Title

Transient Hepatic Deposition of Iron in Primary Hemochromatosis with Iron Deficiency Following Venesection

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Patients with hemochromatosis are known to have increased hepatic deposition of plasma iron (1). Whether this represents an abnormal affinity of the hemochromatotic liver for iron or is merely a consequence of increased plasma iron concentration or plasma iron saturation, decreased plasma iron turnover rate or another as yet undetermined parameter, has not been established.

This study demonstrates increased hepatic deposition of iron in hemochromatotic patients after phlebotomy when plasma iron concentration, transferrin saturation and ^{59}Fe clearance $t_{1/2}$ are either normal or decreased. In such patients the hepatic deposition of iron is transient and shortly after such deposition it re-enters the plasma.

MATERIALS AND METHODS

Four normal subjects, four patients with simple iron deficiency anemia, four patients with hemochromatosis and three cirrhotic patients with iron deficiency were studied. The patients with hemochromatosis were studied before and after therapeutic phlebotomy. In all the studies transferrin bound ^{59}Fe was administered intravenously and complete ^{59}Fe kinetics was performed according to the method of Pollycove and Mortimer (1). In this communication only the data directly related to initial hepatic deposition of iron is presented.

RESULTS

Figure 1 shows the results of external counting rate changes

DISCLAIMER

over the liver in four normal subjects. The abscissa represents time after the intravenous administration of ^{59}Fe and the ordinate the counting rate over the liver expressed as counts per minute at time (t) divided by the counts per minute at time (0). In the normal subjects this ratio initially diminishes as radioiron is cleared from the plasma primarily destined for erythropoiesis and then increases toward unity as radioiron reappears in circulating red cells. In the normal, at no time does this ratio significantly exceed unity (1).

Figure 2 presents results obtained on four patients with iron deficiency anemia. It is clear that in these anemic patients there is no initial increase in external counting rate over the liver.

Figure 3 presents results obtained on four patients with hemochromatosis prior to phlebotomy. There is an initial and gradually increasing external counting rate over the liver.

Figure 4 presents results obtained on these same four patients with hemochromatosis subsequent to a course of phlebotomy when their serum iron was decreased and the plasma latent iron binding capacity increased. There is an initial increase in external counting rate over the liver followed by a decline within two hours.

Figure 5 presents results obtained on three iron deficient cirrhotic patients. All three patients had a long-standing history of alcoholism. It is clear that in these patients there is no initial increase in external counting rate over the liver.

DISCUSSION

The increased iron deposition in the liver of patients with hemochromatosis has been attributed to various causes such as increased

serum iron concentration, increased saturation of serum transferrin, decreased plasma clearance of radioiron and an abnormal affinity of the liver for iron due either to irritated liver cells, such as occurs in cirrhosis, or to a metabolic defect in the liver cell unique to hemochromatosis (2,3,4).

We demonstrate an initial accumulation of iron in the liver in patients with hemochromatosis following phlebotomy therapy when their serum iron and transferrin saturation were decreased and the plasma clearance of iron was normal or increased. This initial accumulation of iron in the liver of iron depleted hemochromatotic subjects and the lack of accumulation of iron in the liver of patients with either simple iron deficiency anemia or cirrhosis with iron deficiency anemia suggests that the liver of hemochromatotic patients has an abnormal and characteristic affinity for iron. Such apparent affinity could be explained by postulating that the liver in patients with hemochromatosis possesses an abnormally large number of iron binding sites or that these binding sites have an abnormal affinity for iron. Since iron normally enters the body through the intestinal tract, such hepatic affinity for iron would favor extraction of iron from portal venous blood and preferential iron accumulation within the liver.

SUMMARY

Studies performed on hemochromatotic patients using counting rate changes of ^{59}Fe activity over the liver show an initial accumulation of radioiron in the liver with prolonged retention when the serum iron concentration is high and the latent iron binding capacity low. However, in these same patients following phlebotomy therapy, when the serum iron concentration is normal or low and the latent iron

binding capacity is normal, the initial accumulation of iron in the liver is followed by its rapid release. Similar studies performed on patients with either simple iron deficiency or cirrhosis with iron deficiency failed to show initial hepatic accumulation of radioiron.

