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Review Article

Iron Withholding: A Defense Against Disease

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Abstract. Excessive and misplaced iron promotes an array of neurodegenerative and endocrine diseases as well as cardiomyopathy, arthropathy, neoplasia and infection. Vertebrates maintain an iron withholding defense system designed to prevent accumulation of redox-active (free) iron in sensitive sites and to sequester the metal in innocuous packages. Numerous genetic, behavioral and environmental factors counteract the defense system. Our increasing awareness of the pathologic roles of iron, as well as of the methods for prevention of iron loading coupled with intensified research and development of tissue specific iron chelator drugs, can be expected to yield marked improvements in human health.

Keywords: Alzheimer's disease, bacteria, cardiovascular disease, cerebrovascular disease, dementia, infectious disease, iron, iron withholding defense, neoplastic disease, neurodegenerative disorders

IRON WITHHOLDING

"The host plays an active part in the depletion of utilizable iron." [66]

In order to safely transport and employ iron, cells must prevent over accumulation of the metal in the redox-active (free) state. The latter is toxic in several ways. The attributes of iron that provide diversified metabolic utility likewise render the metal hazardous for iron-dependent cells [74]. Iron catalyzes generation of hydroxyl radicals which intensify oxidative stress. Consequences include enhancement of radiosensitivity, mutation, lipid peroxidation, polysaccharide depolymerization, enzyme inactivation, degenerative aging and cell death. The metal also is hazardous to hosts by serving as a growth-essential nutrient for invading microbial and neoplastic cells [127].

With the exception of a few bacterial species that use manganese, cells of all other forms of life are iron dependent. Thus vertebrates, invertebrates, plants and nearly all prokaryotes possess systems that attempt to control iron quantity and to withhold excess amounts from sensitive intracellular organelles. An overview of the iron withholding defense system is contained in Table 1 [93,137].

Especially important in lowering redox-active iron levels during the inflammatory defense process are such acute phase reactants as hepcidin, ferritin and lactoferrin. Very early in the process, activated macrophages secrete IL-6 which induces hepatocytes to form hepcidin. This 25 amino acid cysteine-rich hormone binds to ferroportin; the complex then is inactivated in lysosomes [97]. Thus the normal ferroportin-induced iron recycling by macrophages is dampened and plasma iron level is markedly reduced.

To safely contain the intra-macrophage iron surge, synthesis of heavy chain ferritin promptly is activated by TNFα in an NF-kβ-dependent manner [96]. The ferroxidase of H ferritin converts Fe(II) to Fe(III) as iron is being internalized and sequestered in the ferritin mineral core.

Migration of polymorphonuclear neutrophils to the inflammatory site, followed by their degranulation, releases lactoferrin. The pH value at the site tends to be lowered by catabolic metabolism of the host defense

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Table 1
Iron withholding defense system

Constitutive components
Siderophilins
Transferrin in plasma, lymph, cerebrospinal fluid
Lactoferrin in secretions of lachrymal & mammary glands and of respiratory, gastrointestinal & genital tracts
Ferritin within host cells
Processes induced at time of invasion or trauma
I. *Prompt reduction of 80% in dietary iron absorption and 70% reduction in plasma iron*
Increased hepatic synthesis of hepcidin (inactivator of ferroportin) to suppress duodenal iron absorption & release of recycled macrophage iron into plasma
Macrophage enhancement of DMT-1 expression and inhibition of ferroportin synthesis to withhold iron from invaders
Increased synthesis of ferritin to safely sequester withheld iron
II. *Removal of iron from sites of invasion*
Release of neutrophils from bone marrow into circulation and then into diseased sites
Release of apolactoferrin from neutrophil granules followed by binding of iron in diseased sites
Macrophage scavenging of ferrated lactoferrin in diseased sites
Hepatic release of haptoglobin and hemopexin (to bind extracellular hemoglobin and hemin, respectively)
III. *Suppression of microbial iron metabolism*
Macrophage synthesis & secretion of siderocalin which captures microbial siderophores
Macrophage synthesis of nitric oxide (from 1-arginine) which depresses TfR expression and disrupts invader iron metabolism
Suppression of intra-macrophage microbial cell growth via enhanced synthesis of Nrampl by the host cells
IV. *Induction in B lymphocytes of synthesis of immunoglobulins to iron-repressible cell surface proteins* that bind either heme, ferrated siderophilins or ferrated siderophores

