GENETIC HEMOCHROMATOSIS

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Until recently hemochromatosis was considered both rare and "idiopathic". The fully expressed disease is now known to be only uncommon, not rare, and genetically determined. The hemochromatosis gene is carried by about 1 in 10 caucasians. Since two copies of the abnormal gene are required for full expression of this autosomal recessive condition, it can be estimated that one in every 350 to 500 caucasians is homozygous for this trait and so, at least, genetically predisposed to develop hemochromatosis.

The principal and perhaps only "hemochromatosis gene" is located on the short arm of chromosome 6 (Simon 1976, Simon 1980), within the HLA complex between the HLA-A and B loci (Lloyd 1978, Bassett 1979, Edwards 1986). The HLA-A3 allele is closely associated with the hemochromatosis gene. At least one copy of the A3 allele has been found in 74 percent of GH patients as compared with 28 percent of control subjects from the same populations. The GH gene is also associated with the HLA-B14 (26% versus 7%) and B7 markers (44% versus 26%) (Table 2; Simon 1976, Bomford 1977, Bassett 1979, Simon 1980, Motulsky 1979, Piperino 1986) (table 2; figures 1 and 2).

Since it became clear that "idiopathic" hemochromatosis was a genetic disorder, the terminology of iron loading diseases has evolved. In the past, this group of conditions was broadly referred to as hemosiderosis or, if there was iron-induced tissue injury, as hemochromatosis. These conditions were further qualified as idiopathic, or secondary to identifiable sources of iron overload. Currently, the idiopathic condition is designated hereditary- or genetic hemochromatosis (GH), with its "hemosiderosis" stage now being referred to as pre-cirrhotic hemochromatosis. The secondary forms of iron overload are referred to as siderosis or, when iron-induced cirrhosis has developed, as secondary hemochromatosis (table 1) (Kebt 1968).

Most secondary hemochromatosis cases are associated with anemias of two general types - those with a hypoplastic marrow in which the iron derives from repeated transfusions in the absence of blood loss, and those with a hyperplastic marrow plus ineffective erythropoiesis in which there is increased absorption of iron from the diet, with or without the additional burden of transfused iron (Schafer 1981). Dietary iron overload has always been very rare, except for that occurring in the Bantu of South Africa whose excess iron is ingested in the form of Kaffir beer brewed in iron vessels; this condition may decline since preference is said to be shifting toward commercial beers.

It is becoming clear that in a variety of conditions sometimes associated with increased iron stores, this excess it attributable to possession of at least one copy of the hemochromatosis gene. This association has been reported for sideroblastic anemia (Cartwright 1980), hereditary spherocytosis, porphyria cutanea tarda (Kushner 1985, Elder 1985) and heavy iron overload in certain alcoholics.

It is noteworthy that many more persons are genetically predisposed to develop hemochromatosis than actually are known to have the disease. Although failure to recognize the fully expressed disease for what it is was probably a major factor accounting for the rarity of the diagnosis in

the past, such oversight has become less likely with the advent of automated multichannel analyzers (SMA, etc) which have now made the serum iron determination a "routine" test in many areas, as well as the availability of serum ferritin determinations and other means of diagnosing GH which are discussed below. Nevertheless, clinically overt GH remains much less commonly recognized than the 1 in 350 to 500 frequency of caucasian homozygotes would lead one to suspect. Presumably the major contributors to this discrepency are the relative protection provided homozygous women by menstrual and gestational blood loss, and the observation that, for unclear reasons, in some patients the genetic abnormality is not fully expressed and there is less iron loading than expected, or although expressed to the extent of heavy iron overloading, tissue injury does not result from this.

PATHOGENESIS

Tissue injury in GH is directly related to the presence of excess iron (Edwards 1980). Although a given degree of iron overload results in less tissue injury if it is confined to the reticuloendothelial system as opposed to the parenchymal cells (as in the earlier stages of transfusion related siderosis), with continued iron loading, the RE system becomes saturated and further acquired iron "spills over" to the parenchymal cells. Considerable evidence indicates that, whatever the source of iron overload, the same degree and tissue distribution of injury results for any given amount of excess iron in that tissue. The same pattern of disease may develop in the highly transfused thalassemia major patient, for example, as is typical of advanced GH.

The most prominent aspect of the abnormal iron metabolism in GH is the absorption of iron from the GI tract at a rate inappropriately high for existing iron stores. The typical diet contains about 7 mg of iron per 1000 kcal, but under basal conditions only 1 mg/day of this is absorbed by men and 1.5 to 2.0 mg by women (table 3). Another abnormality unique to GH as distinguished from other iron loading conditions, is the relatively greater deposition of iron in hepatic parenchymal cells than in RE cells. Although an increased avidity of the liver for plasma iron has been postulated, the greater problem appears to be the relative inability of the RE cells to store iron. This is reflected in the finding in GH patients of less than expected stainable iron the bone marrow for a given degree of body iron overload, the presence of iron in smaller granules in circulating monocytes (figure 3; Saab 1986), and the lesser degree of iron deposition in the spleen (5 fold greater than normal) than in the liver (30 to 50 fold increased) (table 4).

CLINICAL MANIFESTATIONS OF GH

Excessive iron absorption is presumed to begin at or before birth, but usually does not result in sufficient total body iron accumulation to cause tissue injury until the patient reaches age 30 or more (figure 4). The major clinical features of GH are listed in table 5.

Cardiac involvement is said to be the most common cause of death directly

attributable to hemochromatosis (Cutler 1980, Short 1981, Furth 1985). Most often this presents as congestive cardiomyopathy, but a number of cases with restrictive features have been reported and, after amyloidosis, GH is the most common identifiable cause of restrictive cardiomyopathy in western countries. In addition, supraventricular tachyarrhythmias are frequent. While these features are somewhat proportional to the degree-, and perhaps to a greater extent to the rate of cardiac iron deposition, they do not correlate with the extent of myocardial fibrosis, which is often mild (Buha).

The percentage of **diabetic patients** in different series varies widely (table 3) (Powell 1971, Stocks 1973, Dymock 1972). As in the case of the general diabetic population, the major determinant of diabetes in hemochromatotics appears to be genetic, and the full spectrum of diabetic complications may be observed. The condition is aggravated by iron deposition in the islets, reducing the amount of insulin released in response to a glucose challenge. The diabetes is further aggravated by the development of cirrhosis, which may relate to the insulin resistance observed in some GH patients.

The **endocrinopathy** of GH is largely confined to hypogonadism (Stocks 1968, Kelly 1984). In the majority of cases this is a consequence of gonadotropin deficiency, apparently related to iron deposition in the anterior pituitary. However, a minority of cases (such as case 5 in table 6) are due to primary testicular failure (ref). Clinically significant thyroid or adrenocortical hypofunction is uncommon.

The **cirrhosis** of GH is somewhat atypical in that it is less often associated with ascites, encephalopathy and variceal hemorrhage than seen in patients with other forms of cirrhosis (Kent 1968). The great majority of patients have moderate to marked hepatomegaly. Unlike alcoholic cirrhotics, GH patients do not develop gynecomastia. This difference is attributed to the low normal estrogen levels in GH patients in contrast to the elevated levels of estrogens, derived from conversion of androgens, seen in alcoholic subjects (figure 5; Kley 1985a, Kley 1985b). Hepatocellular carcinoma is a terminal complication of GH in 20 to 30% of cirrhotic patients. Although the increased frequency of other neoplasms has been reported, other authors fail to observe such an association.

The **arthropathy** of hemochromatosis resembles osteoarthritis clinically and, in addition, often has the radiologic features of chondrocalcinosis (pseudogout) (Hamilton 1981). Joints most often involved, symmetrically, are in the hands, notably the second and third metacarpophalangeal joints, the hips and the knees (Kra 1965).

