Studies of Iron Transport in Portal and Systemic Circulation

By M. K. KAJANI AND N. K. M. de Leeuw

THE STUDY of iron absorption in man is hampered by the fact that the amount of iron which is retained in the intestinal mucosa and in the liver during the absorptive process is not known. Technics using whole body counters and stool collections give little or no information about the internal distribution of absorbed iron, except by use of iron and the Anger positron camera. A technic which permits simultaneous sampling of portal and systemic venous blood would appear to be useful in the study of transport of iron across the intestinal mucosa and its passage through the liver.

Using Bonnet's technic, iron absorption was studied in six patients undergoing umbilical vein catheterization for diagnostic purposes. The preliminary results have been published. The data on iron absorption and utilization were compared with those obtained previously in a group of normal men and women.

METHODS

Umbilical Vein Catheterization

Under local anesthesia a small incision was made in the abdominal wall. The umbilical vein was identified in the falciform ligament, and a catheter was advanced into the left branch of the portal vein through a membranous valve separating the umbilical from the portal vein. Blood clotting was prevented by slow heparin drip. Portal pressure was measured and an open liver biopsy was taken. A hepatopancreatogram was performed to check the position of the catheter.

Study of Iron Absorption

With the catheter in place, patients fasted overnight and the next morning 96 ml. of a solution containing 10 to 15 μg. 59FeCl₃, 50 μg. ferrous ammonium sulfate, and 300 mg. ascorbic acid in 100 ml. tap water was administered orally. The remaining 4 ml. was used for standards. For the next 3 hours at 5- to 30-minute intervals, heparinized blood samples were taken simultaneously from the antecubital vein, and from the umbilical vein catheter through a 3-way stop cock (discarding the first 15 ml.); 2 ml. samples of plasma were pipetted into counting tubes. Between 100 and 120 ml. of blood was removed from each patient. The amount of isotope removed by the sampling was less than 0.5 per cent of the
administered dose. During the next 12 days at least three 6 ml blood samples were taken and the packed cells separated. Samples of plasma and packed red cells were counted in a Picker autowell scintillation counter. At the end of the study the red cell mass was calculated from plasma volume (determined by $^{131}$I-tagged albumin) and corrected hematocrit, and $^{59}$Fe utilization was determined.

Since the study of iron absorption by fecal collection method is greatly dependent on completeness of the collections, every effort was made to ensure this. Stools were collected carefully for 12 days. At the end of the study the samples were counted in a well-type scintillation detector (Armac). The amount of isotope which was not excreted was considered to be absorbed.

Iron absorption and utilization were studied previously by Bonnet's technic in 19 normal men and 18 normal women. Using this method in 2 iron-deficient subjects 100.5 per cent and 95 per cent of the administered isotope was recovered in the sum of fecal collections and blood samples. In two thirds of the normal subjects the amount of isotope in the stool was determined by a slightly different technic, i.e., counting a sample of the homogenized total stool collections. With this technic 99.2 per cent of isotope added to a 4-day stool collection could be accounted for. Means and standard deviations of iron absorption and utilization in normal men and women are shown in Table 1.

Body monitoring was carried out in one patient using a Picker Dual Probe System, with scintillator crystals (each probe containing a 1.5 by 1.5 inch thallium-activated NaI crystal and single-hole collimator), pulse height analyzer and rate meter.

At the onset of the experiment, serum iron, using batho-phenanthroline-disulphonate, and the unsaturated iron binding capacity were determined in portal and systemic venous blood. Bone marrow was obtained from the posterior iliac crest. Bone marrow smears were evaluated for morphology and hemosiderin content using previously described methods. Hemosiderin was graded 0 to 4+. Hematologic studies were done using routine methods. Sections of liver tissue were stained for iron with Perl's stain, and graded 0 to 3+. The grading system was similar to that used by Harker et al. A photomicrograph of parenchymal iron (graded 2+) is shown in Figure 5.

## Results

The $^{59}$Fe absorption curves in two patients with decreased iron stores were similar.

### Case 1

H.M. was a 40 year old woman with a history of metromenorrhagia. She had undergone a radical mastectomy for carcinoma of the breast 3 years ago. The umbilical vein was catheterized, and a hepatopancreatogram was performed which showed no evidence of liver metastases. Portal pressure was normal.

