Iron and Chronic Liver Disease

MICHAEL BARRY, M.D., M.R.C.P., Senior Medical Registrar, The Royal Free Hospital, London

The normal adult has a total body iron content of about four grams, of which some 70 per cent is bound tightly to the protoporphyrin prosthetic groups of haemoglobin within the red cells and a further 300 mg fixed in myoglobin. Apart from small amounts contained within various enzyme systems (10 mg) and the minute but dynamic plasma pool (4 mg), the remainder of the body's iron is held as intracellular deposits of soluble ferritin and insoluble stainable haemosiderin, forming a readily available reserve located mainly in the liver, spleen, and bone-marrow.

The body has a very limited capacity to excrete iron and under certain circumstances excessive quantities of the metal accumulate in the tissues, with damaging effect. Of the several iron compartments of the body, only the reserve or storage compartment is capable of significant expansion. In healthy males the size of the stores remains constant throughout life, reflecting an equilibrium between dietary iron intake, iron absorption, and physiological iron loss. There is, however, some variation in storage iron between different populations, depending mainly on differences in iron intake. Because of these population differences the quantitative definition of iron excess is somewhat arbitrary but in the United Kingdom iron stores of more than one gram appear to be most unusual. A moderate increase above this level, though not of itself deleterious, may well signify an underlying iron-loading disorder. Massive iron excess causes disturbance of structure and function in many organs, but the liver, as a parenchymal organ with major iron storage function, bears the impact early and liver disease has long been recognised as the most constant feature of iron excess.

PATHOGENESIS OF IRON OVERLOAD
Iron overload may result from administration of excess iron parenterally, from long-continued hyperabsorption of iron, or from a combination of both factors. Heavy parenteral iron overload is almost always due to multiple blood transfusions and is generally associated with some degree of hepatic fibrosis, provided the patient survives long enough. The severity of structural damage is not simply related to the magnitude and duration of the iron loading, for in patients with aplastic anaemia, in whom the largest iron loads are
encountered, the fibrosis is often relatively slight. Nevertheless, these patients are liable to other manifestations of iron excess and die from cardiac failure and complex metabolic derangements including hepatocellular impairment and multiple endocrinopathies.

Inapropriately increased absorption of iron may result simply from long-continued ingestion of excess iron. This is best exemplified by the South African Bantu who consume large amounts of the metal in alcoholic drinks that have been fermented in iron containers (Charlton et al., 1973). Increased absorption can also occur with a normal iron intake and is then due to inappropriately increased mucosal activity. This is the mechanism for iron accumulation in the iron-loading anaemias; it occurs in response to greatly increased erythropoiesis and is best recognised in thalassaemia and the sideroblastic anaemias. Severe liver damage is a usual consequence.

Inappropriately increased mucosal activity is the crucial factor for iron accumulation in idiopathic haemochromatosis. The role of possible gastric and pancreatic factors in the pathogenesis of this disease have now been discounted. Although idiopathic haemochromatosis is firmly accepted as a hereditary disorder, the exact nature of the biochemical lesion and its mode of inheritance have yet to be determined. The mucosal defect may be part of a more generalised disturbance in the cellular handling of iron. The severity of the lesion varies from subject to subject but the average rate of iron accumulation is about one milligram per day so that by the time the patients present between the ages of 40 and 60 some 10 to 20 g are usually present. The rate of iron accumulation in haemochromatosis is also subject to physiological and environmental factors. The relative infrequency of clinical disease in women is attributable to the iron losses of menstruation and pregnancy, and women presenting with the disease tend to be postmenopausal and nulliparous; nevertheless, occasional examples of fully developed haemochromatosis in menstruating women have been recorded. The rate of iron accumulation and, hence, the expression of the disease may be accelerated by alcohol, which is known to augment iron absorption in normal subjects, and this probably accounts for the observation that some 30 to 50 per cent of patients with idiopathic haemochromatosis drink more than average amounts of alcohol.

