Title
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Iron Absorption in Hemochromatosis Before and After Phlebotomy Therapy

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Introduction

Endogenous hemochromatosis has been considered to be an hereditary defect leading to increased absorption of iron from the diet with subsequent gradual accumulation of iron in liver and other organs, the various symptoms and signs of the disease apparently resulting from tissue damage due to excessive iron deposition (1,2). An alternative hypothesis proposed by McDonald (3) is that the disease is a form of cirrhosis complicated by excessive oral iron intake. Evidence for abnormally high iron absorption in patients with this disease would mitigate against the latter hypothesis.

Smith et al (4) have reported the most extensive iron absorption studies to date on hemochromatotic patients, studying 49 patients using a whole-body counter. They found that iron absorption, which was in the normal range before phlebotomy therapy, increased to levels seen in iron deficient patients during therapy, and remained at this level for up to 5 years after cessation of phlebotomies. The results are reported as averages of groups of patients at various times in the course of therapy; no patients were reported for whom there were absorption studies before, during and after phlebotomy therapy.

In this communication we describe serial iron absorption studies in eight patients with endogenous hemochromatosis, and two siblings with iron overload, performed before, during and after phlebotomy therapy, and relate the results to the state of erythropoiesis and iron stores at the time of each study.

Materials and Methods

Eight hemochromatotic patients and two siblings were studied.

The diagnosis in the propositi was suggested by combinations of the clinical features of diabetes, skin darkening, loss of axillary hair, loss of potency, hepatomegaly, abnormally elevated serum-iron concentration (>170 μgm/100 ml), and hepatic biopsy showing the characteristic markedly increased deposition of iron. In all cases the diagnosis was confirmed by the patients' tolerance to phlebotomy in excess of 25 liters prior to iron depletion. In most cases skin biopsy revealed iron deposition around hair and sweat follicles. Five of the eight cases had neither histories of alcoholism nor previous hepatitis. The two female siblings were essentially asymptomatic with no diabetes, skin darkening or loss of axillary hair. They were initially studied because elevated serum iron values were found. Ferrokinetic studies performed on each propositus and one of the siblings according to the method of Pollycove and Mortimer (5) demonstrated abnormally rapid early deposition of iron in the liver. Net plasma-iron clearance was increased and the incorporation of radioiron into red cells was decreased below normal levels, typical of hemochromatosis (5).

The iron absorption tests were performed as described by Saito et al (6). An oral dose of one to four microcuries of ^{59}Fe with four milligrams ferrous sulfate carrier was administered to the fasting subject, and food was withheld for an additional two hours; two weeks later he was counted in a whole body counter. The radioiron in the body at this time is a measure of total body iron absorption when related to an intravenous dose also measured at two weeks; this technique, previously described in detail (6), minimizes errors due to body geometry and redistribution of the isotope. The whole-

body counting method also eliminates an error inherent in the double isotope method, which measures only that iron absorbed from the intestinal tract which reaches the systemic plasma. When the plasma iron concentration is elevated, as in hemochromatosis, some of the absorbed iron is deposited in the liver as a first-pass phenomenon and does not reach the systemic plasma (7), thus causing an underestimation of the absorbed dose.

Hemoglobin concentration and hematocrit were determined in the routine manner. Reticulocyte counts were performed using slide incubation with new methylene blue; a total of 1000 rbc were observed for reticulum content. Serum iron concentration (SI, expressed as µgm/100 ml or µgm%) was determined by the modification by Peters and co-workers of the Ramsey method (8). (Range in the normal subjects reported here, ± two standard deviations, was 60-150 µgm%). Total iron binding capacity (TIBC) was performed by the method of Peters et al (9). (Normal 200-400 µgm%).

The treatment schedule in the patients with hemochromatosis and in the siblings consisted of one to two 500 ml phlebotomies per week as tolerated. Depletion of iron stores was considered to be complete when the patient no longer tolerated phlebotomy without a precipitous drop in circulating hemoglobin concentration, when circulating red blood cells were markedly microcytic and hypochromic, the SI was less than 70 µgm% for at least one month after the last phlebotomy and the bone marrow aspirate showed little or no stainable iron. Repeat liver biopsies were generally not performed to evaluate directly hepatic iron stores.

Normal subjects were studied as described previously (7). In

three normal subjects the effect of increased erythropoiesis was studied by performing the absorption test before, and five days after a 500 ml phlebotomy. The effect of serum iron concentration was studied by performing the absorption test in iron deficient patients while their SI was low, and in two other such patients when their SI was elevated following intravenous administration of iron dextran (Imferon) one to two weeks prior to the study.

