Progress report
Iron and the liver

The main function of the liver in iron metabolism is to serve as a storage organ, a role in which both the parenchymal and reticuloendothelial cells participate. The liver is also the main site of synthesis of the β1-globulin iron-transport protein, transferrin. Reduced transferrin levels are frequent in severe hepatocellular disease but in themselves are probably of little importance. Four instances of hereditary congenital atransferrinaemia have been described. This disorder, which appears to be due to a recessively transmitted failure of transferrin synthesis, is associated with inadequate delivery of iron to the marrow and severe hypochromic anaemia, responsive to transferrin infusions but not to iron alone. It is, however, in connexion with disorders of iron storage, and especially with iron excess, that iron and liver diseases are particularly associated. The purpose of this article is to review the iron-loading disorders that may lead to liver disease and to consider the proposition that cirrhosis itself is an iron-loading disorder.

The terminology continues to be confusing. The term ‘haemochromatosis’ tends to be used differently by clinicians and pathologists. To the pathologist it has traditionally implied severe fibrosis or cirrhosis accompanied by heavy iron deposition; pancreatic siderosis and fibrosis, and siderosis in other parenchymal organs, complete the picture. However, these criteria do not apply until late in the evolution of an iron overload state; they would exclude mildly affected cases in the early stages of iron-loading and yet include situations in which siderosis is incidentally superimposed on cirrhosis of any cause. To the clinician, who is increasingly recognizing the disease at an early stage of development, the concept of haemochromatosis is biochemical rather than anatomical, implying a progressive iron-loading process in which structural damage is an ultimate rather than a definite feature. In this particular nosological sense it refers especially to the hereditary disorder, idiopathic or primary haemochromatosis. The term ‘secondary haemochromatosis’ is used clinically to refer to iron overload arising during the course of various blood diseases; the presence of the rather characteristic pattern of fibrosis associated with iron excess is then generally intended. Siderosis refers to the presence of histochemically demonstrable tissue iron deposits; such deposits do not necessarily represent excess tissue iron concentrations and so the term should not be used as synonymous with iron overload. Furthermore, the advent of practicable techniques for measuring iron stores now enables a clinical diagnosis of iron overload to be expressed in more exact terms.

The quantitative definition of iron overload is somewhat arbitrary. Moreover, there are considerable population differences in normal iron reserve. Determinations of storage iron by means of quantitative phlebotomy in healthy northern European and American males suggest that 1500 mg is seldom exceeded, with 600-800 mg as an average value. In the same populations normal liver iron concentration seldom exceeds 0·25% dry weight, the mean varying around 0·1% dry weight. Levels in London tend...
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to be lower than in the United States but comparable to those in Sweden13,14,16,18.

Idiopathic Haemochromatosis

This is the classical iron storage disorder and was the only variety recognized in 1935 when Sheldon17 concluded that haemochromatosis was due to an inborn error of iron metabolism. Although the evidence for this is now overwhelming, the underlying biochemical defect and its mode of inheritance have yet to be determined. Few of these subjects have been exposed to dietary iron excess, and inappropriate alimentary absorption of iron must be the crucial factor leading to iron accumulation. At the time of presentation, however, many patients have an iron absorption within the normal range18,19 although in the context of iron excess the values observed may be regarded as being relatively increased. In a recent study20, untreated patients had a mean (±SD) absorption of 9.1 ± 4.8% compared with 3.6 ± 2.4% in controls. Assuming a normal dietary iron intake and normal physiological losses, these findings would account for a mean iron gain of up to 500 mg per year. This would be in keeping with the 10-20 gram iron loads generally found in patients presenting at the age of 40 to 60, iron accumulation starting when growth ceases. In women iron accumulation tends to be nullified by the losses of menstruation and pregnancy and the rare women presenting with the disease tend to be postmenopausal and nulliparous. Nevertheless, instances of the fully developed disease in menstruating women have been reported21,22, suggesting that the severity of the defect may vary, and in men the correlation between age and iron load is far from precise.