Hematologic data, serum iron binding capacities in systemic and portal venous blood are shown in Table 1. Bone-marrow smears were not satisfactory for determination of M:E ratio, nor for assessment of iron stores. The latter were considered to be decreased in view of the history of excessive blood loss. Liver biopsy showed no stainable parenchymal iron and no hemosiderin in Kupffer cells.

Since 34 per cent of the isotope was excreted in the feces in 12 days, 66 per cent was absorbed, 76 per cent of which was utilized for hemoglobin synthesis (or 50 per cent of the oral dose). These data are typical for a female (Table 1).

### Absorption Curves

After oral administration of $^{59}$Fe the isotope was absorbed within minutes,
Table 1.—Hematologic Data and Results of $^{59}$Fe Excretion, Absorption and Utilization

<table>
<thead>
<tr>
<th>Name</th>
<th>Sex</th>
<th>Hgb g%</th>
<th>PCV %</th>
<th>Serum iron $\mu g%$</th>
<th>UIBC $\mu g%$</th>
<th>TIBC $\mu g%$</th>
<th>% Sat. Transferrin</th>
<th>Bone Marrow Hemosiderin</th>
<th>$^{59}$Fe Excreted in stools (%) of administered dose</th>
<th>$^{59}$Fe Absorbed (%)</th>
<th>$^{59}$Fe Utilized (%)</th>
<th>$^{59}$Fe Utilized (% of absorbed dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.M.</td>
<td>F</td>
<td>12.3</td>
<td>36</td>
<td>S:56</td>
<td>P:68</td>
<td>119</td>
<td>175</td>
<td>32 Unsatisfactory</td>
<td>34</td>
<td>66</td>
<td>50</td>
<td>76</td>
</tr>
<tr>
<td>A.C.</td>
<td>M</td>
<td>12.9</td>
<td>39</td>
<td>S:46</td>
<td>P:41</td>
<td>284</td>
<td>330</td>
<td>13 0</td>
<td>*</td>
<td>*</td>
<td>39</td>
<td>*</td>
</tr>
<tr>
<td>F.B.</td>
<td>M</td>
<td>13.3</td>
<td>42</td>
<td>S:46</td>
<td>P:46</td>
<td>73</td>
<td>119</td>
<td>38 2+</td>
<td>50</td>
<td>50</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>E.M.</td>
<td>M</td>
<td>13.9</td>
<td>43</td>
<td>S:39</td>
<td>P:29</td>
<td>73</td>
<td>119</td>
<td>38 4+</td>
<td>35</td>
<td>65</td>
<td>3.5</td>
<td>5</td>
</tr>
<tr>
<td>Y.R.</td>
<td>M</td>
<td>16.4</td>
<td>50</td>
<td>S:36</td>
<td>P:45</td>
<td>128</td>
<td>164</td>
<td>21 4+</td>
<td>67</td>
<td>33</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>R.K.</td>
<td>F</td>
<td>11.7</td>
<td>37</td>
<td>S:25</td>
<td>P:22</td>
<td>110</td>
<td>135</td>
<td>18 3+</td>
<td>*</td>
<td>*</td>
<td>15</td>
<td>*</td>
</tr>
</tbody>
</table>

**Normal range:**

- S:90–130
- 160–240
- 270–340
- 25–50

<table>
<thead>
<tr>
<th>18 normal men</th>
<th>mean</th>
<th>37.06</th>
<th>18.28</th>
<th>45.78</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 normal women</td>
<td>mean</td>
<td>18.61</td>
<td>14.51</td>
<td>17.80</td>
</tr>
</tbody>
</table>

S= in systemic blood
P= in portal blood
0= absent
* = not determined due to incomplete stool collections
Fig. 1.-$^{59}$Fe absorption curves in portal and systemic venous blood. (The net counts per 2 ml. plasma per minute are corrected for a 2 ml. standard of 30,000 counts per minute.)

with rapidly rising counts in portal and systemic circulation (Fig. 1). The ratio of portal to systemic counts decreased from 3.64 to 1.63 in the ascending limbs of the curves. Peak counts were reached after 30 minutes in the portal, and after 45 minutes in the systemic circulation. The descending slopes of the curves coincided, indicating that absorption of the isotope had practically ceased after 45 minutes. The identical declining slopes also ruled out retention of isotope by the liver. At the peak of the absorption curve, 36 per cent of the isotope was present in the systemic plasma.

