Normal Iron Absorption and Decreased Red Cell Iron Uptake in the Aged

By J. J. M. Marx

Absorption of iron was studied with a double-isotope technique that allowed differentiation between "mucosal uptake," "mucosal transfer," and ultimate "retention" of iron. A physiologic dose of ferrous sulfate was administered to 25 healthy young adults, 40 active aged persons, and 20 patients with uncomplicated iron deficiency. Radioactivity was measured with a whole-body scanner. Iron absorption values were not decreased in aged subjects compared to young adults. Mucosal uptake, mucosal transfer, and retention of iron were equally increased in both young and old patients with iron deficiency. In 12 young adults and 33 aged persons red cell iron uptake was studied in addition to iron absorption. Young adults utilized 91% of the retained, orally administered iron and the aged only 66%. An increase in ineffective erythropoiesis in old age is suggested.

Many old people suffer from iron deficiency anemia, which may be a result of improper or insufficient nutrition, blood loss, or an impaired absorption of iron. A decreased iron absorption in old age was reported, but description and selection of control subjects was inadequate. Sex was not mentioned and iron deficiency was not excluded, while even a latent iron deficiency, common in menstruating women, is known to cause a considerable increase in iron absorption. The results of one study were obtained in aged patients suffering from serious gastrointestinal diseases. Because changes in physiologic functions can be a result of disease or of aging itself, only healthy subjects should be included in studies of "normal" values in old age.

An increase of iron stores in old age is reported, while hemoglobin concentration does not change significantly with age. This increase of iron stores can be a result of loss of muscle volume, decrease of erythrocyte volume, or ineffective erythropoiesis but can hardly be associated with an impaired iron absorption. Therefore we compared the absorption of a physiologic dose of inorganic iron (as ferrous sulfate) in apparently healthy aged men and women living in their own homes with the absorption of iron in healthy young adults of both sexes. A similar investigation was performed in young and aged persons with iron deficiency in order to study the ability to adjust iron absorption to higher needs. Bone marrow iron was assessed in all aged subjects and patients with iron deficiency.

In this investigation we differentiated among "mucosal uptake" (the amount of iron taken up by the mucosal cells from the lumen of the gut), "mucosal transfer" (the fraction of iron taken up by the mucosal cells that passes on to the blood), and "retention" (the iron that is still in the body 14 days after ingestion). As an indication for the effectiveness of erythropoiesis, red cell iron uptake was studied in a number of our young and old test subjects.

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MATERIALS AND METHODS

Test subjects. Informed consent was obtained from all healthy test subjects. Persons with possible disturbances associated with changes in iron metabolism, and especially in iron absorption, were not included in this study: excluded were subjects with a known loss of blood, with diseases or former operations of the upper digestive tract, diarrhea, chronic disease (e.g., rheumatic arthritis, malignancies), abnormal serum iron values, and anemia.

Young adult volunteers were members of the hospital staff and medical students. After a medical history, a physical examination, routine hematologic blood tests, and determination of serum iron and iron binding capacity, 15 males and 10 females entered the study. In the selection of "healthy" aged persons, every effort was made to ensure that age was the only important parameter that differed between young and old test subjects. All aged subjects were active members of a social club for senior citizens in Utrecht, living in their own homes. After an informative meeting, which was attended by about 200 members, 93 volunteers of 65 yr and older were subjected to a standard medical history, physical examination, and blood, urine, and fecal tests. Finally, 43 aged subjects were considered as "normal," and iron absorption was studied in these subjects. For technical reasons 3 of them had to be excluded from the study. In addition, 20 patients of all ages with uncomplicated iron deficiency were studied. The criterion for iron deficiency was a lack of iron in the bone marrow reticuloendothelial system (RES).

In Table 1 some hematologic parameters of the test subjects are summarized. Table 2 shows the amount of stainable iron in the bone marrow RES of the healthy aged volunteers.

Test subjects for 59Fe red cell iron uptake studies were chosen at random from those in whom iron absorption studies were performed.

Determination of iron absorption. Iron absorption was studied by a modification of the double-isotope technique described by Boender and Verloop.8 This method is described elsewhere in detail.9,10

An oral test dose was administered containing 7 mg Mohr’s salt [FeSO4(NH4)2SO4 ⋅ 6H2O = 1 mg Fe2+] labeled with 5 μCi 59Fe to which 40 μCi 51Cr (as CrCl3) was added as an inert, nonabsorbable indicator and 10 mg ascorbic acid as an antioxidant. Test subjects were fasting for at least 10 hr before and 2 hr after ingestion of the test dose. Radioactivity was measured with a shadow shield type of whole-body scanner (National Health Institute RIV, Bilthoven, The Netherlands).

