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Iron overload

PAUL M. SMITH
M.B., M.R.C.P.

THE TOTAL body iron content of normal adults is approximately 4 g, of which 2·5 g is incorporated within circulating haemoglobin, 1 g is stored within the reticulo-endothelial system, and 0·5 g is present in myoglobin, plasma and the cytochrome enzymes. This quantity of iron remains fairly constant in the normal subject, absorption being equal to excretion. About 1 mg is lost by excretion each day, and is replaced by the absorption of 5–10% of the normal dietary iron intake of 15 mg/day.

Iron overload may arise as a primary disease as in idiopathic haemochromatosis, or as a phenomenon secondary to a number of different causes (Table 1).

TABLE 1. Classification of iron overload

1. Primary
   Idiopathic haemochromatosis
2. Secondary
   (a) Increased iron ingestion
   (b) Alcoholic cirrhosis
   (c) Transfusional siderosis
   (d) Other causes
3. Focal

In the latter group haemosiderosis usually results; this is iron overload without tissue damage, in contrast to haemochromatosis, in which, by definition, tissue damage is present.

Secondary iron overload

(a) *Increased iron ingestion*

This has been described in three groups of patients. The Bantu drink large quantities of fermented alcoholic beer which contains a high concentration of iron, mainly derived from the pots used in the brewing process. Many Bantu males consume 100 mg or more of iron each day, six times the normal amount (Bothwell *et al.*, 1964). Body iron stores slowly accumulate, so that 89% of Bantu males coming to autopsy have excess iron deposits (Bothwell & Bradlow, 1960), although only 3% develop haemochromatosis (Isaacson *et al.*, 1961).

Prolonged oral iron therapy has been reported in a few cases to give rise to secondary haemochromatosis (Turnberg, 1965; Johnson, 1968), and in Manchuria a generalized siderosis with a crippling polyarthritis, Kashin–Beck disease, is localized to areas where the water and food have a very high iron content (Hiyeda, 1939). Recently, however, the arthritis has been attributed to the ingestion of a fungus (Nesterov, 1964).

(b) *Alcoholic cirrhosis*

This may be accompanied by a secondary siderosis, for many wines contain significant amounts of iron (MacDonald, 1963). Beer and spirits have a low concentration, but alcohol may also enhance iron absorption, perhaps by stimulating the secretion of gastric acid (Charlton *et al.*, 1964). Iron intake can be increased by oral or parenteral iron therapy, sometimes wrongly given for the haemodilutional anaemia associated with the accompanying splenomegaly. In addition, one-third of a series of well-compensated cirrhotics had an increased iron absorption, and the percentage rose to 56% for those with a surgical shunt (Williams *et al.*, 1967). Severe siderosis has been occasionally described following a portacaval anastomosis (Shaefer *et al.*, 1962). The actual mechanism is unknown, but it may be aggravated by the reduced red cell survival (Da Silva *et al.*, 1963).

(c) *Transfusional siderosis*

Patients with an aplastic anaemia, who are maintained by regular blood transfusions, receive a large parenteral iron intake, most of which is taken up by the reticulo-endothelial system, and is only later transferred to the parenchymal cells. Tissue damage is rare. Cappell, Hutchinson & Jowett (1957a), however, found that when cirrhosis was present, the quantity of body iron stores was always considerably greater than that known to have been transfused. This excess iron was presumed to have been absorbed from the gut, and they postulated that iron obtained in this way was more harmful than red cell iron to the tissues. Secondary haemochromatosis is an uncommon, but well recognized, complication of some anaemias associated with erythroid hyperplasia (Kent & Popper, 1960), such as thalassaemia major (Ellis, Schulman & Smith, 1954), pyridoxine-responsive anaemia (Hathaway, Harris & Stenger, 1967), sex-linked hypochromic anaemia (Losowsky & Hall, 1965) and hereditary spherocytosis (Wilson, Scott &

North, 1967). Barry *et al.* (1968b) have recently described five cases of congenital spherocytosis with secondary haemochromatosis, in three of whom no transfusional or oral iron therapy had been given. Erythropoiesis is stimulated by the anaemia, causing dietary iron absorption to increase (Weintraub, Conrad & Crosby, 1965), although Brain & Herdan (1965) found ten out of eleven patients with a sideroblastic anaemia and increased iron stores to have a normal percentage absorption, whereas Losowsky and Hall found their patients to have increased values.