Case 2

A.C. was a 64 year old man with postnecrotic cirrhosis, and portal hypertension (portal pressure 320 mm. H$_2$O), without evidence of collateral circulation. Hematologic data, serum iron and iron binding capacities in systemic and portal venous blood are shown in Table 1. Bone marrow was cellular and normoblastic, M:E ratio 3:1; hemosiderin was absent, indicating an iron-deficiency state. The Kupffer cells and parenchymal cells of the liver did not contain stainable iron. Stool collections were incomplete. Thirty-nine per cent of the administered $^{59}$Fe was utilized for hemoglobin synthesis (Table 1).

Absorption Curves

There was rapid entry of the isotope into the portal and systemic circulation, with highest count ratio of 1.37 in the ascending limbs, and coinciding descending slopes (Fig. 2), indicating that absorption had become negligible, and that no hepatic retention of isotope occurred. Peak counts were reached after 45 minutes in the systemic circulation, at which time 23.8 per cent of the isotope was contained in the plasma.

In the next patient a slower absorption curve was observed.

Case 3

F.B. was a 31 year old man with postnecrotic cirrhosis and portal hypertension (portal pressure 300 mm. H$_2$O), but no evidence of collateral circulation. Hematologic data, serum iron and iron binding capacities are shown in
Table 1. Bone marrow was cellular and normoblastic, M:E ratio 2:1, hemosiderin was 2+. The Kupffer cells and the parenchymal cells of the liver did not contain stainable iron.

Fifty per cent of administered $^{59}$Fe was recovered in the stool during 12 days. Of the 50 per cent absorbed, half (or 25 per cent of the oral dose) was utilized for hemoglobin synthesis. These data are typical for a male (Table 1).

**Absorption Curves**

Portal and systemic counts started to rise 45 minutes after administration of the isotope. Since the patient experienced some abdominal cramps, it was felt that the delay was probably due to delayed gastric emptying. The increase and decrease of counts in the portal and systemic circulation were slower than in the previous patients (Fig. 3). Peak counts were reached after 2 hours, at which time 5 per cent of the isotope was in the systemic circulation. The ratio of portal to systemic counts reached unity after 150 minutes, suggesting that there was no significant hepatic uptake of $^{59}$Fe. This is in agreement with the absence of parenchymal iron in the liver biopsy of this patient.
In the next three patients the pattern of the $^{59}$Fe absorption curves was strikingly different from that in the previous patients.

**Case 4**

E.M., a 59 year old man, developed obstructive jaundice due to metastatic Ca of the pancreas. Portal pressure was normal. Bilirubin was 12.6 mg. per cent. Serum iron values were low in systemic and portal venous blood (Table 1). The UIBC could not be determined photometrically because of hyperbilirubinemia, but starch gel electrophoresis of systemic and portal venous serum showed clearly visible transferrin bands, which could be further identified in autoradiographs by their capacity to take up $^{59}$Fe in vitro. Bone marrow was cellular and normoblastic. M:E ratio 7:1, hemosiderin was 4+. Liver biopsy showed tumor tissue, 1+ iron in liver cells and none in Kupffer cells.

Since the percentage of $^{59}$Fe excreted in the stools after 12 days was 35 per cent, 65 per cent was absorbed by the gastrointestinal mucosa. Incorporation of $^{59}$Fe into hemoglobin was only 3.5 per cent of the oral dose after 12 days. Utilization of absorbed isotope was significantly decreased to 5 per cent (Table 1).

**Absorption Curves**

Isotope counts in portal and systemic venous blood over a 2½ hour period were very low (Fig. 4), indicating that very little of the isotope which was taken up by mucosal cells was transferred to the portal blood.