Hyperpigmentation is often present, but in light skinned people, it may be quite subtle. The sun exposed areas are particularly affected, and the pigmentation ranges for tan to grayish. This range of shades probably reflects varying proportions of melanin and dermal iron deposits. Hemosiderin (i.e., stainable iron) in eccrine sweat glands is particularly characteristic of GH, but not enough so to justify use of skin biopsy as a means of definitive diagnosis.

Chronic **abdominal pain** is frequently noted in GH patients. Many cases are

difficult to explain, but may improve with phlebotomy therapy.

Causes of death among 45 patients studied by Williams et al (Bomford 1976) are listed in table 7.

DIAGNOSIS OF GENETIC HEMOCHROMATOSIS

Since GH is not rare and can usually be ruled out on the basis of results of inexpensive tests, this diagnosis should be considered in any patient with a consistent family- or individual history, symptoms, physical signs or laboratory data.

Markers of iron overload are summarized in table 8 (Valberg 1980). The great majority of patients with clinically manifest GH will have an elevated serum iron concentration (> 170 µg/dl) and a reduced total iron binding capacity, resulting in a greatly elevated "transferrin saturation" (figure 6). (Note: "transferrin saturation" is an obvious misnomer; this is actually a calculation of percent saturation of the TIBC. With the advent of parenteral alimentation, it has become common practice for laboratories to determine the transferrin concentration directly and to calculate the TIBC by multiplying the transferrin concentration by 1.42. This correction factor is based on the realization that each transferrin molecule has two iron binding sites. However, from several studies in which both serum transferrin and TIBC were measured directly in the same serum samples, a more appropriate conversion formula can be proposed; TIBC = 1.25 X [transferrin] (Stromberg 1982, Markowitz 1983, Short 1984).

The serum ferritin concentration is a powerful marker of total body iron stores (figure 8; Worwood 1982). Values are elevated, typically over 1000 µg/l, in essentially all patients with overt hemochromatosis and the great majority of adults with pre-symptomatic GH. However in 5 percent or less of hemochromatosis kindreds, the serum ferritin concentration may seriously underestimate iron stores in pre-cirrhotic homozygotes. On the other hand, ferritin levels may be grossly elevated independent of iron stores in patients with liver cell injury or any cause. This leads to the greatest diagnostic difficulty in alcoholic patients. Serum ferritin levels are also "falsely" elevated in a variety of conditions associated with inflammation, neoplasm, or increased red cell turnover (figure 10). These issues are further discussed below. Different isoferritin patterns, distinguished on the basis of their isoelectric points, are found in different tissues (figure 9). The distinctive properties of these isoferritins is believed to reflect their differing proportions of the two subunits, H ("heart") and L ("liver"). Several years ago Isselbacher et al observed that in heart and other organs of GH patients to isoferritin pattern was abnormal, being the same everywhere as in the liver. The suspicion that this was a primary abnormality of GH patients was disproven when it was shown that the isoferritin distribution returned to normal in iron depleted hemochromatotics.

Cartwright's group has demonstrated that as a screening test for iron overload, transferrin saturation is actually a better marker than serum ferritin concentration (figure 7).

The deferoxamine (Desferal) test - measurement of urinary iron (feroxamine) excretion during the 6 hours to 24 hours following an injection of 0.5 to 1.0 gram of deferoxamine - is no longer used in most centers (Cumming 1969). The effort and expense of performing this test are not justified by the limited value of the information obtained.

Recently interest has developed in measurement of erythrocyte ferritin concentration as a possibly more specific indicator than serum ferritin for total body iron stores (Van der Weyden 1983). A red cell ferritin assay has been established by Dr. Eugene Frenkel and Mr. Jerry White at the Dallas VAMC Nuclear Medicine laboratory. While there has not yet been an opportunity to test the blood of an untreated GH patient in this assay, a sample from a GH patient who has thus far been phlebotomized 85 units had a red cell ferritin concentration among the highest yet found in this laboratory - 650 attograms/cell (normal; 3 to 50 ag/cell). Fifty to 70-fold elevations of RBC ferritin are reported to occur in GH patients, as well as in patients with certain hematologic disorders listed in figure 10. Levels decline when iron stores are depleted by phlebotomy (figure 11). Of greatest importance is the finding that those commonly leading to spurious elevations of the serum ferritin (upper panel, figure 10) have a considerable smaller influence on the red cell ferritin level. Samples from a number alcoholic patients having a highly saturated TIBC and ferritin concentration exceeding 1000 µg/l have been tested in the DVAMC assay; all have had RBC ferritin values only 3 to 6-fold elevated. If further experience with this test verifies its promise as a more specific indicator of iron overload, this will facilitate the confirmation or, more commonly, the exclusion for GH as a serious diagnostic consideration.

A semi-quantitative estimate of liver iron overload can be obtained from the hepatic attenuation values obtained from a computed tomographic image of the liver (Chapman 1979, Howard 1983, Roudot-thoraval 1983) (figures 12-14). However, at the present time, this cannot be regarded as a final diagnostic procedure. Therefore one cannot justify the expense of CT for this isolated purpose.

In most cases of suspected GH, a liver biopsy should be performed for histological examination, iron stain (Perls' prussian blue stain) and quantitative iron determination. When GH is suspected, it is our practice at the time of biopsy to set aside a 5 to 10 mm segment of the needle biopsy in a metal-free vial provided by the Mayo commercial laboratory. This sample is then set aside (refrigerated or frozen; sterility not essential) until results of the tissue iron stain are available. If this stain demonstrates increased liver iron deposits, the sample is sent to the Mayo lab, in the pre-addressed and stamped container provided by them, for quantitative iron determination. Results are usually available, by telephone, within a week; the cost is about $50.00. This assay is also performed locally at the Baylor Hospital laboratory, at the same cost and with the same turnaround time.

As noted, liver iron concentration should be determined if iron stains of the biopsy indicate increased iron stores (Brissot 1981). Various grading systems have been devised to describe the degree of hepatic iron staining. In general, hepatic iron overload can be ruled out if there is either no

stainable iron (grade 0 in all systems) or if there is stainable iron in fewer than 20% of hepatocytes (grade 1). However, significant iron overload may or may not be present if more extensive staining is observed. In such cases a quantitative iron measurement should be performed (figure 15).

The normal value for liver iron concentration is up to about 1000 µg/g, dry weight (dw), or 0.1 percent iron, dw. The great majority of male GH homozygotes over age 40 have liver iron concentrations 10-fold or more greater than the upper limit of normal, that is, more than 10,000 µg/g or 1.0%, dw. Younger GH patients, or female homozygotes of any age may have lesser increases in liver iron; these are often "discovered" cases, identified during screening of relatives of patients with overt GH. A surprisingly good correlation has been demonstrated between liver iron concentration and the total amount of iron mobilizable by phlebotomy (figure 16) (Bassett 1986). Other causes of hepatic iron concentrations exceeding 1.0% dw include those conditions leading to secondary hemochromatosis, that is, in most cases, transfusional iron overload in patients with thalassemia major and hypoplastic anemias. There occasional case reports of extremely rapid and heavy hepatic iron deposition during the few years after portal-systemic shunt surgery of cirrhotics who did not have excessive stainable liver iron at the time of surgery (Sabesin 1964, Ecker 1968, Conn 1972). This phenomenon is rare and poorly understood.

In the majority of patients with hepatic iron overload in the intermediate range of 0.1 to 1.0% are either alcoholics or GH heterozygotes.

SIGNIFICANCE OF THE HETEROZYGOUS GH STATE

As noted above, as many as 10 percent of caucasians are carriers of a single hemochromatosis gene. A number of studies indicate that roughly one fourth of such carriers may have abnormal screening tests for iron overload - elevated serum iron, transferrin saturation and serum ferritin, and depressed TIBC (figure 17; Valberg 1980). Fortunately, the heterozygote ceases his increased rate of iron absorption at a time when only 3 to 5 grams of excess of total body iron have accumulated - never enough to cause tissue injury. This plateau of iron stores is reached by middle age (figure 18). More than this amount of iron may accumulate, and tissue injury result, in heterozygotes who also have other reasons for increased iron absorption, such as sideroblastic anemias or hereditary spherocytosis (table 9) (Bassett 1981, Dadone 1982).