This study suggests that the characteristic initial deposition of iron in the liver in patients with hemochromatosis occurs independent of serum iron concentration, latent iron binding capacity or plasma iron turnover rate. However, the rate of subsequent release of radioiron from the liver is dependent on these factors.

REFERENCES

1. Pollycove, M., Mortimer, R. The quantitative determination of iron kinetics and hemoglobin synthesis in human subjects. J. Clinical Investigation 40:753, 1961.
2. Pollycove, M. Iron metabolism. Ciba International Symposium. Edited by F. Gross. Springer Verlag Berlin, 1964, p. 163.
3. Fawwaz, R.A., Winchell, H.S., Pollycove, M. and Sargent, T. Hepatic Iron deposition in humans. Blood, 30:417, 1967.
4. Heilmeyer, L. Pathogenesis of Hemochromatosis. Medicine 46:209, 1967.

Figure Captions

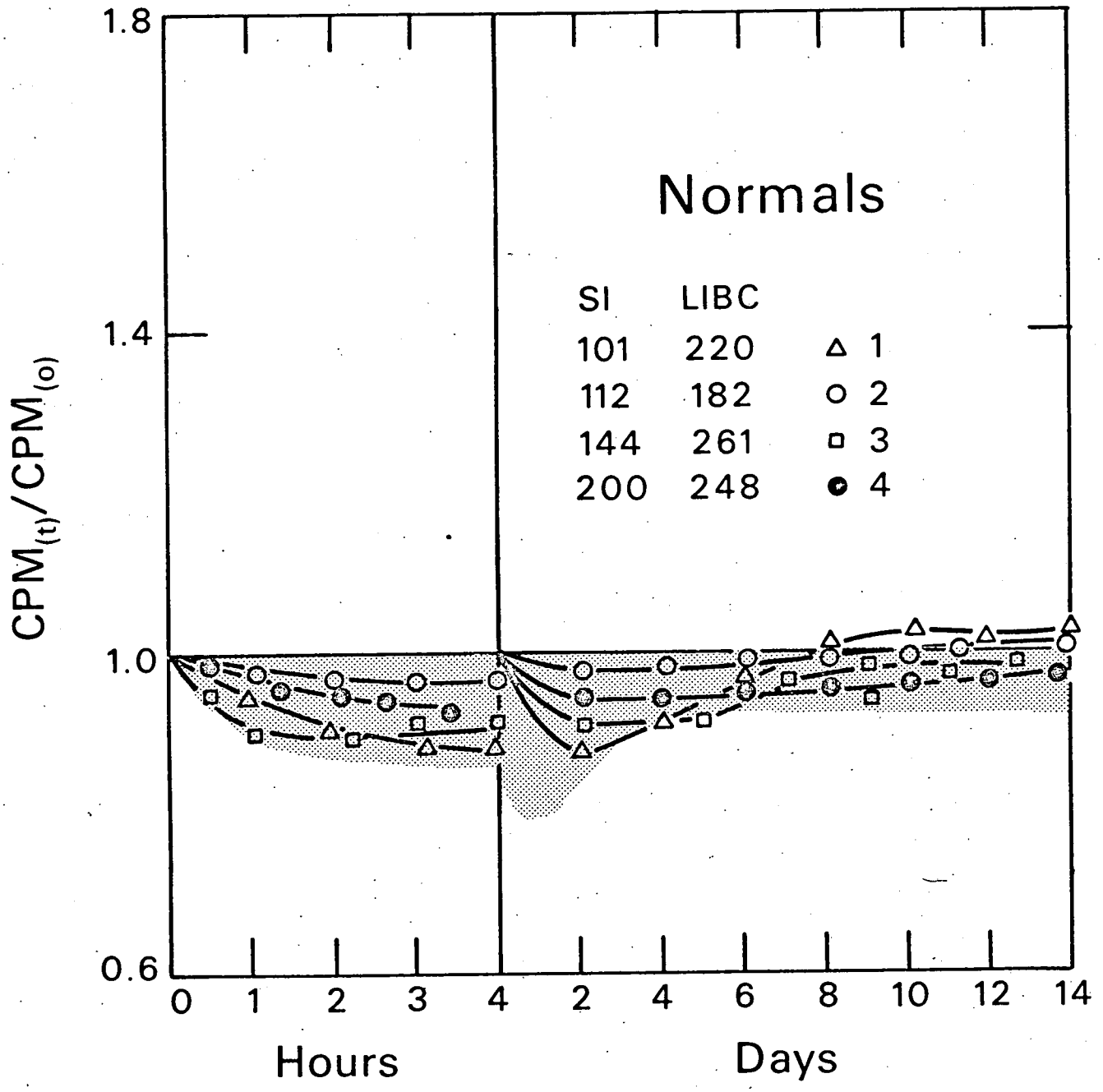
Figure 1 shows the results of external counting rate changes over the liver in four normal subjects following the intravenous administration of ^{59}Fe. In these subjects the average ^{59}Fe initial t 1/2 was 77 minutes.