**Case 5**

Y.R. was a 59 year old man with idiopathic iron storage disease, whose brother had died with the full-blown clinical picture of idiopathic hemochromatosis. The patient had no history of excessive alcohol intake. The liver was 2 fingers below the costal margin and firm; spleen was not palpable. Liver function tests, BSP, and glucose tolerance tests were normal. Four serum iron determinations, taken over a 2 year period, had shown increased values (from 152 to 200 µg. per cent), with increased saturation (52 to 80
per cent) of transferrin. Bone-marrow was cellular and normoblastic. M:E ratio 3:1, hemosiderin was 4+. Two liver biopsies showed 2+ parenchymal siderosis, plus moderate fatty changes in the first one (1965) (Fig. 5) and slight periportal fibrosis in the second (1966), but no evidence of cirrhosis. After intramuscular injection of 600 mg. desferrioxamine HCl (Ciba Company), 24 hour urinary iron excretion was slightly increased to 1.16 mg. (range in 8 normal males: 0.58 to 0.80 mg./24 hours). The patient was admitted for herniorrhaphy. During operation an umbilical vein catheter was inserted. Portal pressure was normal. On the day after operation, $^{59}$Fe absorption studies were carried out.

Serum iron, UIBC, TIBC and transferrin saturation of systemic blood were unusually low, probably related to the post-operative state. In the portal venous blood the serum iron value was similar to that in the peripheral venous blood, but the UIBC was very low with resultant high transferrin saturation. The reason for the discrepancy between systemic and portal blood samples is not clear. Starch gel electrophoresis showed adequate and equal transferrin bands in both samples of serum.

Since 67 per cent of the isotope was recovered in the stool in 11 days, 33 per cent was absorbed by the gastrointestinal mucosa. Incorporation of the administered dose of $^{59}$Fe was only 3 per cent after 12 days, and 7 per cent after 21 days, indicating continued incorporation of iron into hemoglobin. Incorporation of the absorbed isotope was significantly decreased to 9 per cent after 12 days (Table 1).
Twenty-one days after the experiment was started, 0.17 per cent of the isotope was present in a single stool specimen, and on the twenty-eighth to twenty-ninth day, 0.72 per cent of the isotope was recovered in a 48 hour stool collection, indicating continued excretion of isotope in the feces. There was no evidence of gastro-intestinal blood loss.

Absorption Curves

Isotope curves showed negligible counts in the portal and systemic circulation over a 6 hour period (Fig. 4). The discrepancy between the considerable uptake of isotope by the mucosa and the low portal counts indicates retention of iron\(^{59}\) by the intestinal mucosa.

External monitoring of thorax, abdomen and pelvis on the twelfth and thirty-fifth day after oral \(^{59}\)Fe administration showed no significant counts above background, over heart, lungs, liver, and both lower abdominal quadrants. On the twelfth day, significant counts (two to three times background) were recorded in mid and left epigastrum but not elsewhere. Specifically, there was no evidence of radioactivity over the liver. The accumulation of counts in the mid and left epigastric regions suggests prolonged retention of isotope in the mucosa of the upper gastro-intestinal tract. These data are in agreement with the flat portal \(^{59}\)Fe curve, and demonstrate that the main cause of the decreased utilization is not hepatic uptake but failure of the isotope to cross the mucosal barrier.

Case 6

R.K. was a 52 year old woman with disseminated reticulum cell sarcoma. Portal pressure was normal. Hematologic data, serum iron and iron binding capacities in systemic and portal venous blood are given in Table 1. Bone marrow was cellular with active normoblastic erythropoiesis. The specimen was not suitable for determination of M:E ratio; hemosiderin was increased to 3+. There was a slight amount of hemosiderin in Kupffer cells of the liver, but no parenchymal iron was present. Stool collections were not complete. The utilization of administered \(^{59}\)Fe (15 per cent) was rather low for a woman (Table 1).

Absorption Curves

The isotope tracings in portal and systemic circulation were flat, with the exception of a sudden peak of portal counts at 30 minutes (portal/systemic count ratio of 10) (Fig. 6), suggesting hepatic uptake of isotope over a brief period. After 60 minutes, portal vein counts had decreased to negligible values. In contrast, folic acid, which was given to the patient immediately before the isotope, was rapidly absorbed over a 3 hour period.\(^{14}\)

Discussion

It has been shown in rats that absorption of iron is a two-step mechanism consisting of a) mucosal uptake of iron from bowel contents, and b) transfer of mucosal iron to the blood.\(^{15}\) The second step is influenced by the state of
body iron stores, and it is probably this step which is influenced by erythropoietic bone marrow activity. Thus the intestinal mucosal cell can function as a barrier by preventing iron taken up from the lumen to be passed into the blood stream. A similar two-step mechanism of iron absorption has been considered in humans, but so far little direct evidence for its existence has been presented.