Results

I. Relationship between oral iron absorption, reticulocyte count and SI in non-hemochromatotic subjects.

The relationship between the percent absorption of the oral iron dose as a function of the percent circulating reticulocytes in normal subjects is shown in Fig. 1a. This correlation has been previously reported (6), but is shown here with 16 additional subjects. The correlation coefficient is 0.77; the 95% confidence limits for prediction of further measurements are represented by the shaded area, and since the limits are based upon observed data they include random errors of both absorption and reticulocyte measurements. There are no data points for reticulocyte levels greater than 2.0%, and the normal range beyond this is defined only by extrapolation of the regression line and its confidence limits, as indicated in Fig. 1a. The correlation of absorbed dose with reticulocyte count is in keeping with the concept that iron absorption is proportionate to the amount needed for red cell production.

The correlation with reticulocyte count was further tested by giving the absorption test to three subjects before, and five days

after, a 500 ml phlebotomy. As seen in Fig. 1b, the reticulocyte count increased following phlebotomy as expected, with a proportionate increase in iron absorption, the latter remaining in the normal range as defined above. The SI remained within the normal range prior to, and subsequent to phlebotomy in these subjects.

In patients with iron deficiency anemia, in whom the SI is below the normal values (<60 μgm%), iron absorption is above the normal range as shown in Fig. 2. In two such patients who had had intravenous dextran-bound iron (Imferon) injections one to two weeks previous to the test, iron absorption was depressed to well below the normal range; the SI's were abnormally elevated during this time interval but the patients were still anemic and undoubtedly continued to have increased erythropoiesis. The results on these normal, iron deficient and acutely iron loaded patients may be summarized as follows:

1. In normal subjects the fraction of iron absorbed from a standardized test dose varies directly with the reticulocyte count.
2. In iron deficiency anemia absorption of iron is abnormally increased with respect to the reticulocyte count; it was decreased in two such patients when they were given sufficient iron intravenously to abnormally elevate the SI.

II. Iron absorption in patients with hemochromatosis.

The series of eight patients with endogenous hemochromatosis and the two siblings were given iron absorption tests at three stages of their treatment: (1) at the time of presentation, when there had been either no previous phlebotomy or at most only a few; (2) in s

cases during the course of phlebotomy therapy, while the SI was still elevated; (3) after the completion of phlebotomy therapy, in some cases when the patient was still iron deficient as indicated by lowered hemoglobin concentration and SI, and in every case at least two months after the last previous phlebotomy, at a time when the patient was normochromic and normocytic and had a SI within the normal range (60-150 µgm%). Without further phlebotomy certain patients experienced a rather abrupt increase in SI above the normal range and repeat absorption tests were performed at that time.

Table I summarizes the results on the eight hemochromatotic patients and the two siblings, with pertinent clinical information.

In Figure 3, a-h, each figure shows the results of the series of absorption tests on a single propositus. Figure 4, a-b, shows the results for the two siblings.

Patient A.F. (3a) had greatly suppressed absorption before phlebotomy. Six months after completion of a 58 liter course of phlebotomies which produced a hypochromic microcytic anemia, depleted bone marrow iron stores and subnormal SI, two repeat iron absorption studies showed that absorption was greatly elevated even though the SI had spontaneously risen again to abnormally high levels (226 µgm% and 257 µgm% respectively). Only an additional 5 liters of blood was removed before the patient developed all the signs of iron depletion seen after the first course of phlebotomy. Four months after the second course of phlebotomy when his SI was 72 µgm% a repeat iron absorption study was abnormally high.

Patient E.B. (3b) when tested initially had high absorption (40%) despite an elevated SI of 176 µgm%. In relationship to

reticulocytosis this was within the extrapolated normal range. Subsequent to removal of 55 liters of blood, two further absorption tests at 42 and 240 days after the last phlebotomy showed absorption well above the extrapolated normal range at a time when the SI was within normal limits.

Patient J.R. (3c) was first studied after removal of 21 liters of blood, 49 days after the last phlebotomy, and the absorption was found to be within the normal range, despite a SI of 250 µgm%. After depletion of his iron stores, at a time when he was quite iron deficient (SI 3 µgm%) his absorption was elevated as would be expected from iron deficiency alone. Two years later, with occasional maintenance phlebotomies, his SI was within normal limits (149 µgm%) but absorption was still above the extrapolated normal range. In the succeeding 2 months, his SI rose spontaneously to 193 µgm%, at which time absorption was suppressed almost to within the normal range.

Patient T.G. (3d) was first studied after phlebotomies had been initiated; at that time his SI was still elevated, and his absorption was within the normal range. After depletion of stores and while still iron deficient, (SI 41 and 39 µgm%), two absorption tests 77 and 240 days after the last phlebotomy showed the elevated absorption characteristic of iron deficiency.. However, a year later, the SI had risen spontaneously to a normal level (106 µgm%), and absorption was still elevated. Without further phlebotomy, the SI rose to above-normal levels (173 µgm%) and absorption at this time

was suppressed to within the normal range.