Table 2
Some conditions that compromise the iron withholding defense system

Genetic disorders
Aceruloplasminemia, African siderosis, hemochromatosis, transfusion dependent: myelodysplasia, sicklemia, thalassemia
Behavioral factors
– *Ingestion* of excessive amounts of: heme (red meat), iron supplements, ascorbic acid, ethanol, food that has been adulterated with iron
– *Inhalation* of iron-containing items: asbestos, coal, ferriferous ores & metals, tobacco smoke urban & subway air particulates
– *Injection* of excessive amounts: iron saccharates, whole blood, erythrocytes
Pathological conditions
Release of body iron into plasma: efflux of erythrocyte iron in hemolytic conditions
efflux of hepatocyte iron in hepatitis, loss of spleen
myelo-ablative conditioning prior to cell/tissue transplant

cells as well as by any invading microbial or neoplastic cells. Fortunately, among the known siderophilins, lactoferrin uniquely scavenges iron at pH values as low as 3.5 [140].

In the healthy state, there should never be an over-accumulation of free iron. Unfortunately, although humans have an intricate mechanism for controlling intestinal absorption of iron, they lack a mechanism (other than bleeding) for elimination of grossly excessive quantities. The manifold ways in which acquired iron exceeds physiologically appropriate needs are summarized in Table 2. For the past sixty years, some merchandisers of processed foods have claimed that "iron-fortified" foods will make us healthier and stronger. Unhappily, this is true only for the small minority of persons who truly are iron deficient.

In developed countries, accumulation of excess iron in males can begin in early adulthood and then increase almost linearly with age. Females delay over-accumulation by menstruation and/or pregnancy. Post-menopausal women can attain parity with men in iron burden within a few decades. As humans acquire the perilous metal, they are forced to contain it (in ferritin/hemosiderin) within cells in a great variety of tissues. These include, but are not limited to, brain, heart, liver, pancreas, pituitary, joints, bone, lung, spleen and skin.

Organ distribution of contained iron differs widely among individuals. Moreover, the amount of tissue

Table 3
Diseases for which excessive/misplaced iron can be a risk factor*

Cardiovascular	*Obstetric*
atherosclerosis	neonatal hemochromatosis
cardiomyopathy	pre-eclampsia
hypertension	*Oncologic*
ischemic stroke	breast cancer
venous leg ulcer	colorectal cancer
Dermatologic	hepatic carcinoma
porphyria cutanea tarda	Kaposi sarcoma
Endocrine	leukemia
diabetes	lung cancer
endometriosis	*Ophthalmic*
growth deficiency	macular degeneration
hypogonadism	*Orthopedic*
hypothyroidism	gout
Hepatic	hemophilic synovitis
cirrhosis	osteoarthritis
steatohepatitis	osteoporosis
viral hepatitis	*Otologic*
Infectious	aminoglycoside toxicity
bacterial	*Pediatric*
fungal & protozoan	Down syndrome
Neurologic and neurodegenerative	epilepsy
Alzheimer's disease	sudden infant death syndrome
Huntington' disease	*Pulmonary*
multiple sclerosis	cystic fibrosis
Parkinson's disease	ozone lung injury
pantothenate kinase	pneumoconiosis
prion disease	*Renal*
amyotrophic lateral sclerosis	aminoglycoside & vancomycin toxicity
depression	
Friedreich's ataxia	
cerebrovascular disease	

*Modified from Table 28 [139].

damage varies not only with iron quantity but also with the specific tissue. For instance, iron kills anterior pituitary cells at 1.2 μM whereas hepatic cells resist destruction at levels 10-100 times greater [33].