Figure 2 presents results obtained on four patients with iron deficiency anemia following the intravenous administration of ^{59}Fe. In these subjects the average ^{59}Fe initial t 1/2 was 23 minutes.

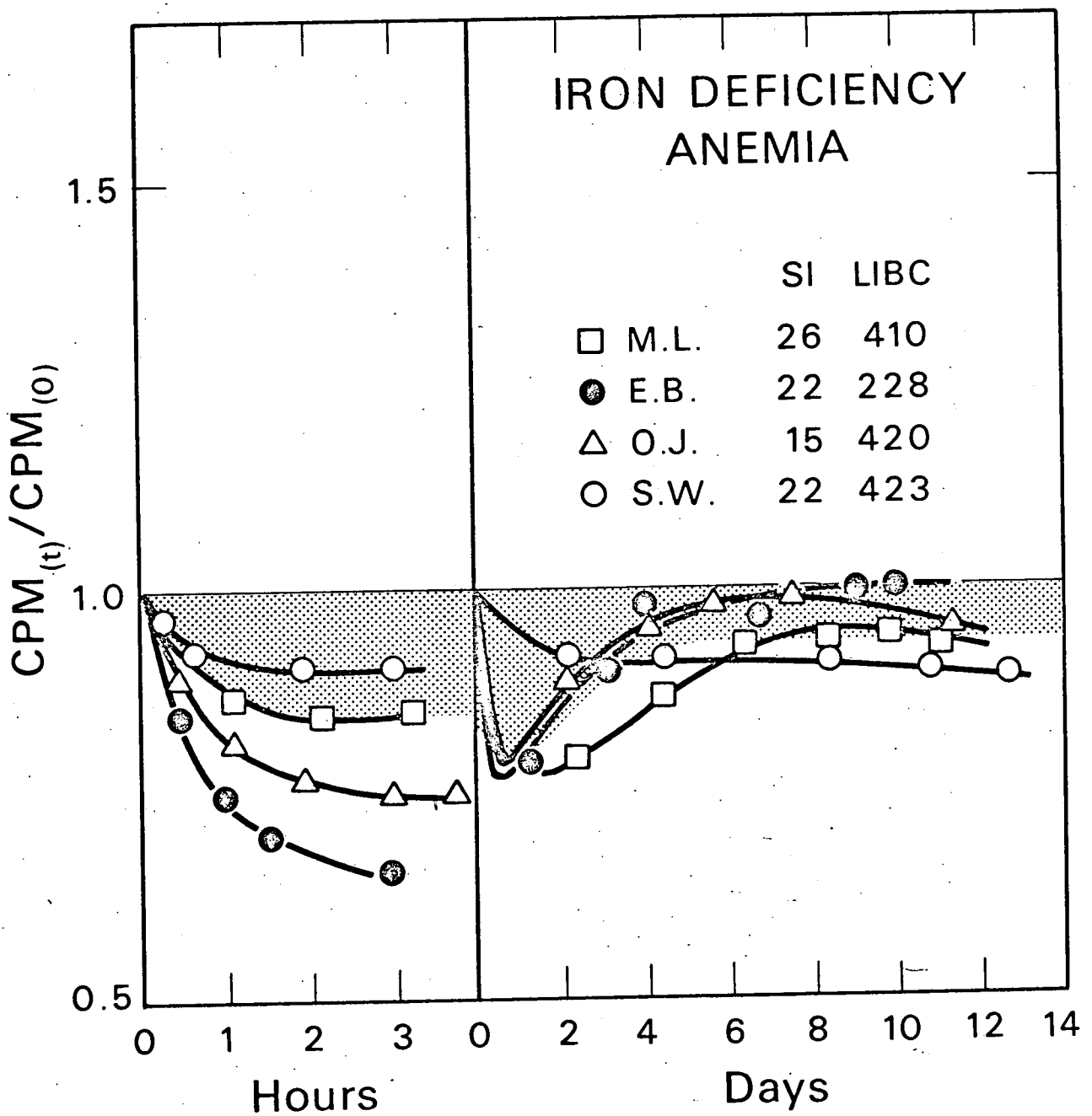
Figure 3 presents results obtained on four patients with hemochromatosis prior to phlebotomy, when the serum iron and the transferrin saturation were increased and the plasma radioiron clearance was decreased. In these subjects the average ^{59}Fe initial t 1/2 was 105 minutes.