The present data show that there are great differences in the rate at which orally administered radioactive iron enters the portal circulation. The results can be grouped into three different patterns of absorption. The most rapid rates of entry of isotope into the portal circulation were seen in two patients (H.M. and A.C.) with low iron stores (Figs. 1 and 2); a slower rate of entry was observed in the patient F.B. with 2+ bone-marrow hemosiderin (Fig. 3), and very slow rates were noted in the three patients with three and four plus bone-marrow iron (E.M., Y.R. and R.K.) (Figs. 4 and 6). It is tempting to interpret these findings as indicating a relationship between rate of entry of iron into portal blood and state of iron stores. However, other factors may have influenced the transfer of iron from mucosal cells to portal blood, such as differences in erythropoietic bone marrow activity and systemic factors. Since there were only moderate differences in erythropoietic activity as evidenced by differences in M:E ratios, it is unlikely that the marked differences in portal entry rates were due to differences in erythropoiesis. However, it is possible that in the last three patients (E.M., Y.R. and R.K.) systemic factors (malignant disease, postoperative state) were responsible for the near failure of mucosal 59Fe content to enter the portal circulation.

In the four subjects (H.M., F.B., E.M. and Y.R.) in whom stool collections were considered complete, there was no correlation between the amount of isotope taken up by the gut (Table 1) and the rate at which the isotope entered the portal blood stream (Figs. 1–4). Thus in patient H.M. mucosal uptake was 66 per cent and the isotope entered the portal blood rapidly, whereas in patients E.M. and Y.R., 65 and 33 per cent of the isotope were absorbed with almost no uptake in the portal blood. It would appear that mucosal uptake and transfer of mucosal iron to the blood are relatively in-

**Fig. 6.** -59Fe absorption curves in portal and systemic venous blood (Net counts are corrected as in Figure 1) and portal folate levels (mg./ml.) after administration of 1 mg. folic acid.
dependent processes. Thus the present data would support the existence of a two-step mechanism of iron absorption in humans.

The observations that in patients E.M. and Y.R. considerable amounts of isotope were taken up by the gut, but that little entered the portal circulation, demonstrate that in humans also the intestinal mucosa may retain iron and prevent its entrance into the circulation. This barrier function apparently exists to a certain extent even in a patient with familial iron storage disease (Y.R.) and may have been responsible for the fact that his iron stores were only modestly increased. It may have been a temporary phenomenon influenced by his post-operative state.

In this patient (Y.R.) the continued excretion of isotope in the stool supports the concept that iron is lost from the gastrointestinal tract in iron-replete subjects, presumably due to desquamation of iron-laden mucosal cells and macrophages.23,24,25

A marked discrepancy between the amount of $^{59}$Fe absorbed and that incorporated into hemoglobin has been noted before in patients with various anemias, Hodgkin's disease and hemochromatosis.23,24 While such a discrepancy could be due to hepatic deposition of iron or decreased utilization of transferrin bound iron, the flat portal isotopic curves observed in patients E.M. and Y.R. show that in these patients the disparity is mainly due to trapping of isotope in the intestinal mucosal cells.

In patient Y.R., the slight increase of $^{59}$Fe utilization after 3 weeks suggests that mucosal iron may act also as a reservoir for a "slow phase" of absorption, as has been demonstrated previously in rats and humans.1,17 Some of the mucosal iron may eventually have been retained by the liver although we could not show this.

Our data show that the level of serum iron does not influence transfer of iron from mucosal cells to portal blood because a decreased serum iron was observed in all our patients (Table 1).

It has been observed that in normal subjects with induced transferrin saturation and in patients with low UIBC iron is quite well absorbed but is deposited to a great extent in the liver. Differences of our data in Y.R. with those obtained previously may be due to inaccurate measurement of the portal venous UIBC by photometric methods, to the low dose of carrier iron administered, or to systemic factors (post-operative state) in the patient studied.