IRON OVERLOAD IN ALCOHOLICS

A number of patients with alcoholic liver injury have abnormal serum iron and ferritin levels, often independent of iron stores as discussed above, as well as modest increases of stainable iron in the liver biopsy (table 10; figure 19) (Chapman 1982). The cause(s) of this minor iron loading is unknown; postulated mechanisms are listed in table 11. Liver iron concentrations fall into the range of 0.1 (the upper limit of normal) to 0.5%, dw. Phlebotomy demonstrates that such patients have accumulated

only a few grams of excess iron. It has been shown that such "therapeutic" phlebotomy is of no benefit to these patients, indicating that this modest degree of iron overload does not aggravate the alcohol-induced liver injury (Grace 1971). Surprisingly, there is little evidence that this group of iron overloaded alcoholics is enriched with GH heterozygotes.

A second, quite different group, consists of alcoholic patients with marked increases in total body iron burden, with liver iron concentrations exceeding 1.0% dw. The study of Le Sage et al at the Mayo Clinic (1983) provides evidence suggesting that such patients are indeed GH homozygotes. The starting point of the Mayo study was a search of pathology records for all liver biopsies in which grade 3 or 4 iron staining of hepatocytes, that is, stainable iron in over 50% of hepatocytes, was observed. (liver biopsies are routinely stained for iron at the Mayo Clinic). A group of 61 such patients was studied. Twenty of these were alcoholic. Relatives of both alcoholic and non-alcoholic patients were examined for evidence of iron overload (figure 20), and such evidence was found in relatives of 9 of the 20 alcoholics and 16 of the 41 non-alcoholics. Quantitative liver iron determinations indicated that all had levels near or exceeding 1.0% dw (figure 21). It is of interest that although the mean liver iron concentration was lower in alcoholic than non-alcoholic subjects (figure 21), the total amounts of iron removable from these subjects were the same in the two groups, averaging 20 grams (figure 22). This finding suggests that the alcoholic patients stored more of their iron burden in extrahepatic sites. It was concluded from this study that if more than 50% of hepatocytes in a liver biopsy stain for iron, quantitative iron measurement should be performed, and if the concentration exceeds 1% dw, regardless of alcohol consumption, the patient probably has genetic hemochromatosis.

TREATMENT

Phlebotomy is the standard treatment for genetic hemochromatosis (Frey 1961, Cohen 1984, Valberg 1985). Patients with overt disease usually have from 10 to 40 grams of excess storage iron. The customary estimate is that each 500 ml phlebotomy removes 250 mg of iron. However, this figure tends to overestimate the effectiveness of phlebotomy somewhat. In the first place, iron is removed at the rate of 3.4 mg per gram of hemoglobin, and consequently the hemoglobin level must be 14.7 g/dl in order to remove 250 mg of iron per unit of blood. At least in the early weeks of phlebotomy, and longer in some patients, hemoglobin levels tend to be lower than this (figures 23 and 24). In addition, soon after beginning a course of venesection, iron absorption from the diet increases from 1 to 2 mg/day, a near normal level (but inappropriately high for the iron stores present) to a level of 4 to 5 mg/day.

The patient is usually bled once or twice weekly, depending primarily on whether he is able to maintain his hemoglobin concentration above 11 g/dl. During the course of phlebotomy it is not essential to monitor any of the iron tests more than every few months. As illustrated in figures 24 and 25, serum iron and transferrin saturation remain elevated and the TIBC depressed until the greatest part of the iron burden is removed, but the

serum ferritin declines progressively as iron stores diminish. Various end points for the phlebotomy program have been suggested, including failure of the hemoglobin to return to 11 grams within 3 weeks, decline of the serum ferritin to less than 20 µg/l, and of the serum iron to less than 100. It may be necessary to continue phlebotomy at reduced, intermediate frequency of once or twice per month as tolerated to mobilize the most resistant residual iron deposits. Finally, when liver biopsy indicates sufficient iron depletion, these patients should be phlebotomized at a frequency of once every 2 to 3 months, as needed to keep the serum iron level below 150, for the rest of their lives. Discontinuation of phlebotomy soon leads to the return of fully saturated transferrin and rising serum ferritin levels (figure 26).

The use of deferoxamine, by daily intramuscular injection or more effectively by daily 12 overnight subcutaneous infusion is the only means available to remove excess iron from most patients with secondary hemochromatosis (Propper 1982). In most instances the fundamental problem of these patients is anemia which (usually) precludes phlebotomy therapy. Since Desferal therapy is less convenient and more expensive than phlebotomy, its use is rarely indicated for treatment of genetic hemochromatosis. Deferoxamine therapy has been advocated occasionally for initial treatment of GH patients with circulatory instability due to iron-induced cardiomyopathy.

EFFECT OF THERAPY

The earliest and, particularly for the patient, most noteworthy effect of phlebotomy therapy is an improvement in the energy level and sense of well-being, displacing the severe physical and mental lethargy and fatigability these patients often present with (Bomford 1976, Niederau 1985). The pigmentation fades, hepatomegaly subsides, and abdominal pain diminishes. Significant improvement in cardiac function has been reported in a number of patients (figure 27) (Easley 1972), but during the first year or so of iron mobilization the patient may continue to have considerable electrical and mechanical cardiac instability, and these persons must be monitored closely (figure 28). In perhaps a third of diabetic patients, insulin requirements diminish and the disease becomes easier to control. However, rarely can insulin be discontinued. Although the hypogonadism has generally been considered irreversible, a recent study has, in fact, demonstrated improvement with phlebotomy therapy (Kelly 1984). Reversal of cirrhosis following phlebotomy therapy has been reported (Knauer 1965); if, in fact, this ever occurs, it is rare.

The arthropathy, in general, does not improve and, in fact, may worsen despite iron depletion. This is only partly attributable to the relative resistance to mobilization of synovial hemosiderin (Kra 1965).

Finally, the high risk for development of hepatocellular carcinoma persists in cirrhotic GH patients even several years after successful maintenance of normal iron stores by phlebotomy. The most hopeful aspect of this matter is Powell's data suggesting that the risk of hepatoma can be reduced or eliminated if the patient's iron stores are normalized prior to the development of cirrhosis.

SCREENING RELATIVES OF GH PATIENTS

Once a patient with GH is identified, it is important to notify, with the patient's permission, his surviving first degree relatives - parents, siblings and children - of the need to be screened for GH (Edwards 1977, Edwards 1984). Obviously, all natural children and both parents will be (at least) obligate heterozygotes and therefore, as noted above, some of these relatives are expected to have abnormal levels the various iron-related screening tests. A copy of the letter which is sent to relatives of Dallas VAMC patients is included in this protocol (not copy-protected).

There is not complete unanimity among various experts as to the optimal screening program for relatives. At minimum, the available first degree relatives should have serum iron and TIBC determined, with calculation of transferrin saturation from these data. Most authors prefer to measure serum ferritin in addition (figure 17), and this test is useful if elevated levels are found (Beaumont 1979). However, as noted before, in 5% of less of kindreds ferritin elevation lags well behind iron loading in pre-cirrhotic GH patients (Wands 1976, Crosby 1977). Since there is considerable diurnal variation in the serum iron levels (but not TIBC), which may be 30 µg/dl higher in the morning than late in the day. Accordingly, it has been recommended the serum iron value should be determined on the basis of the average of 3 consecutive weekly measurements.

If the serum iron, transferrin saturation, and/or serum ferritin values are elevated, liver biopsy for evaluation of histology, iron staining and quantitative iron determination should be seriously considered.