Patient M.T. (3e) had had no phlebotomies when first studied (SI 219 µgm%) and absorption was within the normal range. The next tests were performed 63 and 123 days after completion of a 31 liter course of phlebotomy (SI 66 µgm% and 68 µgm%) and absorption was above normal in both tests. The SI then rose to 216 µgm% and absorption fell to almost within the normal range. Subsequently without further phlebotomy the SI fell to within the normal range, (150 µgm%) and absorption was again found to be elevated.

Patient J.T. (3f) when first studied before any phlebotomies had absorption just within the normal range. One hundred and sixty-five days after the removal of 50 liters of blood had depleted iron stores and the patient was iron deficient, repeat study showed that the SI had already risen to 206 µgm% and absorption was within the normal range. After further phlebotomies this sequence was essentially repeated, the SI rising above normal (162 µgm%) and the absorption still within normal range. After removal of an additional 5.5 liters of blood, an absorption test 62 days later showed an above normal absorption with the SI 62 µgm%. This patient died of a hepatoma 1 1/2 years later.

Patient R.G. (3g) was the only patient studied who showed an elevated absorption when first studied (SI 204 µgm%); a subsequent test, near the end of his phlebotomy regime but with his SI still elevated (234 µgm%) gave a similar result. Following depletion of iron stores after removal of 51 liters of blood, his SI was found to be 100 µgm% 130 days after completion of phlebotomy and his absorption remained abnormally elevated.

Patient P.G. (3h) was first studied before any phlebotomy therapy and her absorption was within the normal range with SI 281 µgm%. After a phlebotomy regimen in which 26.8 liters of blood were removed, an absorption test 104 days after the last phlebotomy was above the normal range with SI 273 µgm%. Removal of an additional 3 liters of blood depleted the patient's iron stores and 240 days later with SI 29 µgm% iron absorption was elevated as in iron deficiency. After maintenance phlebotomies totaling 2 liters, 90 days after the last phlebotomy the SI was in the normal range (132 µgm%) and absorption was still elevated.

Patient C.D. (4a) was a sister of patient J.T. and presented with SI 202 µgm%, increased marrow iron and a normal BSP. When first studied absorption was below normal; ferrokinetics studies (5) revealed increased deposition and retention of iron in the liver. After 6.6 liters of blood had been removed the SI was 33 µgm%, and absorption was above normal as in iron deficiency anemia. Some five months later without further phlebotomies the SI had risen to 129 µgm% and absorption was still above the normal range. Subsequently an additional 5.9 liters of blood have been removed to maintain the SI at normal levels.

Patient L.B. (4b) was also a sister of patient J.T. who was first studied because elevated SI values were found. She had mild hepatomegaly, increased iron in bone marrow and BSP mildly elevated at 8.8%. When first studied before phlebotomy with a SI of 242 µgm%, her absorption was within the normal range. During the course of phlebotomy, after removal of 20.9 liters of blood, absorption was elevated with SI 222 µgm%. Sixty days after removal of an additional

2.4 liters of blood, absorption was above normal in the presence of a normal SI of 99 ugm%. A Technetium-99 sulfur colloid scan at this time showed a normal-appearing liver with an enlarged Riedel's lobe.

The results on these eight patients and two siblings may be summarized as follows:

(1) When the SI was elevated and the absorption test was given prior to phlebotomy (or after prior phlebotomies in 2 cases), iron absorption was within the normal range with regard to reticulocyte count in 6 out of 8 cases; in the other 2 cases, one was above and the other below this range. Of the siblings, one was in the normal range, the other below.

(2) When iron stores had been depleted and the SI was below normal, but in the absence of significant anemia, iron absorption in those patients tested was always above the normal range, as occurs in non-hemochromatotic patients with iron deficiency.

(3) When depleted patients were tested 2 months or more after their last phlebotomy, at a time when they were normochromic, normocytic and the SI was within normal limits, the iron absorption with regard to reticulocyte count was above the normal range in 8 out of 8 patients and both of the siblings.

Discussion

Parameters which affect intestinal absorption of iron have been studied by many workers, and much of this has recently been summarized (10). Some years ago it was shown that an increased level of erythropoiesis generally increased absorption of iron and that iron load

tended to decrease it (11), yet accurately measurable correlations between absorption and either erythropoiesis or iron loading could not be obtained (12). A recent study however has shown a correlation between iron absorption and reticulocytes in rats using a whole-body counting technique (13). In the present study and as reported earlier (6), it was found that in normal subjects the fraction of iron absorbed varies directly with circulating reticulocytes, supporting the concept that it is directly related to erythropoietic rate. Failure of other workers to observe this relationship in human subjects may have been due to use of measures of absorption less accurate than a whole-body counter and use of doses of carrier iron, in many cases, which were far above or below normal dietary levels. A wide variation in absorption among normal subjects and in a single subject at different times has been found by many workers (10). With the method used here, similar variations occur, but always within the confidence limits of the regression line shown in Fig. 1a. The confidence limits of this regression thus define a narrower range of normal absorption than was previously possible. Although intraluminal factors and presence or absence of some foods undoubtedly affect iron absorption, and this correlation may not thus represent absorption of food iron as it normally occurs, nevertheless the use of a physiologic carrier dose of iron and the technique described here provides a consistent and useful way of assessing relative iron absorption.