The rate of iron accumulation may also be subject to environmental factors. In this respect the role of alcohol, which is known to increase iron absorption in normal subjects23, may be relevant. Some 30-50% of patients with idiopathic haemochromatosis drink more than average quantities of alcohol24,25,26 which would be expected to accelerate the process of iron accumulation and hence the expression of the disease.

The mechanism of increased absorption in idiopathic haemochromatosis remains unresolved. Earlier work suggesting deficiency of a gastric27,28 or pancreatic29,30 factor has not been confirmed31,32 and there is little to indicate a defect in the intraluminal phase of absorption. Recent evidence supports the concept of aberrant mucosal function in haemochromatosis33 but whether this is part of a wider defect in the cellular handling of iron has yet to be elucidated.

Ignorance of the fundamental biochemical defect in haemochromatosis precludes a clear understanding of its mode of inheritance. Evidence of increased iron stores currently constitutes the best marker of the disease; however, the influence of physiological and environmental factors on storage iron have always to be taken into account and can make interpretation difficult, eg, in adolescents and premenopausal women. Commonly, several members of a sibship are affected and the disease has occurred in identical34,35 and dizygotic twins36,37,38. It has been less frequently encountered in two or more generations but with thorough screening this may prove to be less rare than formerly believed39,39,40,41. Several comprehensive family studies36,40,41 have shown that iron excess may be found in about 50% of first-degree relatives, suggesting an autosomal dominant mechanism. After
allowing for environmental factors, however, there is no doubt that the severity of the defect varies considerably; while this may be due to variable penetrance, the possibility of intermediate forms of inheritance or even the existence of several different genetic biochemical defects each predisposing to iron accumulation, cannot be excluded.

**Transfusional Iron Overload and Iron-loading Anaemias**

Massive iron overload accompanied by other features of haemochromatosis is well recognized in certain chronic refractory erythropoietic disorders and is attributable to multiple blood transfusions or to inappropriately increased gastrointestinal absorption of iron. In aplastic anaemia iron absorption is not increased and iron accumulation is entirely transfusional in origin. In refractory anaemias marked by erythroid hyperplasia increased absorption of iron contributes to the iron loading and the clinical and pathological picture of haemochromatosis can arise in subjects who have received little or no blood or iron therapy. This occurs especially in disorders associated with much ineffective erythropoiesis such as thalassaemia and the sideroblastic anaemias but has also been reported in hereditary spherocytosis. Intriguingly, in two other cases of hereditary spherocytosis haemochromatosis has developed after splenectomy.

**Oral Iron Overload**

The absolute quantity of iron absorbed increases with the dose ingested. In healthy males storage iron remains constant throughout life, reflecting a balance between iron intake, iron absorption, and physiological iron loss. Some variation in iron stores between different populations is recognized, probably reflecting differences in absorbable dietary iron intake. The iron overload of the South African Bantu can be entirely explained by the high iron content of the native beer, brewed in iron pots. Attention has recently been drawn to the high inorganic iron content of some other alcoholic beverages, wines in particular providing a convenient vehicle for the ingestion of large quantities of the metal. The occurrence of gross iron excess in alcoholic cirrhosis, long known in France, has been recognized in wine-drinking communities in Italy. Very rarely haemochromatosis has been recorded in apparently healthy hypochondriacs ingesting medicinal iron for many years.

**Iron Overload in Cirrhosis**

Some degree of hepatic iron deposition is quite frequent in cirrhosis but the amount is usually slight and the overall histological picture unlikely to be confused with haemochromatosis. Occasionally the intensity of the siderosis approaches that found in haemochromatosis and can give rise to diagnostic difficulty. The occurrence of siderosis, pigmentation, and diabetes in various gradations and combinations in cirrhosis, and of pancreatitis in alcoholics, has tended to blur the distinction between idiopathic haemochromatosis and other forms of cirrhosis, and the concept of idiopathic haemochromatosis as a separate inherited entity has been challenged. However, the alternative argument that the disease is a variant of portal
cirrhosis, with nutritional deficiency or alcoholism causing liver injury and iron excess occurring incidentally, does not fit the facts and is accepted by few.

