ance dose of ferrous glycine sulphate for up to 5 years. Thirty-three have maintained normal haemoglobin and plasma iron on one tablet daily. One man and 2 women began to relapse on this dose but have been maintained on 2 tablets daily.

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Iron Overload in Hæmochromatosis

Idiopathic hæmochromatosis is best considered as a clinical and pathological syndrome. Essential to the diagnosis is hepatic cirrhosis, often inactive, with Grade IV iron-deposition in the liver, iron being present in the cells throughout the liver lobules and in the Kupffer cells and fibroblasts (Williams 1968). Cutaneous pigmentation, gonadal atrophy and diabetes mellitus may or may not be present. The etiology of the iron overload remains the subject of controversy although it has been variously suggested that genetic (Williams *et al.* 1962), environmental (MacDonald 1966) and gastrointestinal luminal factors (Davis *et al.* 1966) may be responsible.

Assessment of Body Iron Stores

Many workers have shown that the iron excretion induced by the chelating agent desferrioxamine is a reflection of iron stores in hæmochromatosis. Verloop (1964) and Vannotti (1964) have suggested that this could be used to differentiate between hæmochromatosis and cirrhosis with siderosis although other workers have disagreed (Walsh *et al.* 1965). The development (Fielding 1965, 1967) of the differential ferrioxamine test in which a marker dose of ^{59}Fe-labelled ferrioxamine is given simultaneously with the desferrioxamine has proved a reliable index of iron stores (Smith, Studley & Williams 1967). Recently we have been able to test the validity of this latter technique by measuring the chelatable iron stores (Fv) serially during venesection therapy. The amount of iron removed from each patient was calculated from the volume and the hæmoglobin concentration of the venesected blood. In the 13 patients studied (Fig 1) there was a close correlation ($R = +0{\cdot}646$, $P < 0{\cdot}001$) between the change in Fv value and the amount of iron removed, and we would conclude that the differential ferrioxamine test is an accurate guide to storage iron.

A high serum iron and an increased percentage saturation of the iron binding capacity are often regarded as a good index of excess iron stores. However, when the Fv value was compared with the percentage saturation of the iron-binding capacity there was an obvious relationship but there was a wide scatter. We found that a number of patients had a high percentage saturation while the Fv value remained normal (Smith *et al.* 1969). This phenomenon occurs frequently during the early stages of iron reaccumulation after venesections cease, when serum iron rises rapidly before a significant build-up of chelatable iron.

Siderosis in liver biopsy specimens has long been regarded as a good guide to iron overload. We have been able to demonstrate a close correlation between the iron content as judged by a histological technique and the tissue iron level as measured by atomic absorption spectrometry, following a wet-ashing procedure. It has also been

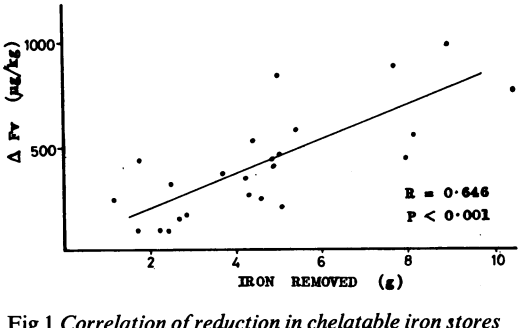

Fig 1 *Correlation of reduction in chelatable iron stores ($\triangle Fv$) with the actual amount of iron removed*

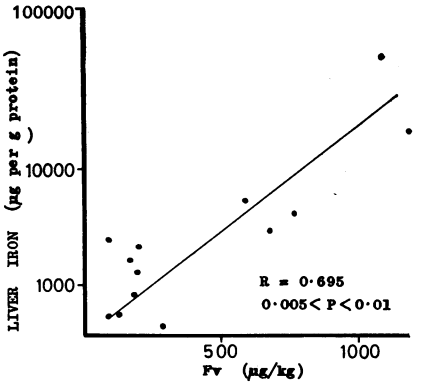

Fig 2 *Correlation of chelatable iron stores (Fv) with liver iron concentration using atomic absorption spectrophotometry*

possible to show a similar close correlation ($R = 0{\cdot}695$, $0{\cdot}005 < P < 0{\cdot}01$) between the Fv value and the liver iron content (Fig 2), both in the propositi and others with considerable iron overload. This technique of measuring tissue iron levels by atomic absorption spectrometry has proved helpful in our hands. For liver iron measurements only half of a standard liver biopsy specimen is required.

Iron Stores in Relatives of Hæmochromatotics

The relatives of patients with hæmochromatosis may show hepatic siderosis (Scheur *et al.* 1962). In a study of seven such asymptomatic relatives (Table 1) all had hepatic siderosis, though to a variable degree. In each patient the serum iron, percentage saturation of the iron-binding capacity, chelatable iron stores and iron absorption have also been measured. In only three instances were the chelatable iron stores increased and in these the increase was not great. Three patients had increased iron absorption suggesting that they might be actively increasing their iron stores and only two patients had a high serum iron and percentage saturation of the iron-binding capacity. Only two of these seven patients showed a high serum iron, chelatable iron stores and increased iron absorption.