During the past several decades, a considerable profusion of diseases have been recognized to be associated with iron mismanagement (Table 3). Provisonally, the deleterious action of iron can be assigned to one of five categories (Table 4). As further clinical and laboratory research becomes available, some of the assignments will require adjustment.

Following are brief summaries of selected items of current interest on toxic iron in five groups of diseases: neurologic, cardio- and cerebro-vascular, endocrine, oncologic and infectious. The review concludes with a section on prophylactic and therapeutic measures to aid iron withholding.

IRON ACCUMULATION AND ALZHEIMER'S DISEASE

"*The underlying pathogenic event in oxidative stress is cellular iron mismanagement.*" [122]

Rapidly accumulating data show that, similarly to inflammation, an involvement of iron and iron-mediated oxidative stress is a common denominator of various neurodegenerative and chronic neuropsychiatric disorders, including Alzheimer's disease (AD) which is the most frequent cause of dementia. Iron is important for brain oxygen transport, electron transfer, neurotransmitter synthesis, and myelin production [120]. Iron homeostasis in the brain is not only important for maintaining normal brain function but also for the prevention of diseases. Redox active brain iron accumulation in aging [72] and in various chronic neurodegenerative and neuropsychiatric disorders [8,64, 79,84,116,151] is well documented. In addition to AD [16,65,78,112,151], increased iron was reported to occur in Down syndrome [40], Parkinson's disease (PD) [7,8,49,64,122], diffuse Lewy body disease (DLBD), amyotrophic lateral sclerosis (ALS) [126], multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal ganglionic degenera-

Table 4
Examples of action of iron in specific diseases*

I.	*Iron, by itself can initiate the disease* cardiomyopathy [91], growth deficiency [107], hypogonadism [9], hypothyroidism [34], hemophilic synovitis [58], lung cancer [132], osteoporosis [138], pneumoconiosis [149]
II.	*Iron can be a cofactor in promoting the disease* Alzheimer's disease [16,78,151], atherosclerosis [62], bacterial infections [129], diabetes [32], endometriosis [26], fungal & protozoan infections [130], gout [50], multiple sclerosis [59], osteoarthritis [110], oto-toxicity [45], ozone lung injury [51], renal toxicity [2,86]
III.	*Iron deposits are observed in disease-associated tissue sites* basal ganglia in pantothenate kinase neurodegeneration [55], brain in prion disease [4], hepatocytes in cirrhosis [90], hepatocytes in steato- and viral- hepatitis [30,39], macula in macular degeneration [57], microglia in Huntington's disease [113], mitochondria in Friedreich's ataxia [104], pulmonary secretions in cystic fibrosis [102], soft tissue in Kaposi's sarcoma [114], substantia nigra in Parkinson's disease [122]
IV.	*Body iron loading is associated with above-normal incidence of disease* amyotrophic lateral sclerosis [126] breast cancer [61], colorectal cancer [89,105], hepatic carcinoma [85] depression [41] Down syndrome [40] epilepsy [60], hypertension [99] inflammatory bowel disease [71,92] ischemic stroke [37], leukemia [31], pre-eclampsia [101], venous leg ulcer [148], porphyria cutanea tarda [13], sudden infant death syndrome [134]
V.	*Maternal antibodies can impair fetal iron metabolism* fetal or neonatal death in neonatal hemochromatosis [143]

*Modified from Table 2 [139].

