Editorial Comment

Stored Iron and Ischemic Heart Disease
Empirical Support for a New Paradigm

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In 1981, Hopkins and Williams\textsuperscript{1} published an exhaustive list of 246 proposed coronary risk factors. It might seem that this would include every plausible coronary risk factor. However, stored iron and serum ferritin were not on the list. They were proposed as risk factors in the same year, after the Hopkins and Williams study was submitted.\textsuperscript{2} A pathophysiological role for "normal" levels of stored iron in ischemic heart disease (IHD) was first suggested as an explanation for the sex difference in disease expression and for the international variation in disease incidence.\textsuperscript{3} The idea that normal levels of stored iron promote IHD has considerable explanatory power.\textsuperscript{3,4} This hypothesis offers a possible explanation for a wide range of phenomena, including not only the sex difference and the international distribution of IHD but also the protective effects of aspirin, fish oils, and cholestyramine and the disease-promoting effect of oral contraceptives.\textsuperscript{5-9} Very few of Hopkins and Williams' 246 risk factors\textsuperscript{1} have comparable explanatory power. In particular, there has been no accepted explanation of the sex difference in IHD based on any of the risk factors on their list.

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In addition to these theoretical considerations, there has been a series of investigations beginning in the mid-1980s of the effects of deferoxamine, an iron chelator, on myocardial reperfusion injury in a number of experimental animal systems.\textsuperscript{5-9} These studies, taken together, overwhelmingly support a major role for iron in myocardial reperfusion injury. They suggest that, in effect, excess iron capable of promoting myocardial injury is present in animals with normal iron status. Other investigators have shown that decreasing levels of stored iron by manipulating iron status in vivo is associated with significant decreases in oxygen radical-induced injury in several tissues other than heart.\textsuperscript{10-14}

In this issue of Circulation, Salonen and coworkers\textsuperscript{15} present a landmark study with the first empirical evidence that serum ferritin is a strong risk factor for acute myocardial infarction. This large prospective study is a confirmation of the prediction that serum ferritin is a strong risk factor for IHD at levels previously regarded as normal.\textsuperscript{2-4} The study represents the first direct empirical evidence in support of a new IHD paradigm based on the conjecture that stored iron promotes and iron depletion protects against IHD.\textsuperscript{2-4} The paradigm may give a unifying explanation for a broad range of observations, including most prominently the sex difference in IHD risk. The study also gives new meaning to the emerging body of experimental work on the role of iron in ischemic myocardial injury.\textsuperscript{5-9}

One of the major strengths of the iron paradigm of IHD is that it suggests a common mechanism for promotion of both atherogenesis and postischemic myocardial injury. Iron depletion appears to enhance antioxidant defenses in vivo.\textsuperscript{10-14} This effect may protect against IHD by inhibiting the oxidative modification of low density lipoprotein (LDL) in vivo\textsuperscript{16} as well as by directly decreasing postischemic myocardial injury and perhaps arrhythmias.\textsuperscript{5-9} Mechanisms of myocardial injury are not addressed by the theory that IHD is a function of the plasma cholesterol concentration.

One of the original arguments in favor of serum ferritin and stored iron as risk factors for IHD\textsuperscript{2} was the apparent cardioselective toxicity of iron in massive iron overload. Orthodox thinking does not recognize a relation between the pathophysiology of IHD and the cardiomyopathy of hemochromatosis and transfusional iron overload. However, the research on deferoxamine and ischemic myocardial injury\textsuperscript{5-9} raises the possibility of an important link between the two. In the aftermath of an ischemic event, pump failure and arrhythmias occur. Pump failure and arrhythmias are also features of iron-overload cardiomyopathy. The deferoxamine experiments suggest that subjects with normal iron status have enough iron present to compromise pump function and cause rhythm disturbances after an ischemic event.\textsuperscript{5-9} In iron overload cardiomyopathy, the heart may be in a chronic postischemia-like state. At the very high levels of stored iron observed in hemochromatosis, the effect may be a full-blown iron-overload cardiomyopathy. At the much lower levels seen in men and women without the hemochromatosis gene, the effect may be limited to an increased propensity to myocardial infarction. The Finnish findings\textsuperscript{15} support this proposed link between IHD and iron cardiomyopathy.