(d) *Other causes*

Excess body-iron stores have also been reported in patients with porphyria cutanea tarda (Epstein & Pinski, 1965) and xanthinuria (Ayvazian, 1964). In the latter condition lack of the enzyme xanthine oxidase has been held responsible for an inability to release ferritin-bound iron from the tissue stores. One case of congenital transferrin deficiency associated with iron overload has been described (Heilmeyer *et al.*, 1961).

Primary iron overload: idiopathic haemochromatosis

This is believed to be caused by the excessive absorption of iron over a long period of time from a normal diet. Fig. 1 shows the results obtained by Williams *et al.* (1966) in a group of patients with idiopathic haemochromatosis. Although initial values lie within or near to the normal range, there is a sharp rise with venesection therapy, and this high level is maintained for some years after treatment has been stopped. It is possible that absorption will return to normal only when the iron stores reach pre-treatment figures of 10–20 g. In contrast, absorption in the control subject returns to normal within a year after an iron deficiency anaemia has been induced by venesection (Conrad & Crosby, 1962).

Genetic factors

The increased absorption of iron and resultant tissue damage has been ascribed to both genetic and environmental factors. Williams, Scheuer & Sherlock (1962) examined clinically and by liver biopsy forty-six close relatives of sixteen patients with idiopathic haemochromatosis. In twenty-eight relatives liver biopsy sections contained free iron, but, apart from pigmentation, clinical signs were slight (Scheuer, Williams & Muir, 1962). Only one relative, a sibling, had cirrhosis, and he also had the most marked iron overload. However, Weinfeld, Lundin & Lundvall (1968) showed that in Sweden stainable iron was present in twenty-three out of twenty-seven normal males, although comparable findings in England have not been described.

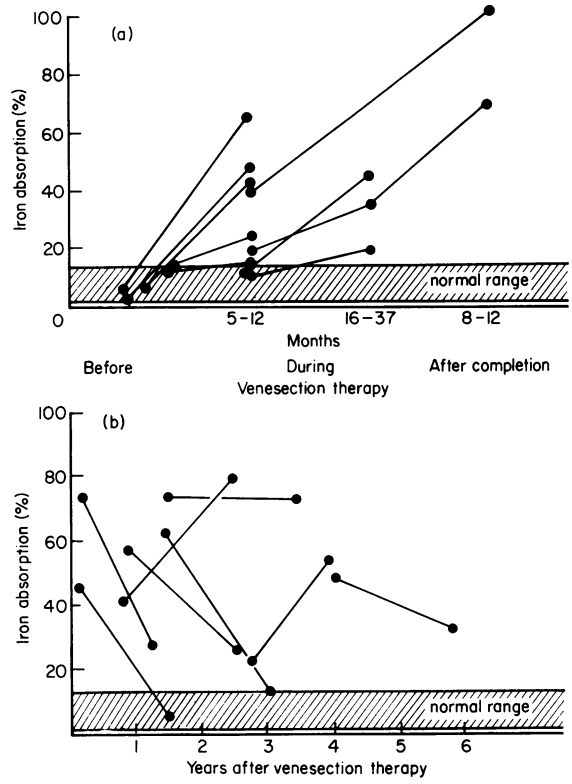

FIG. 1. Serial readings of iron absorption in patients examined at various intervals in relation to venesection therapy (from Williams *et al.*, 1966).

Of more significance is the fact that, in further studies, sixteen out of twenty-nine relatives were shown to have an increased iron absorption (Williams *et al.*, 1965) and 40% of male offspring over the age of 15 were found to have a raised serum iron (Dreyfus & Schapira, 1964). Recently we have seen a family in which three brothers, two of whom were binovular twins, developed haemochromatosis in middle life. So far none of the next generation are affected, but the serum iron in one of them is slightly raised at 200 μg/100 ml. The general experience has been that primary haemochromatosis is uncommon in siblings, and that the fully developed disease is rare in successive generations, perhaps because the offspring have not had time to develop the manifestations (Balcerzak *et al.*, 1966). Some studies suggest that inheritance may follow the pattern of a dominant gene with partial penetrance, although an intermediate form of inheritance was thought to be more likely by Williams (1968), the homozygote developing the disease and the heterozygote only mild abnormalities. An environmental influence, such as alcoholism, may be required for the full manifestations to appear.