Figure 4 presents results obtained on four patients with hemochromatosis subsequent to a course of phlebotomy, when the serum iron and the transferrin saturation decreased and the plasma radioiron clearance was normal or increased. In these subjects the average ^{59}Fe initial t 1/2 was 28 minutes.

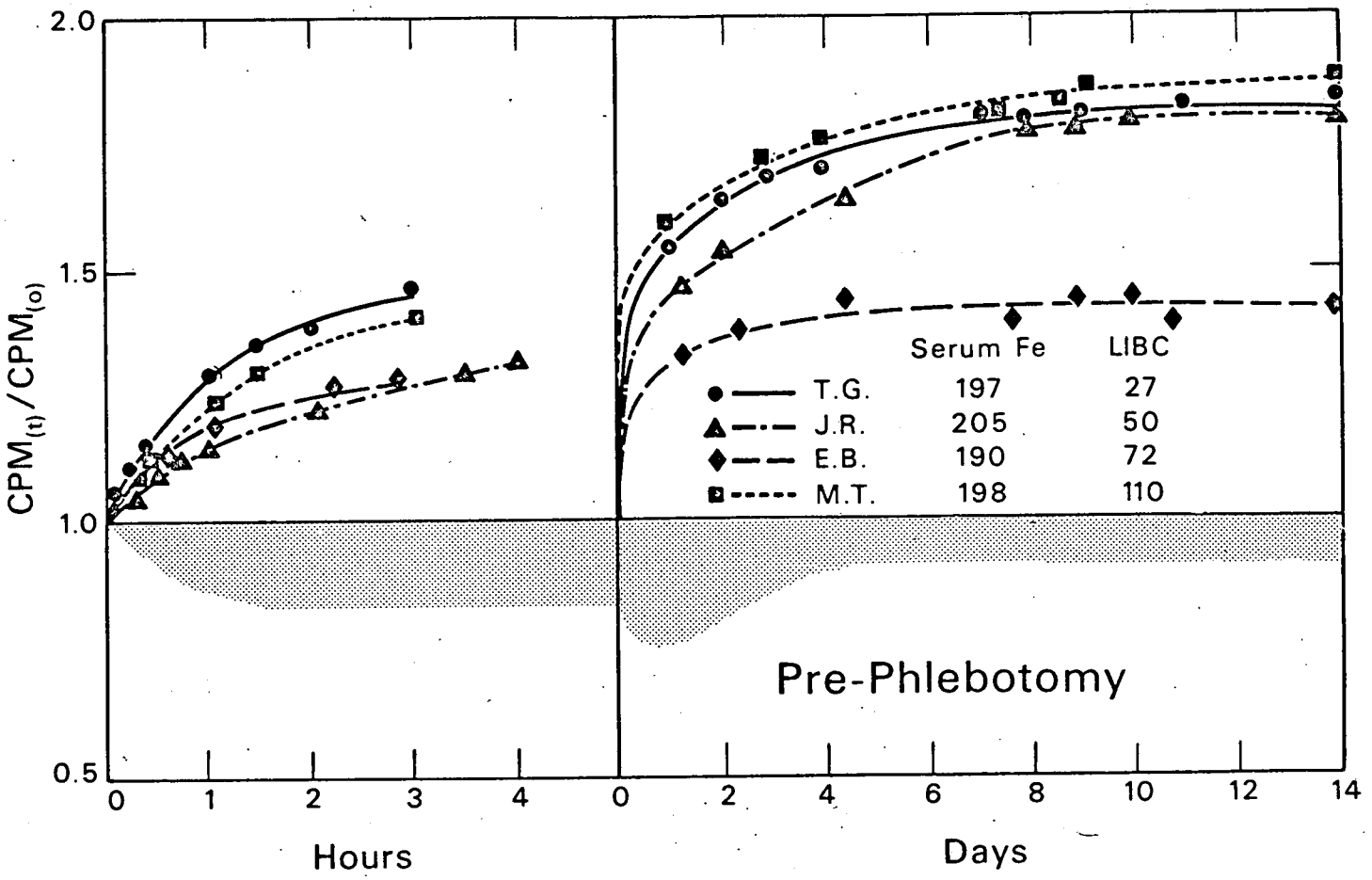
Figure 5 presents results obtained on three iron deficient cirrhotic patients with iron deficiency following the intravenous administration of ^{59}Fe. In these subjects the average ^{59}Fe initial t 1/2 was 20 minutes.


Normals
SI LIBC
101 220 △ 1
112 182 ○ 2
144 261 □ 3
200 248 ● 4
CPM(t)/CPM(o)
1.8
1.4
1.0
0.6
0 1 2 3 4 2 4 6 8 10 12 14
Hours
Days