Much of the confusion about siderosis in cirrhosis unquestionably stems from misinterpretation of the significance of stainable iron as a measure of tissue iron concentration. Until quite recently stainable iron was regarded as an unusual finding in normal liver and even minor degrees of siderosis were thought to represent iron excess. During the last decade, however, it has become apparent that slight or moderate siderosis is more common than formerly realized and not incompatible with normal storage iron levels. Submaximal (grade 3) siderosis invariably indicates a raised liver iron concentration although this may be relatively slight in degree. Absence of stainable iron corresponds to a concentration below the mean value for London controls (0.08% dry weight) and may be regarded as indicating a suboptimal iron reserve. The non-linear relationship between liver iron concentration and histochemical grading reflects the varying distribution of iron between ferritin and haemosiderin at different storage iron concentrations. At low storage levels iron is predominantly held in ferritin which is water soluble and non-stainable. As the stores enlarge an increasing proportion is deposited as insoluble, stainable haemosiderin. In the rabbit and in man ferritin iron reaches a plateau when total liver iron is moderately increased. At this point the fraction of iron stored as ferritin exceeds that in haemosiderin but with further iron loading there is a sharp increase in haemosiderin formation which continues indefinitely.

Iron overload superimposed on cirrhosis occurs mainly under two circumstances: in alcoholic cirrhosis and in patients with large portal systemic shunts. Reference has already been made to the role of heavy wine consumption as a cause of iron overload. Quite apart from the high iron content of some beverages, however, alcohol itself stimulates iron absorption. In Australia, liver iron content was higher in heavy drinkers than in a similar group with low alcohol consumption and showed a significant correlation with both the amount of alcohol and the amount of wine ingested from alcoholic beverages. Swedish alcoholics, on the other hand, tended to have lower values than controls. Heavy iron excess in patients with alcoholic liver disease in London is most unusual, probably reflecting their low wine consumption and the trivial iron content of the native beers and spirits. Slight excess is quite common but liver iron concentrations above 0.5% dry weight are exceptional. In untreated idiopathic haemochromatosis values are usually greater than 2% dry weight.

Mild or moderate iron overload is common in porphyria cutanea tarda. This disease is commonly associated with excessive alcohol consumption which is known to aggravate the complaint. Many cases show evidence of liver damage; this is usually mild but cirrhosis is sometimes found. The high hepatic uroporphyrin content is readily demonstrable in fresh biopsies by the red fluorescence in ultraviolet light. Complete removal of iron by multiple phlebotomies induces a sustained clinical and biochemical remission, even in patients without iron excess. Although the improvement appears to be specifically due to removal of iron the relationship of the iron to the other manifestations of the disease is not yet understood.

A tendency for siderosis to develop de novo, or for preexisting siderosis to increase, has been noted in many patients after portal systemic shunt operations, including end-to-side and side-to-side portacaval anastomosis.
and splenorenal anastomosis. Progressive siderosis has also been observed in association with large spontaneous collaterals. A puzzling feature has been the speed with which heavy siderosis sometimes develops. The frequency of siderosis has varied in different series and the heavy siderosis described in the early case reports appears to be relatively uncommon. Nevertheless, as increased skin pigmentation and diabetes are also quite frequent after a portacaval anastomosis, a haemochromatosis-like picture sometimes results. The only instance in which the finding of heavy siderosis was backed up by direct measurement of tissue iron levels showed that the amount of iron actually present, though increased, fell far short of the quantities found in haemochromatosis. This may well prove generally to be the case.