Environmental factors

MacDonald (1966) has advanced the view that idiopathic haemochromatosis is merely a variant of portal cirrhosis with siderosis, the increased absorption and deposition of iron in the liver being secondary to alcohol or dietary-deficiency-induced liver disease. However, in only 20% of the patients studied by Williams *et al.* (1968) was there a history of alcoholism or malnutrition, and in only eight out of 116 cases of cirrhosis examined by Zimmerman *et al.* (1961) were the iron deposits sufficient to resemble those seen in haemochromatosis. In addition, Powell (1965) has shown that excess iron stores are far more common in the relatives of patients with haemochromatosis than in those of patients with alcoholic cirrhosis and siderosis.

Nature and site of genetic defect

The biochemical defect responsible for the increased iron absorption of idiopathic haemochromatosis has not yet been elucidated, but it is possible that it lies in the intestinal mucosa. Only a proportion of the iron that enters the absorbing cells passes through them and is retained by the body. A variable amount is trapped within the mucosa as ferritin, and is lost when the cells are exfoliated (Conrad & Crosby, 1963). Small accumulations of ferritin (F bodies) are visible on electron microscopy in the intestinal mucosal cells of normal subjects, but are absent in haemochromatosis (Crosby, 1963).

Luminal factors

Murray (1968) reported that a gastro-intestinal secretion may be reponsible for the increased iron absorption of haemochromatosis, but attempts to confirm this work have failed (Smith, Studley & Williams, 1968). Our results show that gastric juice from patients with haemochromatosis will not potentiate iron uptake by everted rat-gut segments (Table 2). Deller and his colleagues have postulated

TABLE 2. Response of everted rat-gut segments to gastric juice

	No. of samples	Index mucosal uptake of ^{58}Fe	
Isotonic saline	10	12·6	(9·6–16·0)
Gastric juice from haemochromatosis patients	4	6·7	(3·8–9·9)
Gastric juice from iron deficiency patients	6	11·5	(6·8–15·7)

that the substance gastroferrin binds with iron in the stomach to render it non-absorbable, and that failure to synthesize gastroferrin is the cause of haemochromatosis (Davis, Luke & Deller, 1966). However, it has recently been shown that the binding of iron by gastric juice is simply a loose association with a glycoprotein, and that this property is present in normal as well as in gastric juice from patients with haemochromatosis (Wynter & Williams, 1968).

High iron absorptions have been found in cases of chronic pancreatitis and cirrhosis, remedied by feeding pancreatin (Biggs & Davis, 1963), but recent work has failed to show any inhibitory effect of pancreatin on iron absorption in patients with haemochromatosis or pancreatic disease. Kavin *et al.* (1967) and Murray & Stein (1967) demonstrated that ligation of the pancreatic duct had no effect on iron absorption in the rat.

Diagnosis of idiopathic haemochromatosis

Patients with primary idiopathic haemochromatosis may be difficult to distinguish from those suffering from cirrhosis and a secodary siderosis, for pigmentation, gonadal atrophy and diabetes can occur in either condition. However, liver biopsy is helpful, revealing gross iron overload (Grade 4) of the parenchymal cells with a relatively inactive cirrhosis, whereas in alcoholic cirrhosis there is much less iron (Grades 1–2, rarely Grade 3), often out of proportion to the activity of the cirrhosis. A raised percentage saturation of the total iron-binding capacity may also occur in either condition but estimations of the iron stores by phlebotomy (Conrad, 1968) suggest that the iron excess of cirrhosis is only 1–3 g, in comparison to 10–20 g in haemochromatosis.