The interpretation of these results suggests that the hepatic siderosis occurs at an early stage before the serum iron rises or the total body chelatable iron stores exceed normal. An alternative explanation might be that the liver iron in this situation is not available for chelation and is not in equilibrium with the serum iron.

Iron Absorption in Hæmochromatosis

Iron loss from the body is restricted to small amounts but only a slight increase in absorption is necessary to account for iron accumulation if it has been present over a prolonged period. In fact, little is known about iron absorption in hæmochromatosis. When it is studied at the time of diagnosis of hæmochromatosis it is usually normal (Smith *et al.* 1969), though of course still in excess of body needs. Venesection therapy produces an immediate and striking increase in iron absorption which is almost certainly due to marrow hyperplasia. After completion of venesections iron absorption tends to fall. In a series of 16 patients followed over a period of years, 11 showed a steady and progressive fall in iron absorption with time. However, it remained above the normal range in 9 of the 11 and only reached normal after $5\frac{3}{4}$ and $7\frac{1}{2}$ years in the other two. It is quite likely that this pattern is similar to that of hæmochromatosis patients in the presymptomatic stage of the disease when iron absorption may be increased but subsequently falls to within the normal range as the iron stores saturate.

Iron Reaccumulation

After venesections have ceased, patients with hæmochromatosis reaccumulate iron. It is possible to ascertain the rate of iron reaccumulation by serial measurements of chelatable body iron stores, to obtain an increment index (µg/kg/month). In Table 2 the parameters during iron reaccumulation are shown during various periods from less than one year to over five years. Mean values are shown throughout. The reaccumulation rate is initially high but then falls progressively with time so that after five years the chelatable iron stores are only increasing slowly. Iron absorption levels remain high during the early period of

Table 1

Results of a study of seven asymptomatic relatives of patients with idiopathic hæmochromatosis

Case No.	*Age and sex*	*Serum iron (µg/100 ml)*	*Saturation of iron-binding capacity (%)*	*Iron absorption (%)*	*Fv (µg/kg)*	*Liver biopsy Grade iron*
1	43(M)	90	24	19	152	I
2	56 (M)	60	28	32	238	I
3	61 (M)	145	51	20	257	III
4	43 (M)	145	54	15	207	III
5	58 (F)	135	51	7	498	I
6	61 (F)	200	82	37	375	II
7	22 (M)	250	96	63	365	II
Normal range		80–180	25–50	5–25	0–300	0

Table 2
Reaccumulation of iron after venesection in patients with hæmochromatosis

Time since last venesection (years)	*No. of cases*	*Iron absorption (%)*	*Serum iron (μg/100ml)*	*Saturation of iron-binding capacity (%)*	*Fv increment (μg/kg/month)*
0–1	10	56	167	60	39·5
1–2	12	53	252	93	32·1
2–5	7	56	241	96	15·8
over 5	7	43	198	82	12·2

iron reaccumulation, but these are mean values and they show a fall after five years.

Iron loss was studied in seven of our patients and compared with six healthy adult controls. After a single intravenous injection of ^{59}Fe citrate total body radioactivity was measured in a whole body counter over a period of 52 weeks. After the 22nd week increased iron loss was evident in the hæmochromatosis patients (Fig 3).

Factors Controlling Iron Absorption

Davis *et al.* (1966) demonstrated the presence in gastric juice of a substance, gastroferrin, which binds iron. They found this substance to be absent in patients with hæmochromatosis or with iron deficiency anæmia and postulated that it bound to iron in the stomach rendering it nonabsorbable. Wynter & Williams (1968) similarly found a binding substance in gastric juice but showed it to be simply a loose association with a glycoprotein, a finding which other workers have confirmed. Wynter & Williams were unable to demonstrate any difference in the iron-binding properties of gastric juice between hæmochromatosis patients and control subjects. We now believe that gastroferrin is an acid mucopolysaccharide although its role in iron absorption awaits detailed elucidation.

The role of ascorbic acid in the facilitation of iron absorption from the gut is well known. Wapnaik *et al.* (1968) noted low leukocyte ascorbic acid levels in two patients with hæmochromatosis and in twelve with transfusional siderosis. In a review of the ascorbic acid status of 63 patients with hæmochromatosis we were unable to demonstrate any correlation between the leukocyte ascorbic acid levels and either the chelatable iron stores or iron absorption. It seems unlikely that ascorbic acid plays any material role in the increased iron absorption of hæmochromatosis.