When the SI falls below normal as in patients with iron deficiency anemia, absorption is above the normal range as defined above. In two iron deficient patients, when the SI had been abnormally

elevated by intravenous iron-dextran, oral iron absorption was suppressed below the normal range. Sölvell (14) also found an inverse relationship between absorption and SI, but he utilized acutely elevated SI. Wheby and Jones (15), however, showed that in rats when iron is absorbed in the presence of saturated transferrin, it is deposited in the liver on its first pass through the portal system; this phenomenon was ultimately demonstrated in humans (7). Wheby and Jones did not find that acutely elevated SI reduced absorption and attributed Sölvell's results to the first-pass phenomenon. In the two patients reported here the saturation of transferrin was chronic rather than acute, which more closely simulates the situation in hemochromatosis, yet is complicated by the presence of the non-natural dextran-bound iron. The suppressed absorption in these two patients could be interpreted as support for the modified mucosal block theory of Crosby (16), in that the chronically high levels of SI would have time to saturate the developing mucosal cells and suppress absorption by the mechanism he has proposed. On the other hand it is hard to see how such a mechanism could account for control of absorption according to the erythropoietic level. The three days required for elaboration of the intestinal mucosal cells before they can influence iron absorption according to Crosby is also approximately the same period required for erythropoietic marrow to respond to an increased need for red cells (11). Thus the work reported here provides no clear evidence on which to distinguish between a mucosal mechanism, intraluminal factors or an erythropoietic control mechanism. Conceivably, the mucosal mechanism, or secretion of intraluminal factors, may act

upon information received from the erythropoietic marrow, although no mechanism for such an information transfer has been found.

Because iron absorption was suppressed in the two patients given iron-dextran, one might expect a similar suppression in untreated hemochromatotic patients because of their elevated SI. The fact that absorption is usually in the normal range in the latter patients indicates that it is nevertheless relatively increased. Furthermore, after depletion of iron stores and at a time when SI and other blood indices were normal, iron absorption was markedly above the normal range. Thus, in these hemochromatotic patients and two siblings it appears that at all times oral iron absorption is in excess of need.

Many workers have reported increased iron absorption in patients with cirrhosis of the liver (17,18,19,20), and hemosiderosis has been reported in association with cirrhosis. In the eight patients reported here, cirrhosis and impaired liver function were present in some degree, although minimally if at all in the siblings. The question then arises whether in these patients cirrhosis may have preceded and been the cause of increased absorption and hemochromatosis, or whether, as is generally believed to be the case, increased absorption of iron was the basic factor resulting in hemochromatosis.

It is difficult to assess the many reports of increased absorption in cirrhosis because to date, all have had one or more of the following features: (1) the carrier dose was unphysiologic, either less than 100 μgm or 50 mg or more; (2) some or most of the patients with cirrhosis were anemic; (3) the "normal" subjects used were in fact not normal but suffered from a variety of other diseases, the

effect of which on iron absorption is unknown; (4) the technique used was either inherently inaccurate (fecal collection) or unable to measure accurately absorption in the presence of iron overload (double isotope). We have recently reported iron absorption in 15 cirrhotic patients using the technique and criteria described here; only one out of the 15 had increased absorption, while seven actually had diminished absorption (21). In spite of the difficulty in comparing these studies, it appears that in some but not all patients with cirrhosis, there may be increased absorption of iron.

In the patients with hemochromatosis reported here, whatever degree of cirrhosis they may have had before therapy, after depletion of iron stores the cirrhosis was either unchanged, or possibly improved; in the siblings there was at most only minimal liver damage. Yet in all cases, with minimal or unchanged cirrhosis, iron absorption was markedly increased after depletion. For four of these patients (E.B., J.R., T.G. and M.T.) results of iron kinetics studies have recently been published (22). When they were iron deficient following phlebotomy therapy, increased iron deposition occurred transiently in the liver; this did not occur in 4 iron deficient patients or in 3 iron deficient cirrhotic patients. The authors interpreted the results as suggesting that the liver in patients with hemochromatosis has an abnormal and characteristic affinity for iron. Thus we feel that the data presented here is in accord with the generally accepted view of the etiology of hemochromatosis (23,24), that abnormally increased iron absorption, probably congenital, precedes and is contributory to cirrhosis of the liver and the characteristic damage to other organs.