Assessment of body iron stores by chelating agents

The recent introduction of the powerful chelators of iron, calcium diethylene triamine pentaacetic acid (DTPA) and desferrioxamine, has provided a simple and convenient method for measuring body iron stores (Powell & Thomas, 1967; Balcerzak *et al.*, 1968). The greater the iron stores, the more iron excreted in the urine after administration of the chelator. Unfortunately only a variable fraction of the chelated iron is excreted. Some is utilized for erythropoiesis, some is retained if renal function is poor and some is taken up by as yet unknown sites. Fielding (1965), therefore, developed a technique in which a marker dose of ^{59}Fe-labelled ferrioxamine is given simultaneously with the dose of desferrioxamine. From the proportion of the isotope that appears in the urine it is possible to calculate the total amount of ferrioxamine formed *in vivo*, the F_v value. A similar technique, using calcium DTPA, has also been developed (Barry, Cartei & Sherlock, 1968a).

Fielding's test has been used in the diagnosis and management of iron overload (Fig. 2). The mean F_v value for the controls was 252 mg/kg, with a range

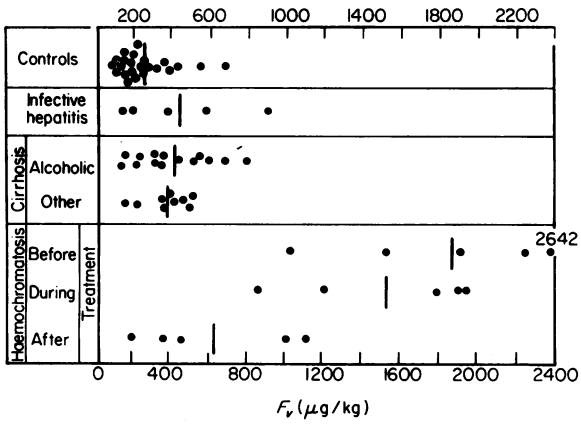

FIG. 2. F_v values in control subjects and various abnormal groups (from Smith, Studley & Williams, 1967).

of 81–693 μg/kg, while figures of from 1000 to 2650 μg/kg were obtained in five untreated cases of haemachromatosis, there being a progressive fall with venesection therapy. In contrast, only one patient with alcoholic cirrhosis had an increased F_v result, although there were ten patients in this group with siderosis on liver biopsy. The raised F_v value seen in one case of infective hepatitis may be due to haemolysis, for there is evidence that iron newly released by haemoglobin breakdown is more readily chelatable than that from the stores (Karabus & Fielding, 1967).

The higher the initial F_v value in haemochromatosis, the greater the body iron stores, and the longer must venesection be continued. Fig. 3 shows the results obtained in a patient who was venesected one pint of blood each week. By drawing a line through the initial F_v values, and extrapolating it to cut the time axis, it was possible to predict the approximate duration of venesection therapy.

Phlebotomy is a recognized method for assessing iron overload (Haskins *et al.*, 1952) and the results so obtained correlate well with measurements using the iron chelator desferrioxamine (Balcerzak *et al.*, 1968) and DTPA (Barry *et al.*, 1968b). This suggests that these chelators provide a reliable and accurate method for assessing body iron stores. In contrast, liver biopsy specimens have provided a far less accurate guide to body iron stores than the F_v value (Fig. 4).

Treatment and prognosis

If haemochromatosis is caused by iron overload, then the logical treatment is to remove the iron. Successful venesection therapy was first reported by Finch (1949), and since then many more examples have been described. The usual practice is to remove

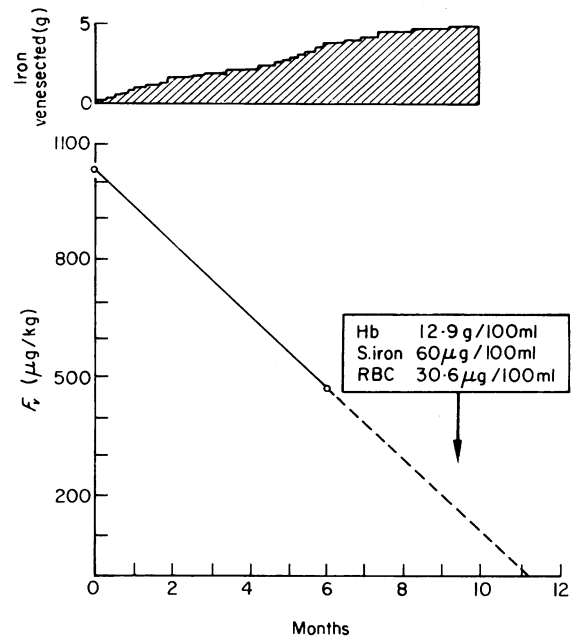

FIG. 3. Use of the differential ferrioxamine test in prediction of the duration of venesection therapy.