The use of HLA typing for screening relatives is more controversial (Bomford 1977). There is general agreement that this would be appropriate if and propositus has siblings age 20 years or less. Such testing, which costs roughly $250.00 for A and B locus typing, is less easy to justify for relatives, particularly males, over age 40 since homozygotes above this age are quite likely to have abnormal screening results leading to liver biopsy and a decision of heterozygous versus homozygous status based on measurement of liver iron concentration (Bassett 1979, Lloyd 1978).

If a homozygote has young children, realizing that there is about one chance in 10 that his wife is (at least) heterozygous for the GH allele, each of his children therefore has roughly a 5% risk of being a GH homozygote. It has been suggested one can more accurately estimate the probability that any such child is a GH homozygote when the status of the unaffected parent is unknown by considering the association between the hemochromatosis gene and the HLA-A3, B14 and B7 antigens (Lin 1985). Accordingly, it was proposed that if the HLA haplotype acquired from the unaffected parent is A3,B14, it is nearly certain that the hemochromatosis gene is also present on that chromosome, and therefore that this child is a GH homozygote. Such a child should be followed very closely in anticipation of the need for prophylactic phlebotomy. At the opposite extreme, if neither A3, B14 or B7 are inherited from the unaffected

parent, these authors calculated that the risk of GH homozygosity is 2.5%, which is less than for a caucasian haplotype selected at random.

Letter to relatives of hemochromatosis patients

(Date)

To the relatives of (parents, brothers and sisters, and children over age 10 years):

Mr. has recently has been diagnosed as having a condition called genetic hemochromatosis. This is an inherited disorder. In patients with hemochromatosis both iron-controlling genes are abnormal, one abnormal gene inherited from each parent. (The parents usually do not have hemochromatosis since one of their iron-controlling genes is normal and this is enough to allow them to handle iron normally.)

In normal persons, only about one-tenth of the iron in the diet is absorbed into the body. Persons with hemochromatosis absorb more than this, and over a period of many years this leads to excessive levels of iron stored in the liver and other organs. If it is not removed in time, the excess iron may cause damage to these organs.

Since hemochromatosis is an inherited condition, there is some chance that you, as a close blood relative of Mr. , may also have this condition. For this reason we advise that you take this letter to your doctor. He should do the following tests; total serum iron (TSI) total iron binding capacity (TIBC), and serum ferritin. If the ratio of TSI/TIBC is above 50%, the TSI and TIBC should be done twice more at times one week apart; if the average TSI/TIBC derived from these three determinations exceeds 50%, further tests to rule out hepatic iron overload should be done. If results of these "screening" tests are normal, it would be reasonable to repeat them in the children every two years until they reach age 20.

If you do not have a personal doctor, I recommend that you contact one of the following physicians, listed alphabetically;

Sincerely,

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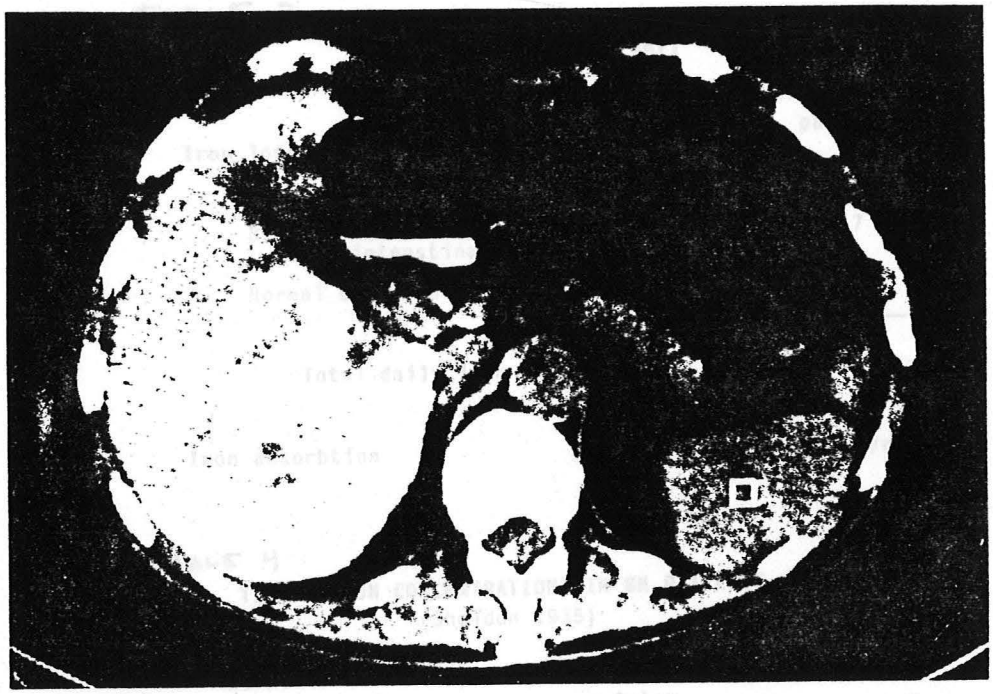


Figure 12: Non-contrast upper abdominal CT image: homozygous GH patient. Liver attenuation (103 HU) is obviously much greater than that of the spleen (53 HU); the marker box overlies the spleen. Spleen and liver attenuation normally are about the same. The liver iron concentration was 2.9%, dw. (Kindly provided by Dr. Sheldon Blend).

Table 2

TABLE 2 FREQUENCIES OF HLA ANTIGENS

	No. of Patients		Frequency (Per Cent)					
			HLA-A_3		HLA-B_{14}		HLA-B_7	
	*IHC**	*Control*	*IHC*	*Control*	*IHC*	*Control*	*IHC*	*Control*
Simon *et al.*[122]	51	204	78.4†	27.0	25.5†	3.4	49.0	27.9
Simon *et al.*[130]‡	154	439	73†	29	31†	8	39	27
Bassett *et al.*[129]	15	–	60†	22	–	–	–	–
Bomford *et al.*[124]	35	95	69†	31	20	6	34	20
Laukens *et al.*[127]	12	40	83.3†	25.0	0	7.5	75.0†	15.0
Walters *et al.*[125] / Shewan *et al.*[126]	13	–	92	–	15.4	–	84.6	–
Cumulative	280 (A_3) 265 (B_7, B_{14})	778	73.9	28.4	26.4	6.6	44.2	25.8

*IHC = idiopathic hemochromatosis.
†Difference statistically significant.
‡These data may include some of Simon's earlier patients.

N. Grace in: Zakim & Boyer: Hepatology 1982

TABLE 3

IRON BALANCE (mg/day)

	Normal persons	GH patients
Iron loss		
Skin and sweat	0.2	0.7
Biliary excretion and shed intenstinal mucosa	0.2	0.7
Normal GI blood loss	0.6	0.6
Total daily iron loss	1.0	2.0 mg/day
Iron absorbtion	1.0	4.0 mg/day

TABLE 4

TISSUE IRON CONCENTRATIONS IN GH PATIENTS
(Sheldon 1935)

Normal or minimally increased
- Brain
- Colon

Moderately increased (<10X normal)
- Spleen (5X)
- Adrenal
- Testis
- Lungs
- Kidney
- Bone

Markedly increased (>10X normal)
- Pancreas (100X)
- Thyroid (20X)
- Salivary glands (60X)
- Heart (10-15X)
- Liver (40 - 50X)

Table 5

Frequency of Major Clinical Manifestations in Three Series of Patients

Manifestation	Reference 13	Reference 14	Present Series
	←	%	→
Hepatomegaly	93	76	54
Increased SGOT*	···	54	46
Cirrhosis (biopsy)	···	94	57
Arthropathy	···	47	57
Heart failure	33	35	0
Hypogonadism†	18	61	29
Skin pigmentation	85	82	51
Clinical diabetes	72	53	6

* SGOT = serum glutamic-oxalacetic transaminase.
† Percentage of male patients.