The status of siderosis after a shunt as an entity, and its pathogenesis, remain matters of debate. In some cases decreased liver cell mass may account for a relative increase in iron concentration, and thus in siderosis. Accepting that in others there is an absolute increase in iron content, excess absorption must be implicated. However, increased iron absorption is common in cirrhosis and the findings in portacaval patients have not differed conclusively from those in other cirrhotics. Furthermore, apart from the theoretical possibility of the shunt itself, factors known to augment iron absorption are not consistently identified in these patients. Experimental shunts in animals are followed by siderosis in the absence of cirrhosis, the siderosis depending on the size and the type of shunt. Although increased absorption is not observed experimentally it may be questioned how accurately such studies represent the circumstances of human disease.

Iron and Tissue Damage

It has long been debated whether iron excess per se causes liver damage or whether adjuvant factors or deficiencies are also implicated. Although most would probably accept iron as the sole culprit, attempts to produce a similar lesion in animals have repeatedly met with failure. Recently, however, an hepatic lesion in many ways resembling that of human haemochromatosis has been achieved by massive chronic parenteral iron loading in dogs. It is not clear why this study succeeded where so many have previously failed and it is to be hoped that it will be confirmed by others.

Necropsy studies in cases of siderosis in Bantu have shown a close correlation between liver iron concentration and severity of fibrosis; severe liver damage increases in incidence as liver iron concentration rises and is present in most, though not all, livers in which iron concentration exceeds 2% dry weight. Techniques for measuring iron concentration in needle-biopsy specimens have enabled similar and serial observations to be made in other iron-loading disorders. In the typical case of idiopathic haemochromatosis liver iron concentration is 2-4% dry weight; severe fibrosis is usually, but not invariably, present. At earlier stages of the disease lower iron concentrations are associated with less severe injury. In the rare group of patients dying from cardiopathy at an early age high iron concentrations have been found with relatively slight fibrosis. In thalassaemic children with transfusional iron overload high liver iron concentrations develop early in the disease at a stage when fibrosis is slight; serial biopsies subsequently show progressive fibrosis with cirrhosis developing during the teens, the degree of
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liver injury being more closely related to the patient's age than to the liver iron level. These observations support the view that iron is a relatively low grade fibrogenic agent and that the duration of iron loading as well as its magnitude determines the severity of liver injury. The massive transfusional iron overload accompanying aplastic anaemia is often associated with relatively mild fibrosis; this may be partly due to the initial protective localization of the iron in reticuloendothelial cells but it is also probably relevant that the survival of these patients is limited by other factors, death occurring before severe damage develops.

The link between iron and the extrahepatic manifestations of iron overload is not understood. This applies to epidermal melanoses and to the arthropathy (common in idiopathic haemochromatosis but only once reported in transfusional iron overload) as well as to the diabetes and the other endocrinopathies. Diabetes is a less constant feature of idiopathic haemochromatosis than formerly thought but nevertheless occurs in 28-63% of cases, depending on the series and in transfusional iron overload and in Bantu siderosis. Traditionally it has been attributed to pancreatic damage and islet cell failure consequent upon massive iron deposition but recent observations indicate that this concept is inadequate, at least in idiopathic haemochromatosis: the occurrence of diabetes correlates with neither the duration nor the magnitude of iron overload; there is a high incidence of diabetes, unrelated to iron excess, in relatives; insulin levels are commonly normal or increased; the response of the diabetes to iron removal is unpredictable.

Heavy iron deposition occurs in the anterior pituitary, thyroid, and the zona glomerulosa of the suprarenal cortex. Clinically, adrenal insufficiency is extremely uncommon in haemochromatosis and hypothyroidism rare; however, hypogonadism is frequent. Atrophy of the testicular germinal epithelium is found but iron is scanty and located mainly in the blood vessels. Although a primary pituitary defect has long been suspected, investigations of pituitary and peripheral endocrine function have given extremely variable and confusing results. Considered overall, the findings suggest that disturbances of pituitary and peripheral glands occur both separately and together in a variable and unpredictable manner. Hypoparathyroidism is another endocrinopathy occasionally observed in transfusional iron overload but not yet described in idiopathic haemochromatosis. Such cases have been found to have subnormal serum parathyroid hormone levels in vivo and no detectable parathyroid tissue at necropsy.