It is of some interest to note that although these patients had apparently lost the control of iron absorption that is related to

erythropoietic rate, they did retain a less satisfactory degree of control in that a chronically elevated SI usually produced a relative suppression of absorption. Some patients were found to have elevated SI within a year following cessation of phlebotomy; it is possible that even when they were judged to be depleted, they had very slowly equilibrating stores of iron, or that hemochromatotics can have elevated SI when iron stores are not excessive.

The measurement of oral iron absorption in hemochromatotics may be of value in assessing rate of repletion of iron stores, which is not possible by other methods such as SI or liver biopsy. It may also be useful in defining the physiologic basis and mode of transmission of the disease, and in detecting it in family members early enough to begin prophylactic phlebotomy and thus prevent irreversible damage.

The results reported here, and those of Smith et al (4), should satisfy one of MacDonald's objections (3) to the concept of hemochromatosis as a congenital disease; namely, that there has been insufficient evidence reported to date of increased iron absorption in hemochromatotic patients. The increased iron absorption found in our treated patients, at a time when their blood indices and SI were normal, supports but does not prove the view that idiopathic hemochromatosis has, as a basic predisposing factor, a congenital defect that permits excessive absorption of iron from a diet containing normal amounts of this element.

Summary

Idiopathic hemochromatosis has been considered to be a heritable disease in which excessive iron is absorbed from the diet,

eventually leading to organ damage from the toxic accumulation of this element. An alternative hypothesis of the etiology of the disease maintains that it is a form of cirrhosis complicated by excessive dietary iron. In the work described here, utilizing a Whole-body Counter, a correlation has been shown in normal subjects between oral iron absorption and circulating reticulocytes; patients with serum iron levels above and below normal have iron absorption below and above, respectively, the confidence limits of the regression line of the correlation. Eight patients with idiopathic hemochromatosis and two siblings were given iron absorption tests before, during and after phlebotomy therapy. In all cases the study after therapy was at a time when the serum iron levels were within the normal range and all blood indices were normal, and in every case at this time the iron absorption was above the normal range. These results are considered to support the concept that in patients with hemochromatosis there is a congenital failure of control of iron absorption from the diet leading to excessive accumulation of this element in the body.

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Figure Captions

Fig. 1 Absorption of a 4 mg oral dose of ferrous iron, vs % circulating reticulocytes:

(a) In 26 normal subjects. The center line is the regression calculated from the distribution of points, and the outer lines are the 95% confidence limits of the regression line. The lines beyond 2% reticulocytes are extrapolated.

(b) In 3 normal subjects, before and 5 days after a 500 ml blood donation. The connecting arrows show the chronological sequence of the tests.

Fig. 2 Iron absorption in patients with iron deficiency anemia, and two anemic patients with transiently elevated SI due to prior I.V. iron-dextran therapy. The numbers inside of each point indicate the serum iron concentration at the time the test dose was given.

Fig. 3 (a-h) Iron absorption of eight hemochromatotic patients before, during and after phlebotomy therapy. SI at time of each test is shown beside the data point. The arrows indicate the chronological sequence of the tests.

Fig. 4 (a-b) Iron absorption of two female siblings of patient J.T., studied in the same manner as is Fig. 3.

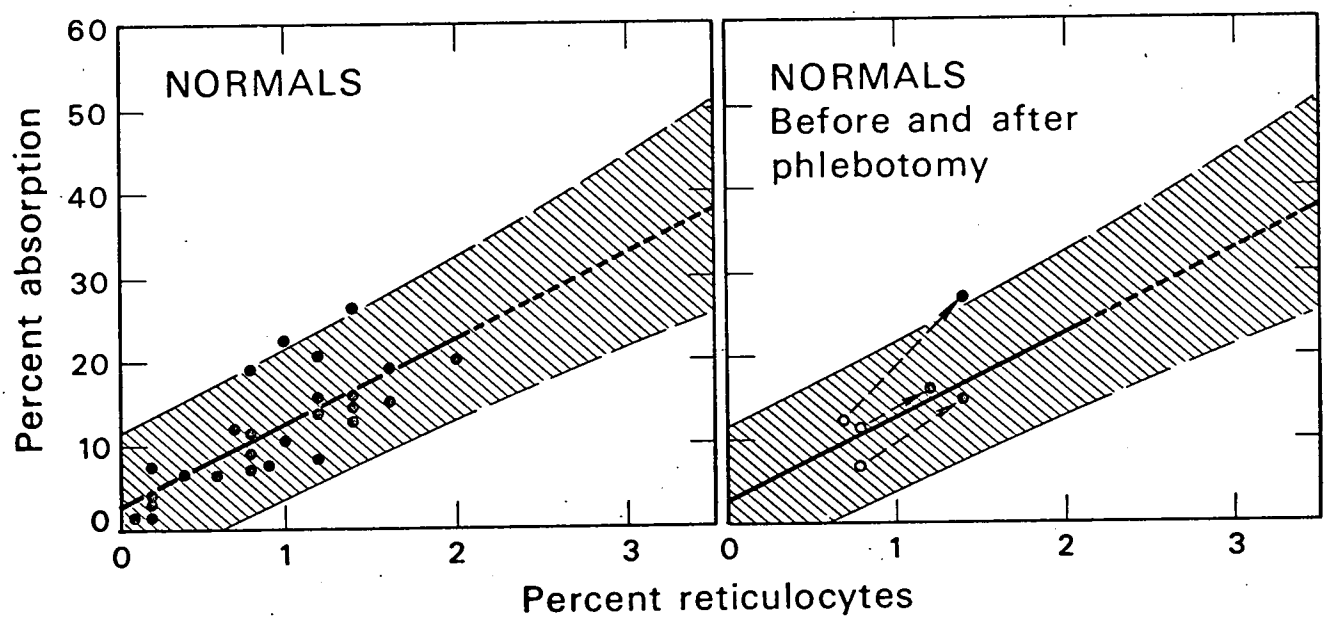
TABLE 1. CLINICAL DATA AND RESULTS OF IRON ABSORPTION TESTS IN 8 PATIENTS WITH HEMOCHROMATOSIS AND 2 SIBLINGS BEFORE, DURING AND AFTER PHLEBOTOMY THERAPY.