Table 6. Testosterone and Gonadotropin Values in Six Impotent Patients

Patient	Testosterone	Dihydrotestosterone	Luteinizing Hormone	Follicle-Stimulating Hormone
	ng/dL		*mIU/mL*	
1	41	10	1.2	2.0
2	230	···	3.4	1.0
3	16	8	1.0	1.0
4	230	···	8.0	4.3
5	230	15	35.0	32.0
6	325	18	7.2	2.1
Normal values	250–1370	18–128	5–25	5–20

Table 7

CAUSES OF DEATH IN 45 TREATED AND 26 UNTREATED PATIENTS

Cause of Death	Treated (%)	Untreated (%)
Hepatoma	29	19
Other neoplasms	22	–
Hepatic failure	11	27
Variceal bleeding	4	15
Congestive cardiac failure	9	12
Myocardial infarction	9	8
Bacterial infections	5	11
Diabetic coma	2	8
Others	9	–

Table 8

INDICATORS OF BODY IRON OVERLOAD

	Normal Subjects	GH Patients
Serum iron (µg/dl)	<170	>170
Transferrin saturation (%)	25 - 50	50 - 100
Serum ferritin (µg/L)	M 20 - 300 F 20 - 120	300 - 5000
Stainable hepatic iron (Grade 0 to 4)	0 - 1	3 - 4
Hepatic iron conc. (µg/g dw)	500 - 1000	10,000 - 50,000

Table 9

SIGNIFICANCE OF THE HETEROZYGOUS GH STATE

- Approximately 1 in 10 caucasians is a GH heterozygote.
- One-fourth of heterozygotes have increased iron absorbtion.
- Increased iron stores limited to 3 to 5 g - no tissue injury.
- The GH heterozygous state may account for the increased iron stores found in some patients with:
  - Porphyria cutanea tarda
  - Sideroblastic anemias
  - Hereditary spherocytosis
  - Myopathy of dialysis patients

Table 10: Increased Hepatic Iron Concentration in Patients with Alcoholic Liver Disease : Possible Causes

1. Direct effect of alcohol on iron absorbtion?
2. Heterozygous genetic hemochromatosis?
3. Red wine?
4. Folate deficiency?
5. Increased hepatic uptake if desialylated TF

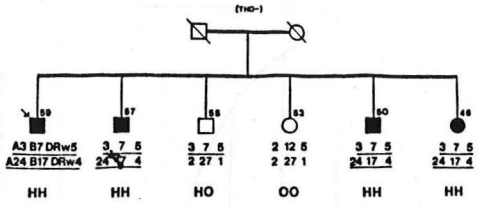


FIG. 1 HLA typing of a hemochromatosis family demonstrating identical HLA haplotypes in affected siblings and nonidentical haplotypes in unaffected siblings. HH: homozygous; HO: heterozygous; OO: homozygous-normal. Ages represented by small numerals. Arrow indicates proband.

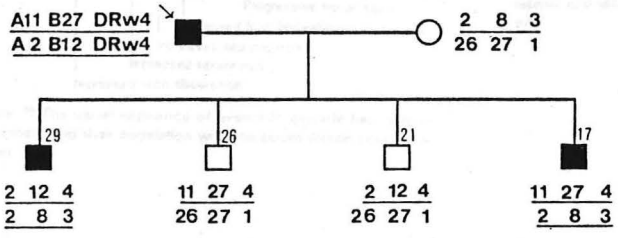


FIG. 2 Family tree illustrating a probable homozygous-heterozygous mating (Family O in Tables 1 and 2). HLA A, B, and DR typing shown. HLA haplotypes putatively carrying the IHC gene are *underlined*. The two affected offspring have inherited a common HLA haplotype from the unaffected parent (A2 B8 DRw3). *Arrow* indicates proband.

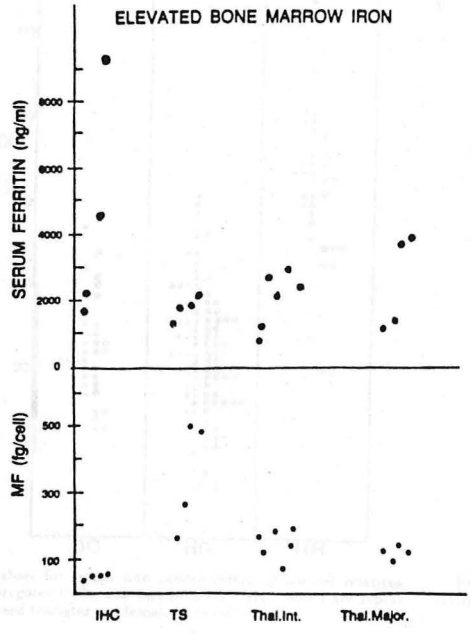


Figure 3 Serum and monocyte ferritin (SF and MF) in IHC, TS, thalassaemia intermedia (Thal. Int.) and major (Thal. Major) with elevated bone marrow iron stores.

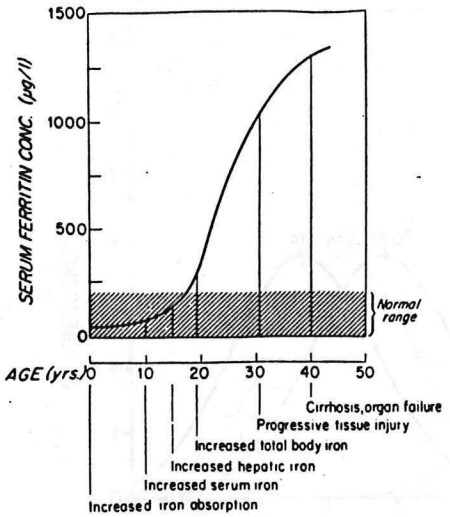


FIG. 4 The usual sequence of events in genetic hemochromatosis and their correlation with the serum ferritin concentration

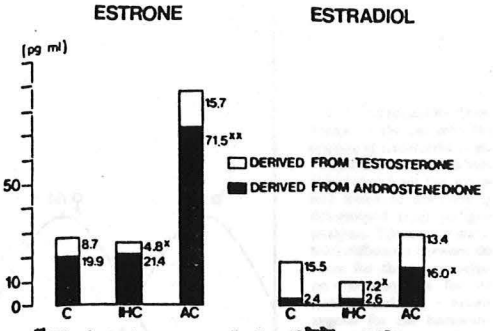


FIG. 5 The instantaneous contribution ($C_{ES}^{Pre_{Pre}} \times PC^{Pre}$) of plasma testosterone and androstenedione in normal men (C), IHC, and AC to estrone and estradiol. ^{x}, $P < 0.05$; ^{xx}, $P < 0.01$ (compared to normal men).

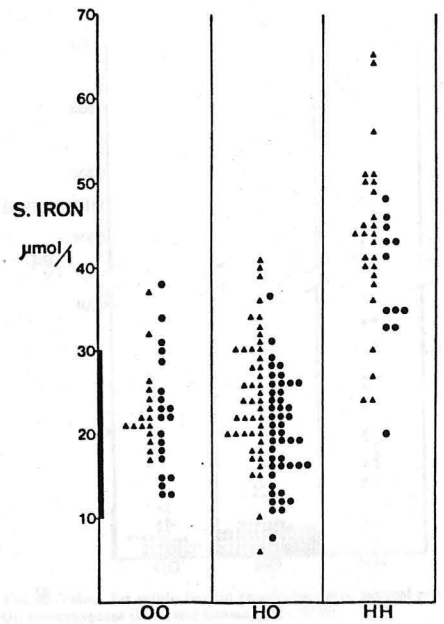


FIG. 6 Values for serum iron concentration in normal relatives (OO), heterozygotes (HO), and homozygotes (HH). Males are represented by closed triangles and females by closed circles.