tion (CBD), ALS/parkinsonism dementia complex of Guam (ALS/PDCG), Huntington's disease (HD) [64, 113], prion diseases [4,14], multiple sclerosis (MS) [59, 116], mood disorders [41], epilepsy [60], aceruloplasminemia, hereditary ferritinopathies [143], panthotenate kinase-associated neurodegeneration type 2 (PKAN) [55], Friedreich ataxia [104], cardiovascular and cerebrovascular diseases [37,62,99] and macular degeneration [57]. An excess of iron generates free radicals and damages cells [68,116], accordingly it is apparent that oxidative stress is intimately involved in the pathogenesis of these disorders. Increased iron in AD in association with senile plaques was first described by Goodman in 1953 [54]. His observation was repeatedly reinforced by others and validated by the use of various specific and sensitive techniques [10,20,21, 23]. Oxidative stress is one of the earliest events in AD and seems to be involved in the onset, progression and pathogenesis of the disease [16,151]. Deregulation in brain iron metabolism is multifactorial and comprises nongenetic and genetic factors. It might occur at multiple levels, including iron uptake and release, storage, intracellular metabolism and regulation [63,151] Iron levels are regulated within cells by iron regulatory proteins (IRPs). IRPs by binding to iron responsive elements (IREs) of several genes encode key proteins such as the transferrin receptor (TfR) and ferritin. Transferrin is involved in the physiological transport and utilization of iron. Transferrin concentration is decreased in AD and in other neurodegenerative disorders. Concurrently, the hypoxia-inducible factor (HIF) has also been shown in previous studies to regulate intracellular iron by binding to HIF-responsive elements (HREs) that are located within the genes of iron-related proteins such as TfR and heme oxygenase-1 (HO-1) [68]. Disruption in brain iron homeostasis through alterations of iron regulatory proteins can increase the vulnerability of cells to oxidative stress [23,98]. Changes in superoxide levels due to alteration of superoxide dismutase (SOD) activity also affect iron metabolism in glial and neuronal cells [24,25]. Lactoferrin (LF) which is secreted by ectodermal tissues is similar in structure to transferrin and plays a role in natural defense mechanisms in mammals. It is upregulated in neurodegenerative disorders. Lactoferrin exerts an anti-inflammatory function via its inhibitory effect on hydroxyl radical formation and, by its antioxydative properties prevents DNA damage [108]. The combination of the C2 variant of the transferrin gene (TF-C2) and the C2 82Y allele of the haemochromatosis (HFE C282Y) gene, or the combination of HFE C282Y and HFE H63D are risk factors for developing AD. Carriers of such combination were at 5 times greater risk for AD. Additional apolipoprotein E epsilon4 (APOE4) allele further increases the risk of AD [22,70,87,106]. Oxidative damage, produced by mutant Cu/Zn superoxide dismutase (SOD1), and an increased frequency of H63D mutation was also reported to occur in ALS [69,147]. Brain ferritin iron may also influence age- and gender-related risk of neurodegeneration [3].

Elevated levels of combinations of cholesterol and iron have been observed to promote AD in animals [52] and to be a risk factor in humans [76]. In a set of 6,558 US adults, followed from 1974 to 1992, an elevated risk of AD occurred if both cholesterol and iron were above normal (Table 5). There is increasing evidence to support a role for both the amyloid-β protein precursor (AβPP) and its proteolytic fragment, amyloid-β

Table 5
Association of cholesterol and iron with development of Alzheimer's disease

Cholesterol mg/dL*	Tf iron saturation%*	Alzheimer's disease %**
< 261	< 34.9	1.00
> 261	< 34.9	1.60
< 261	> 34.9	1.35
> 261	> 34.9	3.00

*Values obtained at baseline for 75^{th} percentile.
**Development of Alzheimer's disease within 18 years after baseline.
Data from figure 1 [76].

peptide (Aβ) in metal ion homeostasis. Iron participates in the aggregation of Aβ and may play a role in neurofibrillary tangle formation, tau phosphorylation and in secretase cleavage of AβPP [1,35,38,103]. It was suggested that transferrin limits fibrillar formation and cytotoxicity of Aβ [53]. Inflammatory processes play a key role in the pathogenesis of AD and several other neurodegenerative and neuropsychiatric disorders including cerebrovascular disorders. Compelling evidences exist that iron is involved in inflammatory reactions, therefore, it is not surprising that both inflammation and iron accumulation are common denominators of these various chronic disorders [150]. *In vivo* magnetic resonance imaging of acute brain inflammation using microparticles of iron oxide was recently reported [80].