Patient	Sex	Age when studied	Alcoholism (+ or 0)	Diabetes (+ or 0)	Days since last phlebotomy	Liters blood removed prior to time of study	Hemoglobin gm/100 ml	Serum iron conc. µgm%	Total serum iron binding capacity µgm%	% saturation of plasma transferrin	% circulating reticulocytes	% of 4 mg Fe^{++} absorbed
AF	M	50	0	+		0	13.2	199	318	63	3.5	0.5
		52			180	58	14.8	226	-	-	1.2	39
		52			210	58	14.7	257	271	95	2.8	74
		53			120	63	14.9	72	233	31	0.4	64
EB	M	54	0	+		0	15.0	176	262	67	3.6	40
		57			42	55	13.9	81	-	-	2.6	68.4
		59			240	56.6	14.6	67	307	22	3.0	74
JR	M	56	0	+	49	21	15.6	250	291	86	1.3	19.5
		58			33	52	11.4	3	190	1.5	2.2	60
		60			120	61	14.4	149	261	57	2.6	67
		60			188	61	15.6	193	241	80	3.3	60
TG	M	54	0	+	23	36	14.6	238	396	60	1.2	13
		55			77	62	12.0	41	352	12	0.6	29.5
		56			240	62	15.0	39	350	11	0.6	55.
		57			390	63	15.3	106	350	30	1.0	37.5
		58			720	63	16.2	173	272	64	1.4	20.4
MT	F	66	0	0		0	13.8	219	364	60	1.7	15
		69			63	31	14.0	66	-	-	1.2	49
		69			123	31	14.2	68	-	-	1.0	62
		69			207	31	12.5	216	231	92	2.0	36
		70			360	31	12.6	150	-	-	2.6	51
JT	M	53	+	+		0	14.0	296	322	92	2.4	16.8
		55			165	50	15.4	206	366	56	2.3	31
		56			139	54.5	14.4	162	349	46	2.8	23
		59			62	62	15.5	61	323	19	1.4	67
RG	M	64	+	+	21	.5	13.0	204	319	64	1.4	53
		66			42	43	13.0	234	-	-	1.0	57
		67			130	51	11.7	100	273	37	1.6	71
PG	F	54	+	+		0	12.9	281	295	95	2.4	29
		56			104	26.8	14.4	273	301	91	2.0	85
		57			240	29.8	13.0	29	476	6	1.9	37
		58			90	31.8	12.7	132	488	27	2.0	45

TABLE 1. Continued

	Patient	Sex	Age when studied	Alcoholism (+ or 0)	Diabetes (+ or 0)	Days since last phlebotomy	Liters blood removed prior to time of study	Hemoglobin gm/100 ml	Serum iron conc. ugm%	Total serum iron binding capacity µgm%	% saturation of plasma transferrin	% circulating reticulocytes	% of 4 mg Fe^{++} absorbed
*	CD	F	58	0	0		0	13.8	202	292	69	1.8	7
			59			27	6.6	11.4	33	330	10	1.6	41
			60			185	6.6	14.2	129	375	34	1.3	37
*	LM	F	60	0	0		0	13.4	242	308	79	1.6	14
			62			90	20.5	13.1	222	410	54	0.8	53
			62			60	22.9	13.4	99	345	29	0.8	33