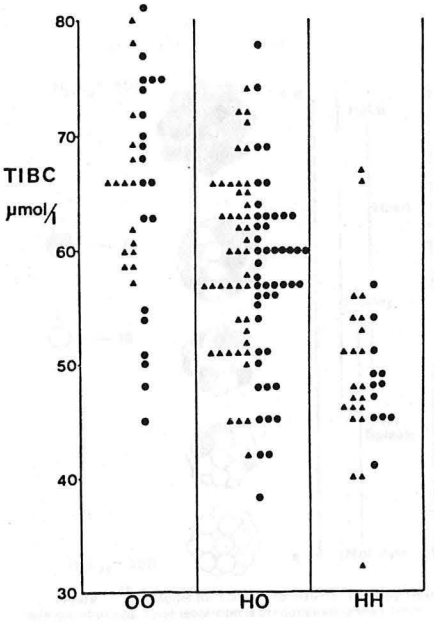


FIG. Values for TIBC in normal relatives (OO), heterozygotes (HO), and homozygotes (HH).

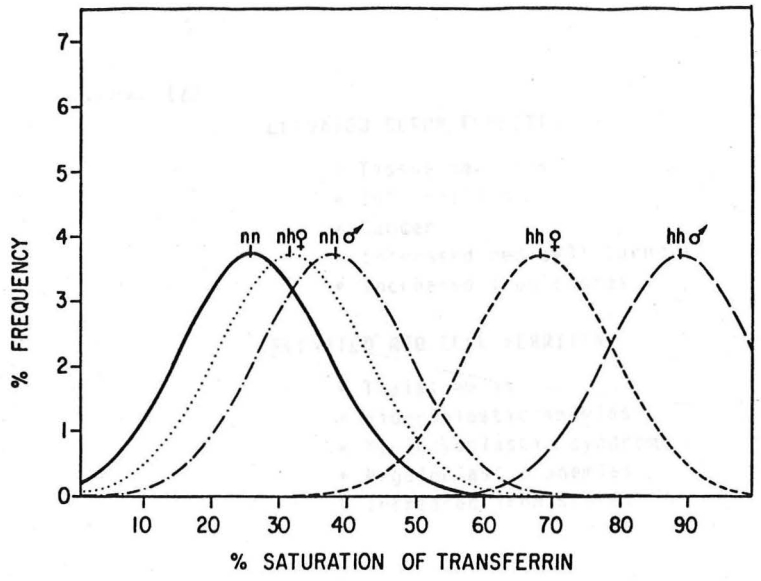


FIG. 7 Probability distribution of the per cent saturation of transferrin by genotype and sex. Curves were calculated from the means and standard deviation as determined from pedigree analysis. There is no statistical difference between the sexes for the nn genotype. nn = homozygous for the normal allele; nh = heterozygous for the hemochromatosis allele; hh = homozygous for the hemochromatosis allele; ♂ = males; ♀ = females.

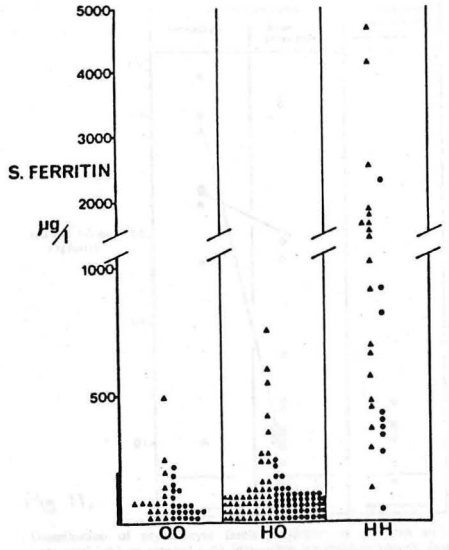


FIG. 8 Values for serum ferritin concentration in normal relatives (OO), heterozygotes (HO), and homozygotes (HH).

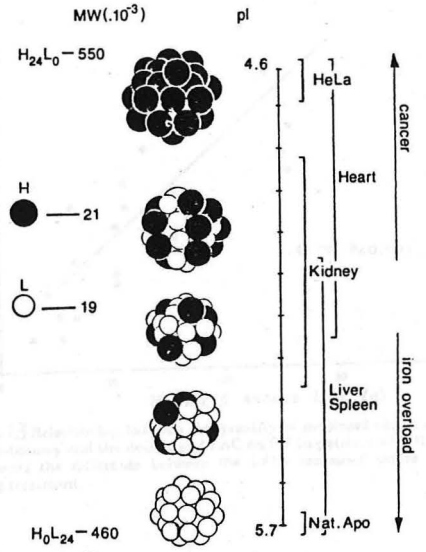


Figure 9 Model for human isoferritins, showing typical tissue distributions. Liver isoferritin is predominantly the L form.

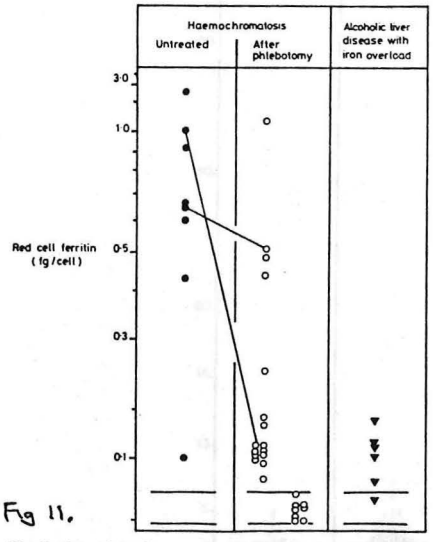
Figure 10

ELEVATED SERUM FERRITIN

- Tissue necrosis
- Inflammation
- Cancer
- Increased red cell turnover
- Increased iron stores

ELEVATED RED CELL FERRITIN

- Thalassemias
- Sideroblastic anemias
- Myelodysplastic syndrome
- Megaloblastic anemias
- Increased iron stores



Fg 11.

Distribution of erythrocyte ferritin content in patients with untreated (●) or treated (○) idiopathic haemochromatosis and patients with alcoholic liver disease with iron overload (▼). Horizontal bars indicate normal range.

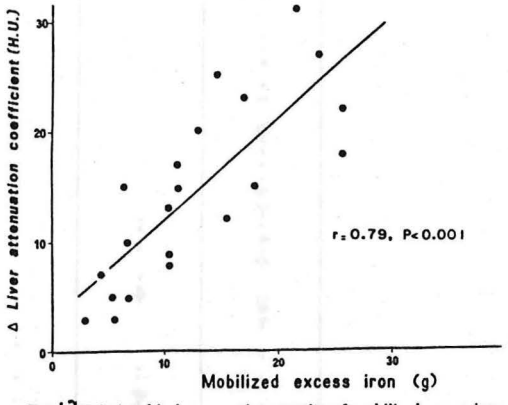


FIG. 13 Relationship between the quantity of mobilized excess iron by phlebotomy and the decrease of LAC on CT in patients with IH. Δ represents the difference between the LACs measured before and during treatment.

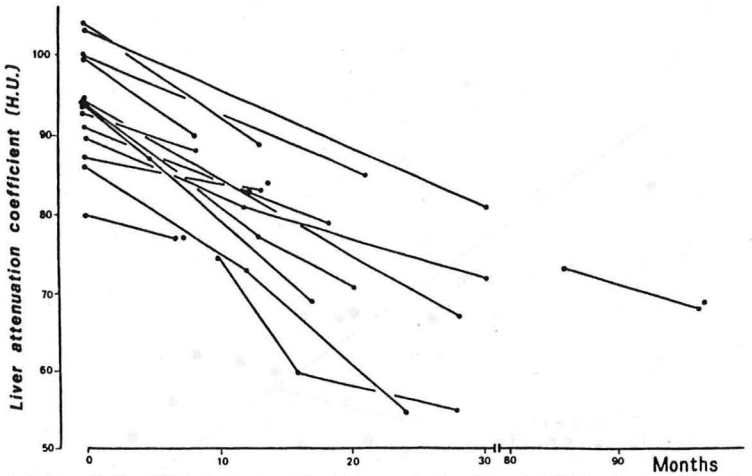


FIG. 14 Evolution of LAC on CT during treatment by phlebotomy in 15 patients with IH. *, patients with irregular treatment.