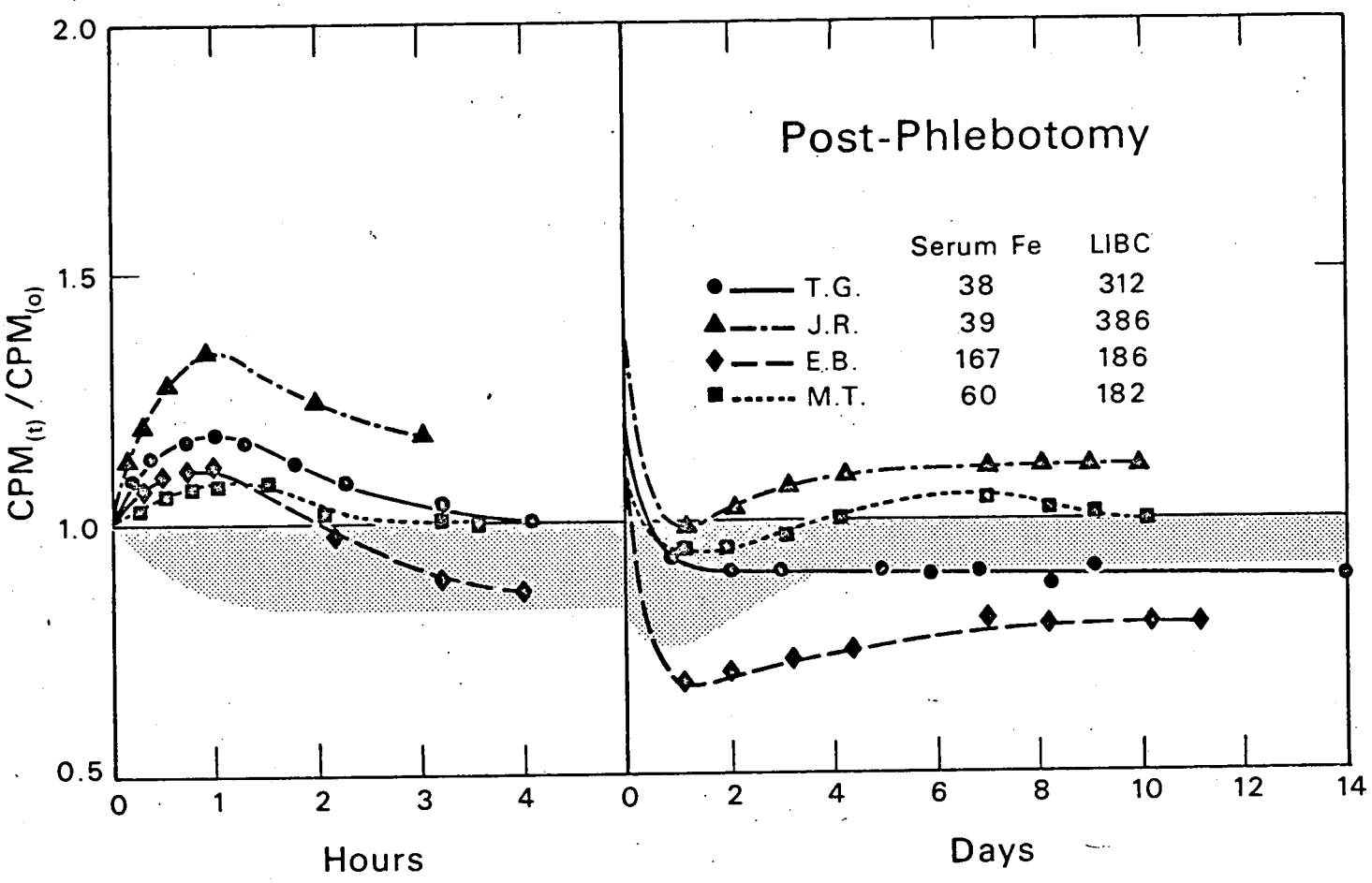
DBL 681-4540


IRON DEFICIENCY
ANEMIA
SI LIBC
M.L. 26 410
E.B. 22 228
O.J. 15 420
S.W. 22 423
1.5
1.0
0.5
CPM(t)/CPM(0)
0 1 2 3
Hours
0 2 4 6 8 10 12 14
Days