**Clinical Aspects**

Iron accumulation proceeds insidiously and large amounts may be present with few or no symptoms. Moreover, the various manifestations associated with iron excess do not correlate well with the degree of iron loading. These generalisations are especially true of idiopathic haemochromatosis which can be regarded as the archetypal iron-loading disorder. Although this disease can
present in many guises, signs of liver disease are almost invariably present. Hepatomegaly develops early, sometimes preceding fibrosis, and often is discovered incidentally at a routine medical examination or during an intercurrent illness. The large liver may be accompanied by other features of chronic liver disease such as spider naevi, palmar erythema, splenomegaly and Dupuytren’s contractures, at a stage when iron load is relatively slight and before cirrhosis has developed; however, these signs are by no means constant and hepatomegaly may be the only finding. Dutournier’s triad of hepatomegaly, pigmentation and diabetes mellitus is widely regarded as the hallmark of the disease but the pigmentation is often inconspicuous and can be readily overlooked, while diabetes is present in only 28 per cent of the cases seen at the Royal Free Hospital (Fig. 1).

Some patients present with impotence, cardiac failure, or arthropathy. The cardiac disorder is one of function rather than structure, resulting in cardiac

| CLINICAL FINDINGS       | % CASES POSITIVE |
|-------------------------|------------------|
| Hepatomegaly            | 100              |
| Pigmentation            | 60               |
| Hair Loss               | 50               |
| Spider naevi            | 40               |
| Splenomegaly            | 30               |
| Palmar erythema         | 20               |
| Arthropathy             | 10               |
| Dupuytren’s contractures| 5                |
| Diabetes mellitus       | 0                |
| Ascites                 | 0                |
| Jaundice                | 0                |

Fig. 1. Clinical findings in 45 propositi with idiopathic haemochromatosis.

failure and arrhythmias. Although reversible by iron removal, the course can be rapidly progressive, especially in younger patients (Charlton et al., 1967). Arthralgic symptoms are elicited in approximately 50 per cent of patients with
haemochromatosis (Dymock et al., 1970). Pain or stiffness may be experienced in many joints but swelling of the second and third metacarpophalangeal joints is the commonest clinical finding; the appearances superficially resemble rheumatoid arthritis but ulnar deviation, marginal erosions and positive serology do not occur. Some patients have attacks of acute calcium pyrophosphate crystal synovitis but, even without such episodes, radiological evidence of calcification may be found in various articular and ligamentous structures, especially the menisci.

Abdominal pain is a common symptom in haemochromatosis. It is sometimes attributable to gallstone disease or duodenal ulceration but often remains unexplained. Rarely, patients present with an acute abdominal crisis marked by severe pain, peritonism and circulatory collapse; they tend to be admitted as surgical emergencies and die rapidly with or without laparotomy, the diagnosis being made at autopsy (MacSween, 1966). The cause of this syndrome is obscure.

As the presenting features of haemochromatosis are often non-specific, diagnosis largely depends on thorough investigation of the hepatomegaly. Routine liver function tests are of little help. Jaundice is unusual and when present may indicate advanced disease, gallstones, or primary liver carcinoma. The serum alkaline phosphatase is as often normal as it is raised; the transaminases are usually slightly raised but can be normal. The serum iron is usually elevated but a value within the normal range does not rule out the diagnosis. Liver biopsy is the essential procedure and often reveals the diagnosis when it has been overlooked clinically. In haemochromatosis heavy hepatic iron deposition precedes fibrosis, the extent of the latter depending to a large extent on the duration and degree of iron loading. Fibrosis is initially portal and perilobular in distribution but spiky septa later penetrate the lobules from the periphery. The septa are iron-laden but inflammation is typically slight. At a later stage lobular distortion occurs and ultimately a micronodular cirrhosis develops. This characteristic pattern of fibrosis is essentially identical in all forms of iron overload although some variation may be seen in the distribution of iron between reticuloendothelial and parenchymal cells and in the rate of progression of the fibrosis.

IRON OVERLOAD IN OTHER FORMS OF CIRRHOSIS
Once the presence of heavy hepatic iron deposition has been established, differential diagnosis lies mainly between idiopathic haemochromatosis and cirrhosis with secondary siderosis. Confusion with iron-loading anaemias should not occur, as subjects with idiopathic haemochromatosis are very rarely anaemic; exceptionally, patients with well-compensated haemolytic states,
who have never been significantly anaemic, present with secondary haemochromatosis, but careful haematological assessment will reveal the underlying disorder.