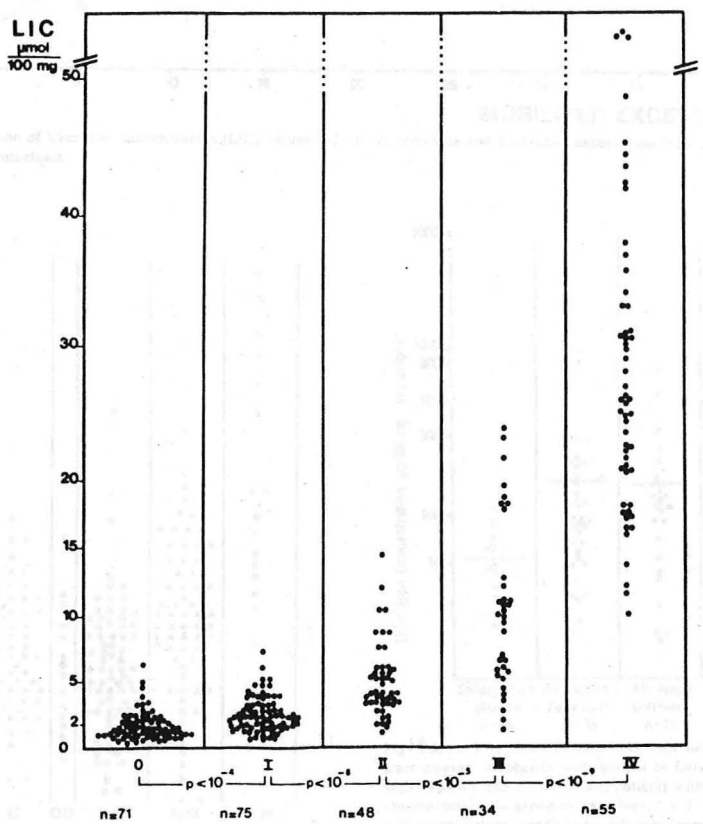


Figure 15 Comparison of stainable liver iron (grades 0 to IV) with liver iron concentration (LIC) values.

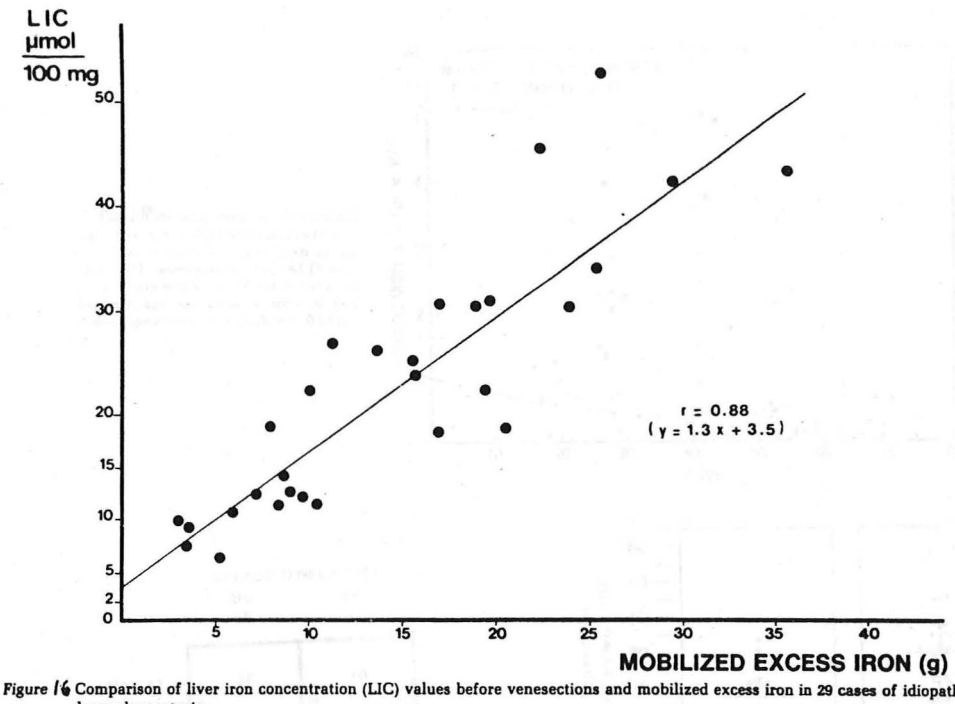


Figure 16 Comparison of liver iron concentration (LIC) values before venesections and mobilized excess iron in 29 cases of idiopathic hemochromatosis.

Figure 17 Serum Ferritin Concentrations in Family Members of Patients with Hemochromatosis.

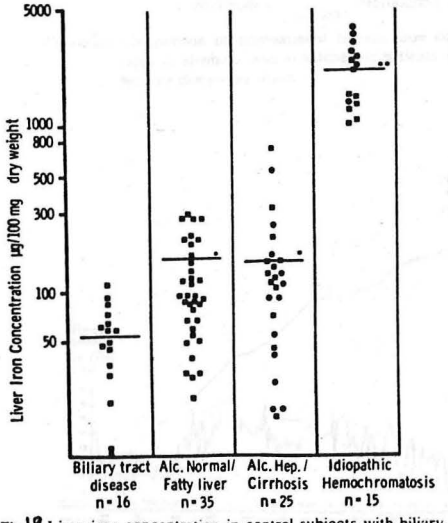


Fig 19 Liver iron concentration in control subjects with biliary tract disease, alcoholics with normal or fatty liver, alcoholics with hepatitis and cirrhosis, and patients with idiopathic hemochromatosis. —— group mean values; * = $P < 0.05$, ** = $P < 0.01$ mean values significantly different from the mean of the control group. ● = patients with cirrhosis.

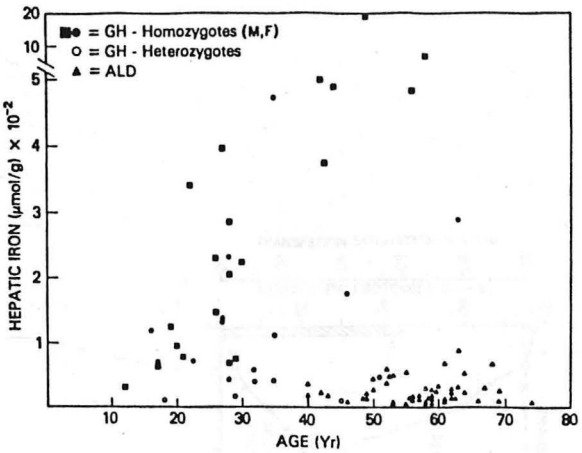


FIG. 18 Hepatic iron concentration values vs. age of GH homozygotes (males shown as *squares*, females shown as *circles*), GH heterozygotes and ALD subjects. There was a significant correlation between age and hepatic iron in GH homozygotes only ($r = 0.55$, $p < 0.01$).

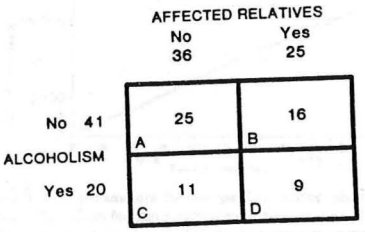


Figure 20 Distribution of the 61 study patients categorized with respect to alcoholism and presence of altered iron metabolism in first-degree relatives.

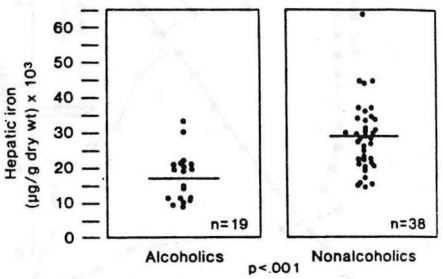


Figure 21 Comparison of pretreatment hepatic iron concentrations in alcoholic and nonalcoholic patients. *Horizontal line* designates mean.