Therapeutic strategies derived from application of iron chelators and new drugs diminishing iron accumulation and oxidative stress is promising and warrant further investigational effort in AD and other neurodegenerative and neuropsychiatric disorders [8,103].

CARDIO- AND CEREBROVASCULAR DISEASES

"It is now quite apparent that excessive iron in either arteries or heart muscle cells is detrimental to a properly functioning cardiovascular system." [136]

Cardiomyocytes are highly susceptible to iron loading. In thalassemia patients who receive monthly blood transfusions but inadequate iron chelation, cardiomyopathy is the leading cause of early death [146]. Iron deposits are associated with cardiac hypertrophy and dilation as well as with degeneration of myocardial fibers. In iron loaded gerbils, the metal is contained in high amount in left ventricular cells and in the epicardium [91].

A link between iron loading and atherosclerosis has been observed often in animal models [117]. For instance, in rabbits fed a 1% cholesterol diet, a seven-fold increase in iron concentration had occurred in arterial tissue by the onset of lesion formation. Iron reduction by bleeding or chelation suppressed lesion development [100].

Human arteries, likewise, develop atherosclerosis in association with iron. Arterial lesions have been reported to contain 3–17 times more iron than healthy controls [115]. Iron loaded macrophages support growth of such intracellular bacteria as Chlamydia [118] and Coxiella [135] that have been linked with the chronic inflammatory process of atherosclerosis.

Additionally, oxidative stress of lipids induced by iron may play a role in artery damage. In a sample of 13,932 US adults, elevated C-reactive protein was associated with increased ferritin plus high LDL or low HDL [77]. In a study of 38 atherosclerotic patients, the level of low molecular mass iron in plaques removed in endoarterectomy was directly correlated with body iron loading and the severity of the disease [67].

In 9,178 persons followed for 24 years, 504 developed ischemic cerebrovascular disease of whom 393 had ischemic stroke [37]. In those who were H63D homozygotes, the incidence of stroke was increased between two and three fold. No increase occurred in persons with the C282Y mutation. Indeed, hemochromatotic persons who are homozygous for the C282Y mutation appear also to be protected from developing atherosclerosis. Because this mutation results in lack of hepcidin, their macrophages are very low in iron [141].

Ferritin levels of 134 consecutive acute stroke patients treated with i.v. tissue plasminogen were tested for ferritin at the time of treatment. Patients whose ferritin was greater than 79 ng/ml had increased risk of poor clinical outcome, hemorrhagic transformation and brain edema [83]. In a study of 38 men with essential hypertension and of 40 healthy controls, 21% of the former and none of the latter were hyperferritinemic [99]. Elevated iron was associated also with insulin resistance.

ENDOCRINE DISEASES

"*Despite its frequency and effect on the endocrine system, haemochromatosis has attracted surprisingly little attention in endocrinology and fertility textbooks.*" [123]

A majority of humans who develop iron loading, irrespective of the cause, proceed to have one or more impaired endocrine glands. Especially sensitive to iron toxicity are cells of the anterior pituitary. When iron loading occurs early in life, as in thalassemia, a deficiency of growth hormone results in short stature. When excessive iron occurs in older individuals, suppression of gonadotrophic hormones causes impotence in males and amenorrhea, loss of fertility and early menopause in females [9,29].

Furthermore, the metal destroys pancreatic insulin-forming beta cells. Thus glucose intolerance often develops. Noted especially is a marked increase in patients with type 2 diabetes [42,119]. At least one-third of patients with type 2 diabetes have elevated serum ferritin [145]. Reduction in insulin secretion often is accompanied by increased insulin resistance. In hereditary hemochromatosis, up to 60% of untreated patients may develop type 2 diabetes. Lowering of iron load either by phlebotomy or chelation can result in a significant reduction in Hgb A1C and improvement or reversal of the diabetic condition [145].

Late onset of type 1 diabetes likewise is associated with iron loading. In a group of 716 adults who had onset after 30 yrs, those homozygous for the C282Y gene mutation were 4.6 times more likely to have the disease than were normal persons [36].