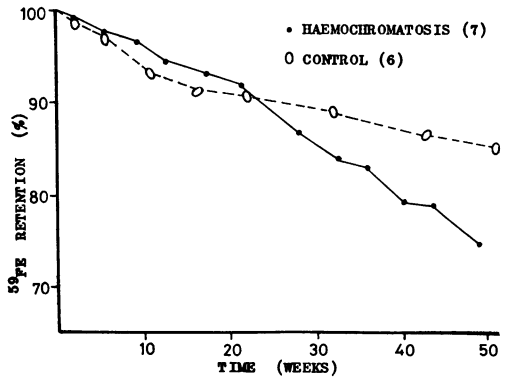

Fig 3 *Iron loss in hæmochromatosis patients and healthy control subjects measured as percentage retention of intravenously administered ^{59}Fe citrate*

Treatment of Hæmochromatosis

Regardless of the mechanism of the abnormal iron absorption in hæmochromatosis and how iron stores are increased, it is quite certain that the excess iron should be removed. The most effective means of accomplishing this is by venesection therapy. These patients tolerate venesections well and one pint can be removed weekly in most of them without ill effects. This effectively removed about 250 mg of iron and in most patients the excessive quantities stored are in the region of 10 – 20 g. Chelating agents have little to offer in the management of these patients in view of the slow rate of iron removal. Venesection therapy markedly improves the survival in hæmochromatosis and in the recent series of Williams *et al.* (1969) the 5-year mortality in the treated patients was 11% compared with 67% in those who were not venesected.

Arthritis

One complication of hæmochromatosis which does not respond to venesection therapy is the arthropathy. This is particularly disabling and affects principally the metacarpophalangeal joints of the hands. Other joints may be involved but much less frequently. Almost half of our patients have developed this complication, which is much more frequent in those whose first symptom of hæmochromatosis occurred before the age of 50 (Dymock, Laws, Hamilton & Williams 1970). Radiologically there is cyst formation and siderosis in the subchondral base with loss of articular cartilage. Chondrocalcinosis due to calcium pyrophosphate deposition may occur especially in the larger joints. Biopsy of these joints reveals synovial iron deposition (Dymock, Ansell, Hamilton & Williams 1970). The disorder is probably multifactorial: in addition to the presence and duration of iron overload, the age of the patient at the first symptom of hæmochromatosis appears to be important.

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Some Epidemiological Aspects of Iron Deficiency Relevant to its Evaluation

Iron deficiency is considered to be of sufficient importance in this and many other countries for substantial efforts to be directed towards its prevention. In Great Britain a considerable sum is spent each year in adding to flour a form of iron which radioactive isotope studies have shown to be almost completely unavailable to man (Ministry of Health 1968). In addition, some £5–6 million is spent each year on oral hæmatinic preparations prescribed under the National Health Service. Recently widespread population screening procedures to detect iron deficiency have been strongly advocated. Add to this the fact that in the USA and to a lesser extent in this country, powerful voices are calling for increased efforts to be directed at a national level towards the prevention of iron deficiency. Finch (1965), White & White (1968) and the US Council on Foods & Nutrition (1968) have all called for a very substantial rise in iron intake by an increase in the level of iron enrichment of foods. All these efforts to detect and more especially to prevent iron deficiency rest on the assumption that it is an important cause of morbidity in the community.

If anæmia matters then it should be possible to detect associations between circulating hæmoglobin level, and realistic indices of morbidity or function. If valid associations are found, then it should be possible to define a point, in terms of circulating hæmoglobin level, below which harmful effects occur which can be reversed by giving iron. The definition of such a point should be one of the main objectives of research on hæmoglobin level, or indeed on any quantitative variable.

Table 1
Change in symptoms with treatment of anæmia: Partial correlation coefficients ('r') of change in symptom grade on change in hæmoglobin level; age and initial hæmoglobin level held constant

Symptom	*'r'*
Irritability	− 0·12
Palpitation	− 0·03
Dizziness	− 0·05
Breathlessness	+ 0·01
Fatigue	− 0·13
Headache	+ 0·15

These results are not significant

However, an evaluation which is valid for the community must be based on representative population samples. Neither hospital patients, medical students nor laboratory animals adequately represent the community and there is no substitute for population samples. Then for an evaluation to be realistic, meaningful indices of morbidity or function should be used. Thus the measurement of symptoms may be crude but they may be a more realistic measure of morbidity than cardiorespiratory function, the interpretation of which in terms of morbidity may be very difficult. Futhermore, for an evaluation to be unprejudiced it is essential that all possible effects, whether harmful or beneficial, are examined and assessed. No less a figure than Galton complained that beliefs 'when they are of long standing, become fixed rules of life and assume a prescriptive right not to be questioned'. Since the era of leeching and bleeding passed, it has been unacceptable to question the belief that anæmia is harmful and that rich red blood is indicative of health and virility. Yet Walker (1969) questions whether the current assumption that to raise hæmoglobin level improves health is founded on any better evidence than was cupping and leeching.

This paper simply presents evidence relating to the importance of anæmia in the community.

Among the supposed harmful effects of anæmia are an increase in symptoms, an impaired cardiorespiratory function, an impaired psychomotor function, and an impaired ability to cope with stress, such as surgery. A series of studies in which we have looked at these and certain other effects are described. These studies have not been conclusive, indeed never can be, as one can never examine all the possible effects of iron deficiency.

Symptoms and Iron Deficiency

We have repeatedly failed to detect an association between hæmoglobin level and the severity of