* Siblings of patient J.T,



DBL 703-5594

Fig 1a,b

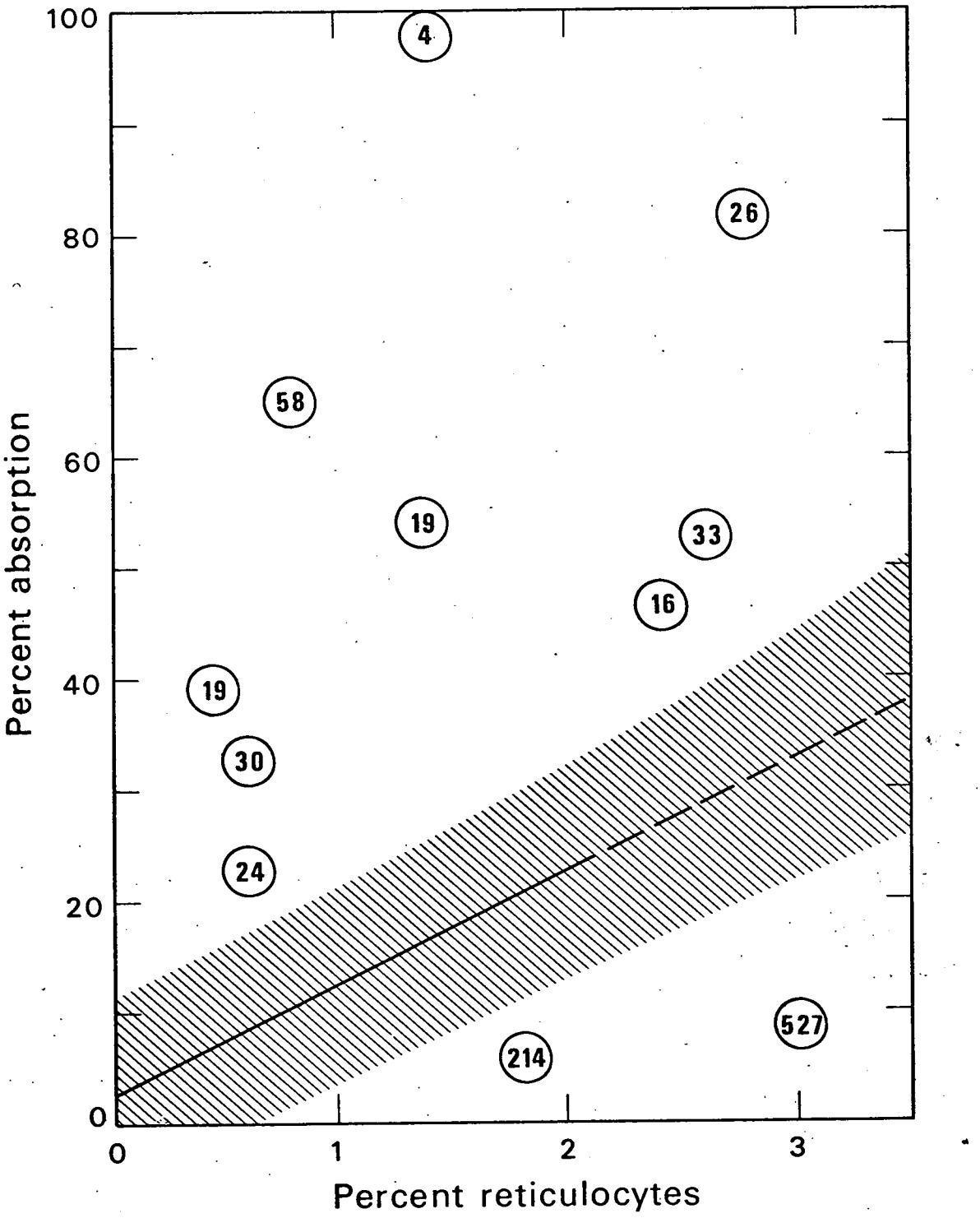

100
80
60
40
20
0
Percent absorption
0
1
2
3
Percent reticulocytes
4
26
58
19
33
16
19
30
24
527
214
DBL 703-5595