In a group of thalassemic teen-aged children, 8.5% had impaired glucose tolerance and 20% diabetes [17]. In a prospective study of 1,038 randomly selected individuals, those in the highest quartile of body iron were 2.4 times more likely to become diabetic within the next four years [145].

As in the pituitary and pancreas, iron loading occurs also in the thyroid gland. Accumulation of iron up to 25 times normal has been observed in the thyroid in untreated hemochromatotic patients [34]. Damage to the parathyroid gland also has been noted [95].

ONCOLOGIC DISEASES

"*One might worry about the iron injectable compounds which are being tested and used. One could almost guess that someone is going to find iron dextran carcinogenic,*" [46]

Iron is carcinogenic as a mutagen, as an inhibitor of the tumorcidal action of macrophages, and as an essential nutrient for growth of cancer cells [128]. In both animals and humans, primary neoplasms develop at body sites of excessive iron deposits. Inhaled iron is associated with respiratory tract cancers [132], ingested iron with colorectal malignancies [15,89], skin-exposed iron with sarcomas [114], and whole body iron loading with hepatomas [128].

Body iron that is increased because of gene mutations involved in iron metabolism has been linked to a variety of neoplasms. In patients with multiple myeloma ($n = 92$), breast cancer ($n = 165$) and colorectal cancer ($n = 173$), the odds ratio for carriers of the C282Y mutation as compared with the wild type was 2.0. The odds ratio was increased to 7.17 in C282Y carriers who also were homozygous for a transferrin receptor mutation at serine 142 [5]. Other studies have reported associations of hemochromatosis mutations with breast cancer [56, 61] and with colorectal cancer [105,111]. In a set of 27 patients with acute lymphoblastic leukemia (ALL), 44% carried the H63D mutation whereas in normal controls, the frequency was 25% ($P = 0.02$) [124]. In that study, no difference was observed between controls and patients with acute myeloid or acute premyelocytic leukemia.

Tissue iron that is increased because of behavioral factors similarly has been linked to a variety of neoplasms. Numerous studies have reported that workers in ferriferous industries have an elevated risk of respiratory tract cancers [132]. Likewise, persons who inhale varieties of asbestos that are comprised of iron (but not magnesium) silicates are at high risk for development of lung cancer and of mesothelioma [132]. Moreover, the risk of lung cancer in persons who inhale iron-contaminated tobacco smoke is well documented [132].

Dietary behavior also is important in accumulation of excessive body iron. Of special concern is the readily absorbable heme iron content of red meat. In a study of 90,659 premenopausal women, 1,021 developed invasive breast carcinoma [18]. Greater red meat intake strongly was related to elevated risk of estrogen and progesterone receptor-positive breast cancer but not to cancers that were estrogen and progesterone negative.

World wide areas of high incidence of Kaposi sarcoma are characterized by a substrate of fertile reddish-brown volcanic clay soil [114]. After aluminum, the

Table 6
Microbial genera with strains whose growth in body fluids, cells, or intact vertebrate hosts is stimulated by misplaced or excess iron

Fungi: Aspergillus, Candida, Cryptococcus, Histoplasma, Paracoccidioides, Pneumocystis, Pythium, Rhizopus, Trichosporon
Protozoa: Entamoeba, Leishmania, Naegleria, Plasmodium, Toxoplasma, Trichomonas, Tritrichomonas, Trypanosoma
Gram positive & acid fast bacteria: Bacillus, Clostridium, Corynebacterium, Erysipelothrix, Listeria, Mycobacterium, Staphylococcus
Gram negative bacteria: Actinobacter, Aeromonas, Alcaligenes, Campylobacter, Escherichia, Helicobacter, Klebsiella, Legionella, Moraxella, Neisseria, Pasteurella, Proteus, Pseudomonas, Salmonella, Shigella, Vibrio, Yersinia

*Modified from Table 1 [131].

most abundant mineral in the clay is iron. Barefoot peasants acquire ultra-fine soil particles through the skin of their soles. In Africa, persons with both the environmental skin invasion plus a genetic tendency to iron loading (African siderosis) are especially at risk.