Some degree of hepatic iron deposition is quite frequent in cirrhosis but the amount is usually slight and the overall histological picture is unlikely to be confused with haemochromatosis. In a few cases the intensity of 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 (MacDonald, 1964). However, the alternative argument that the disease is but a variant of portal cirrhosis, with nutritional deficiency or alcoholism determining the liver injury and iron excess occurring incidentally, does not fit the facts and is accepted by few.

One factor contributing to the confusion has been the difficulty in interpreting the significance of stainable liver iron in terms of the amount of iron actually present. Until quite recently the presence of stainable iron was regarded as an unusual feature of normal liver (Wachstein, 1963) and even minor degrees of siderosis were thought to represent iron excess ('haemosiderosis'). This view has had to be revised during the last decade. The relationship between liver iron concentration and stainable liver iron, graded on a conventional histochemical scale, is shown in Fig. 2. Absence of stainable iron corresponds to storage levels below the mean value for London controls (80 μg/100 mg of dry liver) and not until the transition from grade 2 to grade 3 (submaximal) siderosis can iron excess be predicted on histochemical grounds although the increase may still be relatively modest.

It is in patients with grade 3 iron deposition that distinction between cirrhosis with secondary siderosis and haemochromatosis can be difficult. In this situation quantitative measurement of storage iron is essential. Although iron chelation tests have proved valuable (Barry, 1973) direct measurement of storage iron in liver biopsy specimens is technically the simplest and most reliable approach (Barry and Sherlock, 1971). When, as is so often the case, heavy iron deposition has been discovered unexpectedly, the rest of the specimen may be used for the biochemical estimation. In untreated idiopathic haemochromatosis liver iron concentration is usually in the range 1.8 to 5.0 per cent dry weight, whereas in cirrhosis with siderosis values in excess of 1 per cent dry weight are exceptional (Fig. 3). As a general rule, when liver iron concentration is less than 1.5 per cent dry weight the iron is unlikely to be the cause of the cirrhosis.
Iron excess superimposed on cirrhosis mainly occurs under two circumstances: after a surgical shunt operation and in patients with alcoholic cirrhosis. Hepatic iron deposition develops, or is noted to increase, in perhaps 20 per cent of patients who have undergone a surgical shunt and has been observed with several of the various types of procedure employed (Conn, 1972). In a minority of cases the siderosis is heavy, and as both pigmentation and diabetes are also quite frequent after a portacaval anastomosis a haemochromatosis-like picture can arise; however, direct measurement of tissue iron in such cases has indicated that the amounts actually present fall far short of those found in idiopathic haemochromatosis (Grace and Balint, 1966). The pathogenesis of the syndrome remains uncertain but increased iron absorption is presumably involved. In some cases decreased liver cell mass may account
for an increase in stainable iron without any increase in total liver iron content.

Iron overload in alcoholic cirrhosis has been recognised in France for many years (Gilbert and Grenet, 1896; André, 1961) and, more recently, in other wine-drinking populations (Perman, 1967). Wines have a high iron content (Fig. 4) and provide a convenient vehicle for the ingestion of large amounts of the metal. In addition, alcohol is known to increase iron absorption, perhaps by stimulating gastric secretion (Charlton et al., 1964) and liver iron content has been found to be higher in heavy drinkers than in a similar group of subjects with low alcohol consumption (Powell, 1966). Nevertheless, iron excess occurs in only a minority of British alcoholics and then seldom amounts to a total load of more than four grams, probably reflecting the low wine consumption in this country and the trivial iron content of our native beers and spirits. In the very rare cases with larger iron loads certain distinction from
idiopathic haemochromatosis may be impossible; under these circumstances it is justifiable to assume the latter diagnosis, treating the patient by multiple venesections and screening the relatives for positive evidence of the familial disease (Powell, 1965).

**TREATMENT OF IRON OVERLOAD**

*Idiopathic Haemochromatosis*

The aim of treatment is to remove iron by the most efficient and convenient means practicable and, since marrow function is usually normal in idiopathic haemochromatosis, repeated venesection is the method of choice. Under maximal stimulation the healthy marrow can produce about 120 ml of red cells daily, provided enough iron is available to supply the regenerative response; in the iron-loaded subject this need is readily met by mobilising the excess stores and, in haemochromatosis, the removal of 500 ml of blood every third day is a practicable undertaking. In most cases it is generally convenient to perform two 500-ml venesections weekly but in elderly subjects or in patients with occlusive vascular disease it may be advisable to reduce the volume of each bleed. The approach to treatment should not be too leisurely,
as iron absorption increases greatly in response to venesection, offsetting the
effect of blood removal. Venesections performed at intervals of more than a
week achieve a less efficient negative iron balance and disproportionately
prolong the total duration of treatment.