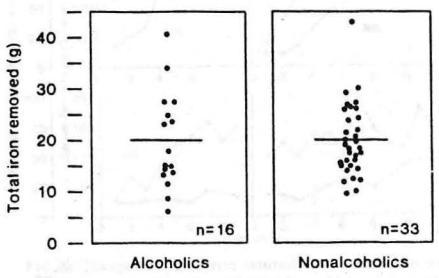


Figure 22 Comparison of total mobilizable iron removed by phlebotomy in alcoholic and nonalcoholic patients. *Horizontal line* designates mean.

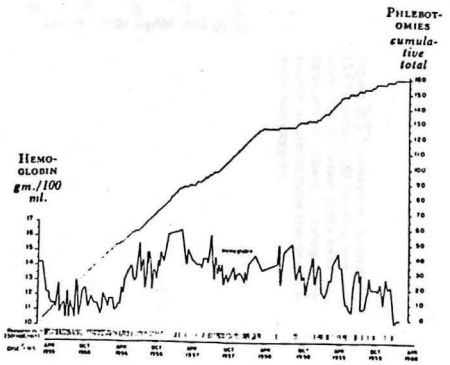


FIGURE 23 *Five-Year Phlebotomy Record, with Varying Hemoglobin Levels, in Case 1.*

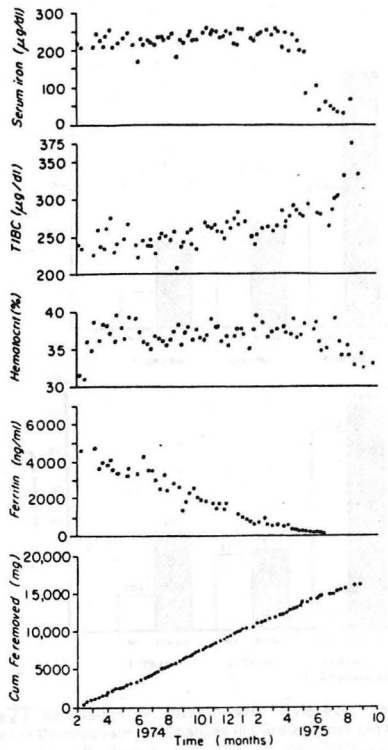


FIG. 24 Iron parameters in one patient during phlebotomy therapy. The serum ferritin progressively decreases and the iron binding capacity increases slightly as iron stores are removed. When the serum ferritin falls below 50 μg/liter, the plasma iron and hematocrit fall while the total iron binding capacity rapidly increases.

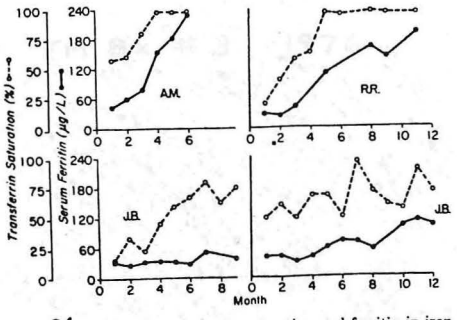


FIG. 26 Changes in transferrin saturation and ferritin in iron depleted hemochromatotic patients after phlebotomies were stopped. The transferrin of two patients became saturated with iron at 4 months, whereas the third patient did not become saturated over 8 and 12 month intervals. Phlebotomies were then resumed, permitting an estimate of accumulated iron and of the rate of absorption. Daily absorption was calculated to be 4 mg/day in patients AM and RR but no more than 2 mg/day in JB.

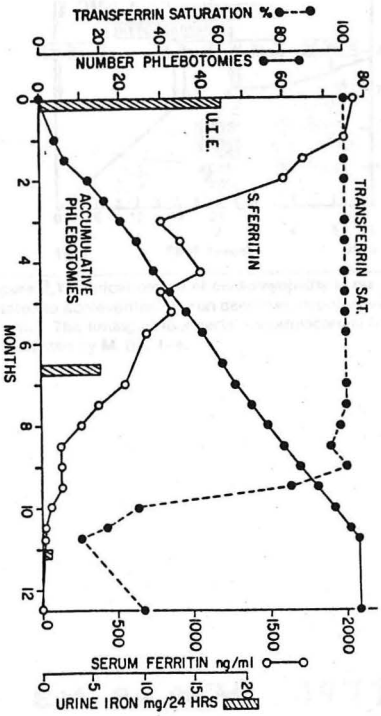


Figure 25 Transferrin saturation (SAT), serum (S) ferritin, and urinary iron excretion (UIE) after deferoxamine (bars) during the course of phlebotomy therapy in a male homozygote.

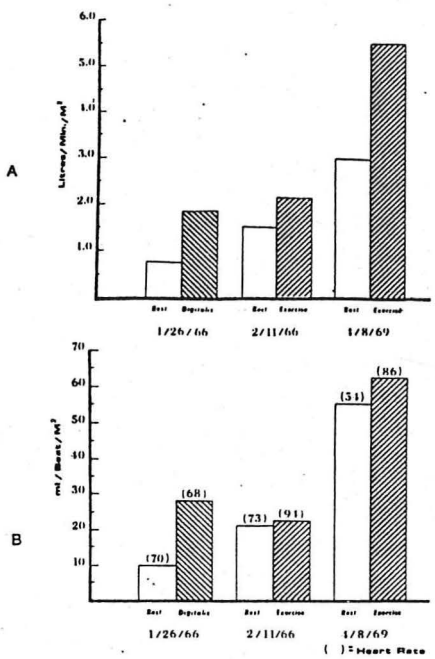


Figure 27 Representative Hemodynamic Data from Three Studies to Demonstrate the Changes in Cardiac Index (A) and Stroke Index (B) before and after Acute Digitalization (1/26/66) and before and after Exercise (2/11/66 and 4/8/69).

In 1966 the patient was in severe cardiac failure, whereas in 1969 he was on no specific medications and all the hemodynamic indexes returned to normal.

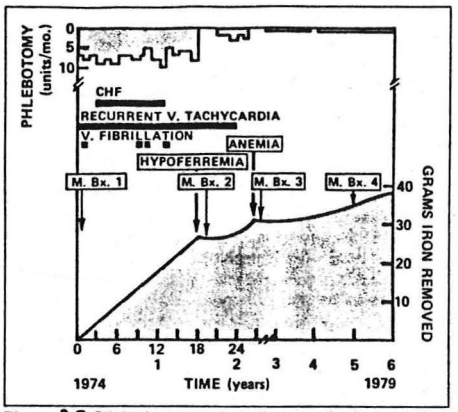


Figure 28 Clinical course of cardiomyopathy in our patient related to achievement of iron depletion, hypoferremia and anemia. The timing of four serial endomyocardial biopsies is indicated by M. Bx. 1–4.

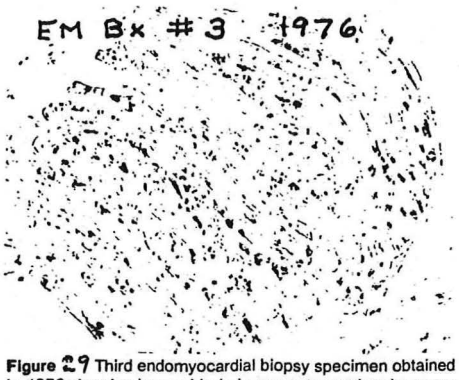


Figure 29 Third endomyocardial biopsy specimen obtained in 1976 showing hemosiderin in myocytes and an increase in interstitial fibrosis despite clinical hypoferremia and microcytic anemia. Perl's iron stain; magnification × 120, reduced by 34 percent.

Figure 30 Fourth endomyocardial biopsy specimen obtained in 1979 showing no hemosiderin deposits. Perl's iron stain; magnification × 120, reduced by 34 percent.