INFECTIOUS DISEASES

"Of the myriad of competitive interactions known to occur between host and colonizing or infecting microbes, the struggle for micronutritional iron is among the most prominent." [88]

Bacterial fungal and protozoan pathogens (Table 6) have one or more strategies for securing host iron. These include (1) cell surface binding of ferrated transferrin or lactoferrin and extraction and assimilation of the metal; (2) synthesis of low molecular mass siderophores that extract the metal from transferrin with subsequent binding and uptake of the ferrated siderophore or of the metal; (3) lysis of erythrocytes, digestion of hemoglobin, and binding and assimilation of heme; and (4) assimilation of host intracellular iron derived from pools of low molecular mass iron binding compounds [94,129,131].

Successful pathogens often employ differing strategies depending on the particular biochemical environment. Flexibility especially is important for microbial strains that, at various times, live in different tissues of the host, in different hosts, or outside of hosts. For example, *Helicobacter pylori* obtains iron directly from lactoferrin when growing in the gastric lining but uses heme when it invades the gastric wall.

Some potential pathogens are sufficiently impaired in iron acquisition ability so as to be dangerous mainly in hosts with such iron loading conditions as African siderosis, β-thalassemia, or hemochromatosis [133]. However, even in iron-normal hosts, increased risk of infection can be acquired simply by over-ingestion of iron [47,109,121], over-inhalation of iron [132], or over-injection of iron [121].

The important role of iron in infection and the risk of infection following redox active iron accumulation are both well established [94,133,134]. It is noteworthy that dementia can be caused by chronic bacterial infection resulting in a slowly progressive cognitive decline which may occur decades following the primary infection. One characteristic lesion of this syphilitic paretic dementia (general paresis) caused by the spirochete Treponema pallidum is the accumulation of iron in the brain. Fast detection of the so called "paralytic iron", at the time of autopsy on macroscopic brain samples, was used as diagnostic tool for syphilitic infection [81].

PREVENTION AND THERAPY OF IRON LOADING

"... unavailability of meat or prolonged and heavy use of tea leaves, which eventually led to development of iron deficiency, may result in better survival in epidemics." [27]

In a cohort of 1401 US adults, 67–96 yrs, 70% had ferritin level $>$60 ng/ml whereas only 2.7% were iron deficient and only 1.2% had iron deficiency anemia [44]. Elevated iron was significantly associated with consumption of (1) non-heme iron supplements, (2) red meats (high in heme iron), and (3) fruit (high in ascorbic acid, an enhancer of non-heme iron absorption). In contrast, consumption of whole grains (high in phytates that inhibit iron absorption) was inversely correlated with elevated iron.

In a 12 yr study of 9,229 persons, 35-70 yrs at baseline, persons who had elevated transferrin saturation and who reported high dietary iron or high meat consumption had a three-fold increased risk of dying within the study period [75].

The phenolic iron chelating natural products in green and black teas have a strong affinity for non-heme iron and thus are especially useful in preventing absorption of the metal that has been indiscriminately added to processed foods. In the Netherlands, a set of 3454 adults, above 55 yrs, were free at baseline of cardiovascular disease [48]. They were observed for 3 yrs for possible development of calcified plaques in the ab-

dominal aorta. With 1–2 cups of green tea per day, plaque development was lowered by 50%; with 4 cups per day, by 67%.

Because of the pervasive addition of readily absorbable forms of non-heme iron to processed foods in the US, tea consumption is strongly indicated. Moreover, the quantity of added iron listed on the labels of processed foods may be erroneous. A US Food & Drug Administration assay of the actual amounts of iron adulteration of dry cereals showed, in some cases, up to 380% higher quantities than that stated on the labels [144].

To ensure excellent respiratory tract health, all sources of inhaled iron should be avoided. A very common source is tobacco smoke [132]. Indeed, was the tobacco plant to be genetically modified so that its leaves would no longer sequester remarkably high amounts of iron, the tobacco product might become quite safe to smoke. Urban air particulates, especially those in subways, are highly contaminated with iron.