The haemoglobin concentration during treatment usually runs between
10.5 and 13 g/100 ml. The terminal stage of iron removal is heralded by a
progressive fall in haemoglobin level and the development of hypochromia.
This reflects diminishing iron availability as the stores near exhaustion,
marrow iron perfusion becoming relatively inadequate for the greatly in-
creased erythropoietic demand. By appropriate spacing, several more vene-
sections are possible over the ensuing weeks, complete iron depletion ultimately
being indicated by persistent anaemia, hypoferraemia and reticulocytopenia.
At this stage the adequacy of treatment should be checked by liver biopsy and
some quantitative assessment of storage iron.

Soon after the end of treatment the haemoglobin concentration, serum iron,
and total iron-binding capacity return to their pre-treatment levels. This does
not denote significant iron reaccumulation, for further venesections at this
stage rapidly restore the features of iron deficiency. Nevertheless, to prevent
reaccumulation, the patient should have a venesection every three to four
months for the rest of his life.

The screening of relatives forms an important part of the management of
every case and is most conveniently done by means of a chelation test. Those
with evidence of iron excess should be admitted for definitive evaluation,
including liver biopsy and direct determination of storage iron levels, before
being treated with venesections to restore and maintain the stores at a normal
level. It should be remembered that for physiological reasons adolescents and
pre-menopausal women may have normal iron stores at the time of study but
will go on to develop excess later.

Before the introduction of venesection therapy in the 1950s the average
survival time after diagnosis was about five years. The commonest single cause
of death was cardiac failure but, collectively, liver failure, variceal haemor-
rhage, and primary liver carcinoma were more important (Finch and Finch,
1955). The advent of venesection therapy has transformed this outlook
(Williams et al., 1969). In treated patients, hepatomegaly decreases and the
liver function tests return to normal. Weight is regained and a normal sense of
well-being restored. Cardiac failure can also be reversed, although sometimes
the course of these patients is too rapid for treatment to be of avail. The
arthropathy and the gonadal failure usually show little improvement with
treatment, and the response of the diabetes is unpredictable. Although
hepatic fibrosis may decrease it is questionable whether established cirrhosis
can be reversed despite claims to the contrary (Weintraub et al., 1966a; Powell and Kerr, 1970). The liability to primary liver carcinoma is unaffected by treatment and it is now the commonest single cause of death in idiopathic haemochromatosis; it may be related to the duration of the cirrhosis rather than to the iron itself, underlining the importance of early diagnosis.

**Venesection Therapy in other Disorders**

Phlebotomy is seldom feasible in iron-loading anaemias, owing to the refractory nature of the erythropoietic disorder, but has proved possible in hereditary spherocytosis after splenectomy (Barry et al., 1968), in pyridoxine-responsive anaemia (Weintraub et al., 1966b) and in other forms of mild sideroblastic anaemia (Crosby and Sheehey, 1960). Venesection in cirrhosis with siderosis usually yields only small amounts of iron before the onset of iron deficiency. In cases with a larger (i.e. moderate) excess it is hard to assess the extent to which the iron aggravates the underlying liver disease. When liver function is poor, venesection is not well tolerated. Porphyria cutanea tarda is commonly accompanied by slight or moderate iron excess and clinical and biochemical remission can be induced by a course of venesections (Turnbull et al., 1973). The beneficial effect of venesections in porphyria cutanea tarda appears to be due to the removal of iron but also occurs in those cases in whom the stores are normal, and the relationship of iron to the other manifestations of the disease remains to be elucidated.