Since in the first two patients (H.M. and A.C.) absorption of isotope had become negligible during the declining part of the curve (Figs. 1 and 2), the declining slope of the systemic isotope curve may be considered to indicate the disappearance rate of intravenously injected transferrin-bound iron. Since this slope was linear on semilog plot, and the plasma volume was known, the per cent of isotope which entered the systemic circulation during the observation period could be calculated.27 Using linear systems theory it was calculated that in patient H.M. 56.4 per cent, and in patient A.C., 32.9 per cent (The method was proposed by Mr. H. C. Lee, Biomedical Engineering Unit, McGill University).
cent of the isotope was transported in the systemic circulation. These data correlate closely with the 50 per cent and 39 per cent of $^{59}$Fe which were utilized, respectively, by these patients for hemoglobin synthesis. The correlation of the percentage of isotope transported in the systemic circulation with that utilized for hemoglobin synthesis should be examined in a large sample.

In the sixth patient (R.K.) the high portal/systemic counts ratio at 30 minutes suggests hepatic uptake of iron over a brief period. It has been reported that pharmacologic doses of folic acid improve absorption of ferrous sulfate in patients with gastric hypo-acidity. It is conceivable that folic acid, which was given just before $^{59}$Fe was administered, caused a temporary shift of iron from mucosal cells to the liver where both were retained. These data need confirmation. Comparison of the absorption curves of $^{59}$Fe and folic acid shows that the rates of entry of inorganic ferrous iron and folic acid into the portal blood were greatly different.

**Summary**

Simultaneous $^{59}$Fe absorption curves in portal and systemic venous blood showed different rates of entry of the isotope into the portal (and systemic) circulation: the most rapid entry was seen in two patients with decreased iron stores, whereas negligible counts were obtained in two patients with increased iron stores. These data, combined with $^{59}$Fe excretion data, indicate a barrier function of the intestinal mucosa for the passage of iron in two iron-sufficient patients, with evidence of prolonged excretion of $^{59}$Fe into the bowel in one of these. The data support a two-step mechanism of absorption of inorganic ferrous iron in humans, the first step being uptake of iron by the intestinal mucosa; the second step transfer of mucosal iron to the portal circulation.

In the two patients with decreased iron stores the shape of the absorption curves ruled out significant hepatic deposition of isotope; the amount of isotope transported in the systemic circulation correlated closely with that utilized for hemoglobin synthesis.

Different rates of absorption of inorganic ferrous iron and folic acid were demonstrated in one patient.

**SUMMARIO IN INTERLINGUA**

Curvas del absorption de $^{59}$Fe obtenite simultaneemente in sanguine portal e del circulation major ha revelate differente intensitates de entrata. Le entrata le plus rapide esseva observate in duo patientes con reducite reservas de ferro, durante que negligeble contationes esseva obtenite in duo patientes con augmentate reservas de ferro. Iste observationes—in combination con datos relative al excretion de $^{59}$Fe—indica que le mucosa intestinal ha le function de un banniera pro le passage de ferro in duo patientes con carentia de ferro, con evidentia de un prolongate excretion de $^{59}$Fe ad in le intestino in un del duo. Le datos supporta le theses de un mechanismo biphasic de absorption de inorganic ferro ferrose in humanos, i.e., un mechanismo le prime phase del qual consiste in le acception de ferro per le mucosa intestinal, durante que le secunde phase es illo del transferimento de ferro mucosal ad in le circulation portal.

In le duo patientes con reducite reservas de ferro, le conformation del curvas de absorption exclude le possibilitate de un significative deposition hepatic del isotope. Le quantitate de isotope transporte in le circulation major esseva intimemente correlationate con illo utilisate in le synthese de hemoglobina.
Diferente intensitates de absorption de inorganic ferro ferrose e de acido folic esseva demonstrate in un del patientes.

ACKNOWLEDGMENTS

The data on folate absorption in the sixth patient was kindly provided by Dr. V. M. Whitehead.

The calculations of the percentage of isotope transported in the systemic circulation were carried out by Mr H. C. Lee, Biomedical Engineering Unit, McGill University.

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