Ascorbic acid deficiency and osteoporosis are interrelated metabolic defects associated with iron overload. Their pathogenesis has recently been reviewed. Frank scurvy is well documented in Bantu siderosis and subnormal tissue levels of ascorbic acid occur in transfusional iron overload and idiopathic haemochromatosis. Iron overload directly causes chronic ascorbic acid deficiency, excessive deposits of ferric iron accelerating the oxidative catabolism of ascorbic acid. In turn, ascorbic acid deficiency secondarily affects iron metabolism by inhibiting the release of iron from reticuloendothelial cells, an important clinical consequence of which is a marked impairment in the response to chelating agents used for therapeutic or diagnostic purposes. Defective osteogenesis is another effect of the ascorbic acid deficiency. The iron overload-osteoporosis-
ascorbic acid deficiency syndrome observed in the Bantu\textsuperscript{113,119} has been reproduced experimentally in guinea pigs, in which the bone changes are largely preventable by ascorbic acid supplementation\textsuperscript{118}. Osteoporosis has also been reported in idiopathic haemochromatosis\textsuperscript{120,121}.

**Treatment of Iron Overload**

Repeated venesection (phlebotomy) is established as the method of choice for iron removal in idiopathic haemochromatosis. As a rule two 500-ml venesections are performed weekly until depletion of iron stores results\textsuperscript{122,123}. Compared with repeated venesection, iron chelation therapy is too inefficient to merit a place in the management of this disease, even as an adjuvant form of treatment. Preliminary determination of liver iron concentration in a biopsy specimen, or indirect assessment of storage iron by means of a chelation test\textsuperscript{123} or by immunoradiometric assay of serum ferritin\textsuperscript{124}, greatly facilitates the conduct of treatment by enabling a patient's venesection requirement to be reliably planned in advance.

Complete treatment is associated with return of liver function tests to normal, regression in hepatomegaly, decrease in skin pigmentation, and marked improvement in survival time and mortality rate\textsuperscript{125}. Hypogonadism and arthropathy do not improve. An early decrease in the fibrosis does not usually occur. A few reports\textsuperscript{122,126,127} have suggested that even quite severe damage may revert towards normal but assessment of long-term structural changes in needle-biopsy specimens can be discrepant owing to conversion to a macronodular cirrhosis. Primary liver carcinoma remains a significant risk despite effective iron removal and is now the commonest single cause of death\textsuperscript{125}. This may be related to the duration of the cirrhosis rather than to the iron itself. The importance of early diagnosis of haemochromatosis and, as a corollary of this, the detection and treatment of all affected relatives, is thus underlined.

In iron-loading anaemias venesection therapy is feasible only when the underlying blood disease is amenable to treatment, eg, in hereditary spherocytosis\textsuperscript{49} and pyridoxine-responsive anaemia\textsuperscript{48}. Otherwise long-term chelation therapy offers the only practicable means of iron elimination. Desferrioxamine and diethylenetriamine penta-acetic acid (DTPA) are the two chelating agents employed. Both are given parenterally, desferrioxamine usually by daily intramuscular injection and DTPA intravenously with blood transfusions\textsuperscript{128}. A six-year trial of continuous chelation therapy in thalassaemia revealed a significant but limited reduction in liver iron concentration in the treated children compared with matched controls maintained on a similar high transfusion regime. In contrast to the controls, the chelator-treated patients showed no discernible tendency towards progressive fibrosis during the period of study\textsuperscript{129}. The implications of these findings in terms of clinical benefit, quality of life, and ultimate survival have yet to be determined.

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