**Iron-loading Anaemias**

In thalassaemia, other refractory haemolytic and non-haemolytic anaemias, and transfusional iron overload states, venesection is usually totally impracticable and long-term treatment with iron chelating agents offers the only hope of eliminating iron from the body. The two compounds employed, desferrioxamine (0.5 g i.m. daily) and diethylenetriamine penta-acetic acid (given i.v. with blood transfusions, 2 g per unit), complement each other in clinical usage and, dose for dose, elicit comparable urinary iron excretion in the iron-loaded subject (10 to 40 mg per gram chelating agent). Desferrioxamine may also provoke significant biliary iron loss. Unfortunately, neither compound is effective by mouth. A prospective trial of long-term chelation therapy has recently been reported in thalassaemia major (Barry et al., 1973; Risdon et al., 1973). After six years of continuous treatment liver iron concentration was significantly lower than in controls maintained on a similar high transfusion regime. Although the children given chelation therapy did not achieve iron balance until liver iron concentration had reached 3 per cent dry weight (i.e. well within the haemochromatosis range) they showed no
discernible tendency towards progressive hepatic fibrosis over the period of study, in marked contrast to the controls. The implications of these findings in terms of clinical benefit, quality of life, and ultimate survival, remain to be determined.

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References

André, J. (1961) *Revue internationale d'Hépatologie*, 11, 113.
Barry, M. (1973) In *Clinics in Haematology*, Vol. II, No. 2. (Ed. S. T. Callender). London: Saunders.
Barry, M. and Sherlock, S. (1971) *Lancet*, 1, 100.
Barry, M., Flynn, D. M. and Letsky, E. (1973) In the press.
Barry, M., Scheuer, P. J., Sherlock, S., Ross, C. F. and Williams, R. (1968) *Lancet*, 2, 100.
Charlton, R. W., Abrahams, C. and Bothwell, T. H. (1967) *Archives of Pathology*, 83, 132.
Charlton, R. W., Bothwell, T. H. and Seftel, H. C. (1973) In *Clinics in Haematology*, Vol. II, No. 2. (Ed. S. T. Callender). London: Saunders.
Charlton, R. W., Jacobs, P., Seftel, H. and Bothwell, T. H. (1964) *British Medical Journal*, 2, 1427.
Conn, H. O. (1972) *Gastroenterology*, 62, 61.
Crosby, W. H. and Sheehey, T. W. (1960) *British Journal of Haematology*, 6, 56.
Dymock, I. W., Hamilton, E. B. D., Laws, J. W. and Williams, R. (1970) *Annals of Rheumatic Diseases*, 29, 469.
Finch, S. C. and Finch, C. A. (1955) *Medicine*, 34, 381.
Gilbert, A. and Grenet, A. (1896) *Comptes rendus hebdomadaires des séances de l'Académie des Sciences*, 3, 1078.
Grace, N. D. and Balint, J. A. (1966) *American Journal of Digestive Diseases*, 11, 351.
MacDonald, R. A. (1964) *Hemochromatosis and hemosiderosis*. Springfield, Illinois: C. C. Thomas.
MacSween, R. N. M. (1966) *Quarterly Journal of Medicine*, N.S. 35, 589.
Perman, G. (1967) *Acta medica Scandinavica*, 182, 281.
Powell, L. W. (1965) *Quarterly Journal of Medicine*, N.S. 34, 427.
Powell, L. W. (1966) *Australasian Annals of Medicine*, 15, 110.
Powell, L. W. and Kerr, J. F. R. (1970) *Australasian Annals of Medicine*, 19, 54.
Risdon, R. A., Flynn, D. M. and Barry, M. (1973) *Gut*, 14, 421.
Scheuer, P. J., Williams, R. and Muir, A. R. (1962) *Journal of Pathology and Bacteriology*, 84, 53.
Turnbull, A., Baker, H., Vernon-Roberts, B. and Magnus, I. A. (1973) *Quarterly Journal of Medicine*, N.S. 42, 341.
Wachstein, M. (1963) In *The Liver: Morphology, Biochemistry and Physiology*. (Ed. C. Rouiller). Volume I. New York: Academic Press.
Weintraub, L. R., Conrad, M. E. and Crosby, W. H. (1966a) *Medical Clinics of North America*, 50, 1579.
Weintraub, L. R., Conrad, M. E. and Crosby, W. H. (1966b) *New England Journal of Medicine*, 275, 169.
Williams, R., Smith, P. M., Spicer, E. J. F., Barry, M. and Sherlock, S. (1969) *Quarterly Journal of Medicine*, N.S. 38, 1.