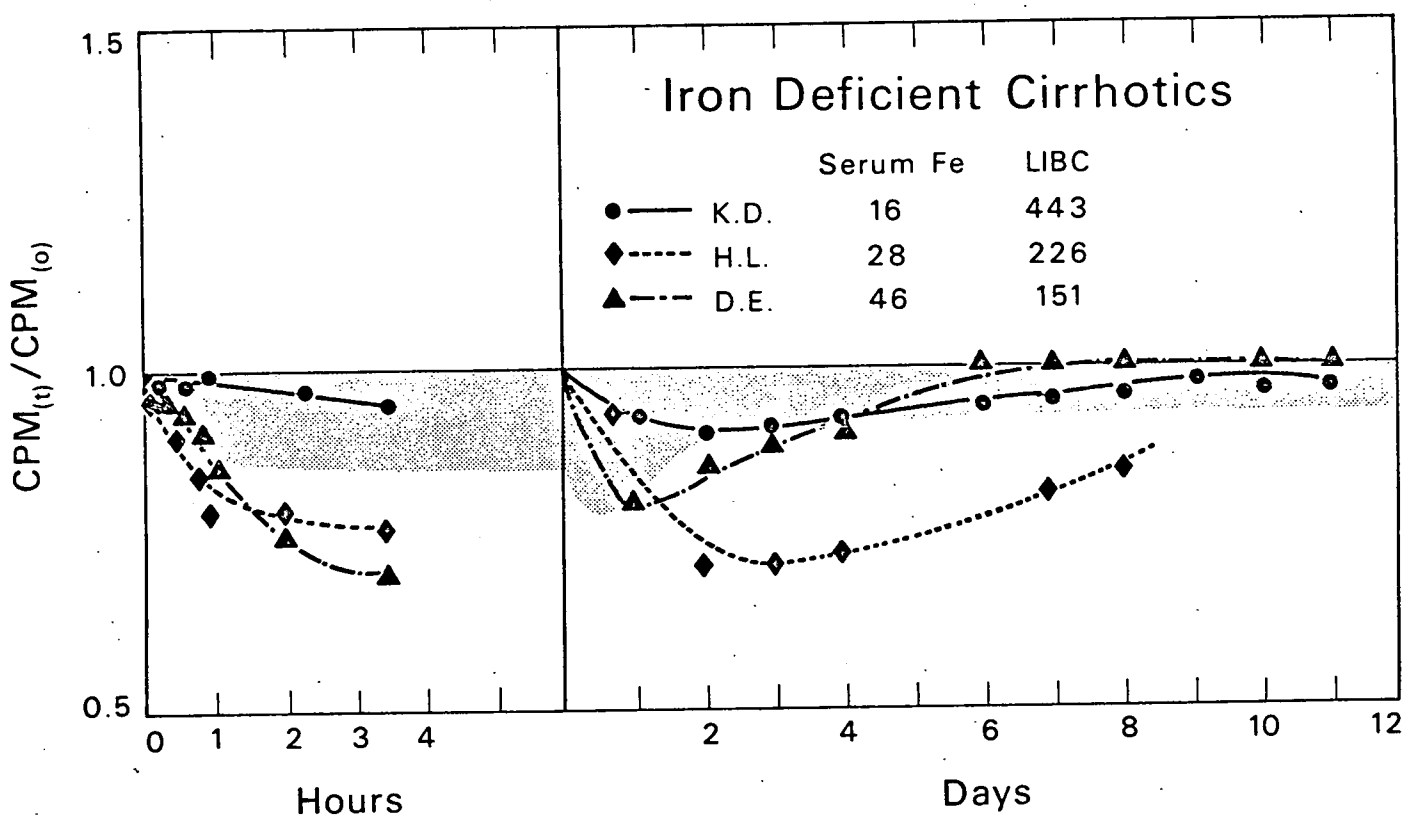
DBL 706 5783


2.0
1.5
1.0
0.5
$CPM_{(t)}/CPM_{(o)}$
0
1
2
3
4
Hours
0
2
4
6
8
10
12
14
Days
Serum Fe
LIBC
T.G. 197 27
J.R. 205 50
E.B. 190 72
M.T. 198 110
Pre-Phlebotomy

DBL 681-4537


Post-Phlebotomy
Serum Fe
LIBC
T.G. 38 312
J.R. 39 386
E.B. 167 186
M.T. 60 182
CPM(t) /CPM(o)
2.0
1.5
1.0
0.5
0 1 2 3 4
Hours
0 2 4 6 8 10 12 14
Days

DBL 681-4538


Iron Deficient Cirrhotics
Serum Fe
LIBC
K.D. 16 443
H.L. 28 226
D.E. 46 151
1.5
1.0
0.5
CPM(t) / CPM(o)
0 1 2 3 4
Hours
2 4 6 8 10 12
Days

DBL 704-5680