Industrial workers exposed to airborne iron and especially coal and iron miners are advised to wear masks. Their on-the-job clothing must be carefully laundered to prevent their family members or laundry workers from being exposed to iron dust. The past indiscriminant use of iron varieties of asbestos has been curtailed. Persons who live near outcroppings of iron-containing deposits of tremolite asbestos are warned to avoid using the mineral as whitewash on the inner or outer walls of their homes [73].

Reduction of body iron by routine blood donation is an effective way for reducing risk of disease. Whole blood contains about 0.5 mg iron/ml. Thus donation of one pint releases 250 mg of iron. This quantity is approximately representative of 50 ng of serum ferritin [28]. Normal menstruation results in excretion of 180–360 mg iron/yr. Non-menstruating women as well as all normal men can maintain low body iron burden by donating blood 2–3 times/yr. Daily ingestion of aspirin, by causing intestinal microbleeding, lowers iron to an extent comparable to that of menstruation.

In a cohort of 181 men followed for five years, blood donations not only lowered iron but increased insulin sensitivity [43]. In a set of 1,277 persons (mean age 67 yrs), those randomized to iron reduction by graded phlebotomy during a six year period had a 36.7% reduced risk of cancer occurrence ($p = 0.023$) and a 66.6% lowered cancer mortality ($p = 0.003$) compared with controls. Reduced cancer risk was observed for most cancer types and occurred over the entire patient age range [28].

For such whole body iron loading conditions as thalassemia, sicklemia and myelodysplasia, phlebotomy cannot be utilized. Thus commercially available iron chelating drugs (deferoxamine, deferiprone, deferasirox) are employed. It would be useful, also, to have iron chelating drugs available for iron normal patients who have cancer, infection or a chronic disorder associated with iron-induced oxidative damage.

Acceptable compounds must have high specificity for iron; low specificity for such other physiologically important metals as zinc, copper and manganese; ability to deplete the iron loaded abnormal site but not iron-normal sites; abstention from redistribution of iron to such iron-sensitive sites as heart or brain; abstention of donation of iron to neoplastic or microbial cells that might be latent in the patient; efficient excretion of the iron chelate in urine or bile; and be available at reasonable cost. The chelator should be employed early in the disease before the damaging effect of oxidative stress has occurred [16].

Among compounds presently being considered for iron withdrawal in neurologic diseases, deferiprone (at one-fourth of dose employed in whole body deironing) has shown possible utility in lowering excessive mitochondrial iron in patients with Friedreich's ataxia [12]. In rodents, VK-28 has provided protection from 6-hydroxy-dopamine pathology [6]. In neuroblastoma cells, degenerative-modifying effects have been obtained with the green tea chelator (-)-epigallocatechin-3-gallate [142]. The comparative properties of low molecular mass iron chelators in clinical use and an evaluation of novel compounds under development have been recently summarized [11].

Two protein iron chelators, transferrin and lactoferrin, now are available for therapy of specific iron loading sites. Transferrin has been extracted from human serum, de-ironed and purified [125]. This product can be used in short-term conditions in which the patient's transferrin saturation is highly elevated. An example is the myelo-ablative conditioning prior to a cell/tissue transplant. The product may be useful, also, in serious cases of bacterial sepsis. Recombinant human lactoferrin is being tested/employed in a considerable diversity of pharmaceutical applications [140]. In most, but not all, the mechanism of action of lactoferrin is considered to be that of iron chelation.

CONCLUSIONS

Excessive/misplaced iron in specific tissues and cells is a prominent risk factor for development of an array

of neurodegenerative and endocrine diseases as well as for cardiomyopathy, arthropathy, neoplasia and infection. Our iron withholding defense system attempts to prevent accumulation of the metal in sensitive sites and to contain it in innocuous packages. The defense system can be compromised by genetic, behavioral and environmental factors. Growing recognition of the ubiquitous iron hazard with increasing use of methods of prevention and therapy can be expected to markedly improve human health.

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