The study by Salonen et al\textsuperscript{15} may hold the key to understanding the limited ability of primary prevention trials\textsuperscript{17} to reduce coronary mortality. None of the single- or multiple-risk factor interventions attempted to date have a significant effect on stored iron levels. The one possible exception is cholestyramine.\textsuperscript{18,19} Inhibition of iron absorption by cholestyramine\textsuperscript{18,19} could have de-
creased iron stores in the experimental group in the Lipid Research Clinics Coronary Primary Prevention Trial (LRCCPPT).\textsuperscript{20} The effects of cholesteryramine on stored iron in the experimental group cannot be determined from the published data. Serum ferritins were not reported, and hemoglobin values are not a sensitive measure of stored iron reductions unless the reductions are large enough to cause anemia. Perhaps the coronary mortality reductions in the LRCCPPT were small and of marginal statistical significance because the cholesteryramine dosages were not adequate to lower iron storage levels appreciably. Other interventions\textsuperscript{17} would not be expected to have a significant impact on stored iron. Dietary changes, even if they include substantial decreases in dietary iron, do not rapidly reduce the level of stored iron in subjects in affluent societies. In the absence of parasitic infections or other medical conditions that cause chronic occult blood loss, iron is very efficiently stored and recycled. A large store of iron would not be readily lost with risk factor interventions of the durations reported to date. Future trials with interventions that cause iron depletion\textsuperscript{21} may be successful in significantly and substantially reducing coronary mortality.

The finding that ferritin is a strong heart disease risk factor is especially relevant to the hypothesis that low iron stores protect young women from heart disease. The finding is pertinent despite the exclusion of women from the Finnish study. A study of ferritin as a risk factor in a group with both men and women would be likely, at the least, to show lower risk and lower ferritin in the women. Such a study might not be a convincing demonstration of the protective effects of low ferritin because the effects of other postulated factors associated with femaleness might be confounded with those of low ferritin.

Additional studies including women will of course be necessary to establish that serum ferritin is a risk factor for IHD in women. Studies with young menstruating women are essential to extend the Finnish study to include an adequate population of iron-depleted subjects. Very few of the Finnish men were iron depleted. If decreased iron stores protect against IHD by a mechanism involving decreased reperfusion injury and LDL modification by ferritin-derived iron, then clearly the lowest risk condition should be the absence of ferritin, i.e., complete iron depletion. The extremely low incidence of IHD in young menstruating women may be, in part, an indication of the maximal protection achievable by iron depletion. The greatest relative increment in risk associated with serum ferritin may thus be seen at the lower end of its observed range. The findings of Salonen and coworkers are particularly notable because they show serum ferritin to be a strong risk factor at levels generally much higher than those seen in menstruating women. Further research will be needed to confirm that differences in serum ferritin account not only for some of the relatively small differences in IHD risk among adult men but also for the immense difference in risk between men and menstruating women.

The study by Salonen et al\textsuperscript{12} marks the beginning of a new era of investigation into the role of iron in the pathophysiology of IHD. It should also inspire a broader debate on the definition of normal iron status. Perhaps iron depletion, defined as the absence of iron stores without anemia, should be regarded as physiologically normal iron status. What other benign “condition” eliminates a major injury-promoting substance from the body? Stored iron in the form of ferritin is not essential for life or for preventing anemia, but it can powerfully promote tissue injury.\textsuperscript{14-16} A comprehensive debate on the redefinition of normal iron status should address questions on the role of iron not only in IHD, but also in neoplasia,\textsuperscript{22} infectious disease,\textsuperscript{23} neonatal disorders,\textsuperscript{24} brain diseases,\textsuperscript{14} arthritis,\textsuperscript{12} and aging.\textsuperscript{25}

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