacea                     |                                         |                          |
| Endocrine                  |                                         |                          |
| diabetes                   |                                         |                          |
| endometriosis              |                                         |                          |
| growth deficiency          |                                         |                          |
| hypogonadism               |                                         |                          |
| hypothyroidism             |                                         |                          |
| Hepatic                    |                                         |                          |
| cirrhosis                  |                                         |                          |
| steatohepatitis            |                                         |                          |
| viral hepatitis            |                                         |                          |

Modified from Table 3 (Weinberg et al.)

Table 2  Association of iron with morbidity

• Iron, by itself, has been observed to initiate the disease
  cardiomyopathy
  growth deficiency
  hemophilic synovitis
  hypogonadism
  lung cancer
  osteoarthritis
  osteoporosis
  pneumoconiosis

• Iron can be a cofactor in promoting the disease
  Alzheimer
  atherosclerosis
  bacterial infections
  diabetes
  endometriosis
  esophageal adenocarcinoma
  fungal & protozoan infections
  gout
  hepatojenesis
  multiple sclerosis
  osteoarthritis
  oto- & renal toxicity
  ozone lung injury
  pulmonary alveolar proteinosis
  viral infections

• Iron deposits are observed in disease-associated tissue sites
  basal ganglia in PKAN
  hepatocytes in cirrhosis, steatohepatitis & viral hepatitis
  mitochondria in Friedreich ataxia
  pulmonary secretions in cystic fibrosis
  retina in macular degeneration
  skin cells in rosacea
  skeletal muscle in aging
  substantia nigra in Parkinson
  thyroid in hypothyroidism

• Body iron loading is associated with above normal incidence of morbidity
  ALS
  breast cancer
  colorectal cancer
  depression
  Down syndrome
  epilepsy
  hypertension
  ischemic stroke
  leukemia
  pre-eclampsia
  pneumoconiosis
  prion disease
  sudden infant death syndrome

• Maternal antibodies can impair fetal iron metabolism
  fetal or neonatal death in neonatal hemochromatosis

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