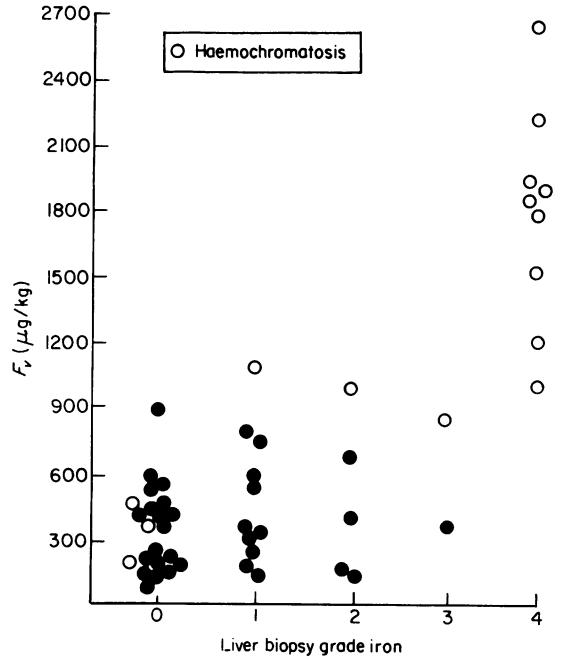

FIG. 4. Correlation of F_v values with liver biopsy stainable iron (from Smith *et al.*, 1967).

1 pint of blood each week, which contains approximately 250 mg of iron, but most patients will tolerate the venesection of up to 3 pints weekly (Crosby, 1958).

The haemoglobin concentration falls at first, but usually settles at 11–12 g/100 ml. After the removal of 50–80 pints iron deficiency is produced, shown by the appearance of an anaemia and the fall of the serum iron level to a low figure. The enlarged liver shrinks in size and the liver function tests return to normal. The enlarged liver shrinks in size and the liver function tests return to normal. The patient loses his lethargy and pigmentation and cardiac function improves. Insulin requirements may fall, but libido and body hair are not restored if absent. Repeat liver biopsies demonstrate disappearance of the tissue iron but usually little change in the underlying cirrhosis. However, no improvement occurs in the arthropathy associated with idiopathic haemochromatosis (Hamilton *et al.*, 1968). This consists of a progressive polyarthritis, together with chondrocalcinosis, usually starting in the metacarpophalangeal joints, but frequently involving the hips as well.

In a recently analysed series of forty treated patients the average amount of iron venesected was only 12·0 g in patients bled regularly and weekly (Williams *et al.*, 1968), considerably less than the quoted figures of 20–50 g (Finch & Finch, 1955). The survival rates of a group of patients, seen in the years before venesection had been introduced, were compared with a more recent, treated group. Whereas fifteen out of eighteen untreated patients died from causes related to haemochromatosis, only six of the forty treated patients so perished. Although hepatomas developed finally in both groups (three of the untreated and four of the treated group), liver failure as a cause of death appeared to have been eliminated by venesection therapy.

Focal iron overload

Idiopathic pulmonary haemosiderosis is a rare disease, characterized by repeated haemhorrhages into the lungs (Soergel & Sommers, 1962). The frequent occurrence of glomerulonephritis suggests that the vascular lesions of the lung are the consequence of antigen–antibody reactions, resulting in the rupture of small pulmonary blood vessels. The red cell iron is extravasated into the lungs, where it is fixed by alveolar and interstitial macrophages. In contrast, iron deposits are absent from all other organs, and an iron deficiency anaemia is present.

Renal haemosiderosis occurs whenever there is a a persistent glomerular filteration of free haemoglobin, as may occur in intravascular haemolysis, if the binding capacity of circulating haptoglobin and albumin is exceeded. Reabsorption of haemoglobin by the kidney and its consequent breakdown results in the storage of ferritin in the tubular cells, but renal function is not impaired as these cells turn over rapidly.

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