Fig 2

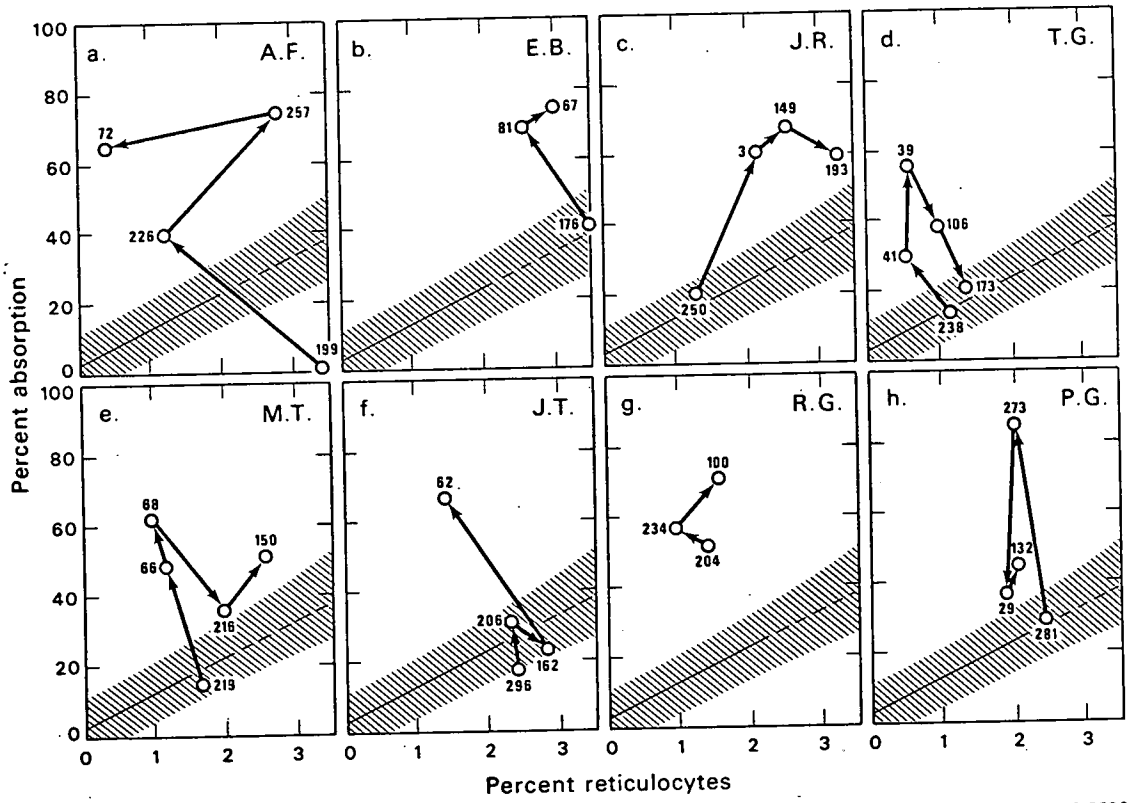

a. A.F.
b. E.B.
c. J.R.
d. T.G.
e. M.T.
f. J.T.
g. R.G.
h. P.G.
Percent absorption
Percent reticulocytes
DBL 703-5596

Fig 3, a-h

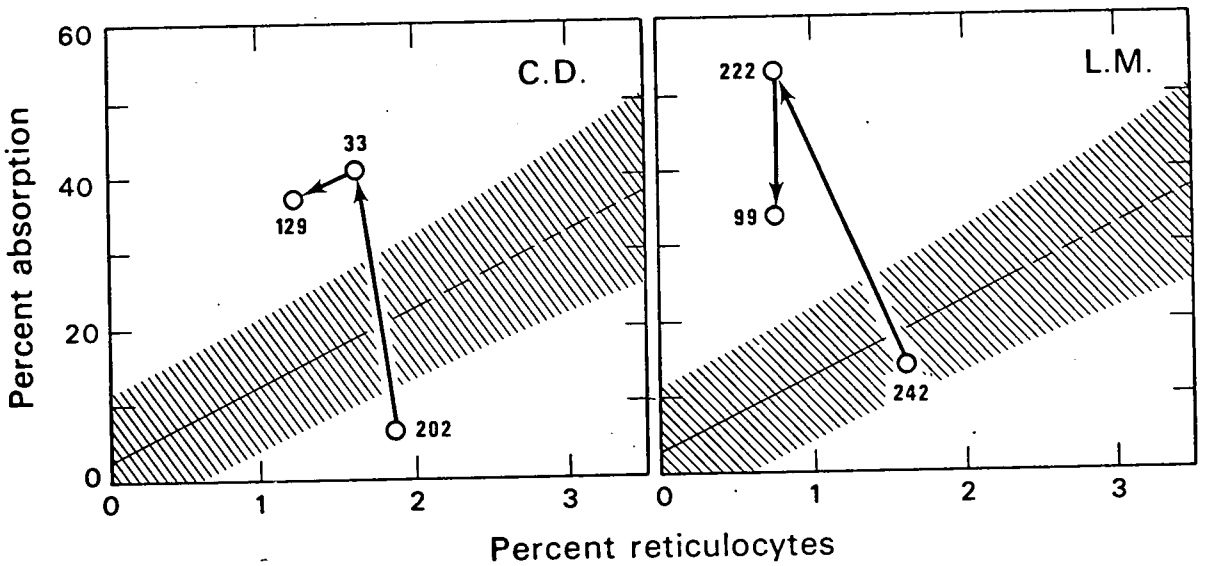

C.D.
L.M.
Percent absorption
Percent reticulocytes
60
40
20
0
0
1
2
3
33
129
202
222
99
242
DBL 712 5659

Fig 4 a, b