Mucosal iron uptake (a) was calculated from the amount of 59Fe and 51Cr administered (both considered as 100% measured 1 hr after ingestion of the test dose) and the amount of 59Fe (At) and 51Cr (It) found within the body 1 day later using

\[
a = \frac{100}{100 - \frac{At}{It}}
\]

At and It were expressed as percentages of the amount of 59Fe and 51Cr administered. Mucosal iron uptake values are reliable only if determined within 48 hr after ingestion of the test dose.11,12

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No</th>
<th>Age (yr)</th>
<th>Hb (g/dl)</th>
<th>MCV (fl)</th>
<th>SI (μmol/liter)</th>
<th>TIBC (μmol/liter)</th>
<th>SRE (mm/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>15</td>
<td>30 ± 8</td>
<td>16.2 ± 0.7</td>
<td>93 ± 7</td>
<td>26 ± 7</td>
<td>62 ± 10</td>
<td>3</td>
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<tr>
<td></td>
<td></td>
<td>(22-48)</td>
<td>(15.1-17.3)</td>
<td>(83-111)</td>
<td>(17-40)</td>
<td>(40-84)</td>
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</tr>
<tr>
<td>Females</td>
<td>10</td>
<td>25 ± 9</td>
<td>14.3 ± 0.5</td>
<td>92 ± 5</td>
<td>25 ± 6</td>
<td>67 ± 7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(19-49)</td>
<td>(13.4-15.2)</td>
<td>(84-99)</td>
<td>(18-32)</td>
<td>(57-80)</td>
<td></td>
</tr>
<tr>
<td>Patients with iron deficiency:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>49 ± 21</td>
<td>12.0 ± 2.7</td>
<td>83 ± 13</td>
<td>7 ± 5</td>
<td>73 ± 12</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(16-84)</td>
<td>(6.8-16.4)</td>
<td>(53-105)</td>
<td>(1-18)</td>
<td>(54-97)</td>
<td></td>
</tr>
<tr>
<td>&lt; 60 yr</td>
<td>14</td>
<td>37 ± 13</td>
<td>11.5 ± 2.7</td>
<td>82 ± 15</td>
<td>6 ± 5</td>
<td>75 ± 12</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(16-57)</td>
<td>(6.8-14.7)</td>
<td>(53-105)</td>
<td>(1-17)</td>
<td>(57-97)</td>
<td></td>
</tr>
<tr>
<td>&gt; 65 yr</td>
<td>6</td>
<td>75 ± 7</td>
<td>13.1 ± 2.7</td>
<td>86 ± 10</td>
<td>11 ± 5</td>
<td>69 ± 13</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(67-84)</td>
<td>(8.8-16.4)</td>
<td>(72-95)</td>
<td>(6-18)</td>
<td>(54-85)</td>
<td></td>
</tr>
<tr>
<td>Aged males</td>
<td>24</td>
<td>73 ± 5</td>
<td>16.3 ± 0.9</td>
<td>92 ± 4</td>
<td>23 ± 7</td>
<td>54 ± 5</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(66-83)</td>
<td>(14.1-17.9)</td>
<td>(86-98)</td>
<td>(11-39)</td>
<td>(43-67)</td>
<td></td>
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<tr>
<td>Aged females</td>
<td>16</td>
<td>70 ± 3</td>
<td>14.7 ± 0.8</td>
<td>91 ± 4</td>
<td>18 ± 2</td>
<td>57 ± 7</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(65-77)</td>
<td>(13.2-16.1)</td>
<td>(86-105)</td>
<td>(14-24)</td>
<td>(46-72)</td>
<td>(3-31)</td>
</tr>
</tbody>
</table>
Table 2. Amount of Stainable Iron in the Bone Marrow RES of Healthy Aged Volunteers

<table>
<thead>
<tr>
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<th>+   + +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>No</td>
<td>2</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>(%)</td>
<td></td>
<td>(8.3)</td>
<td>(41.7)</td>
<td>(29.2)</td>
</tr>
<tr>
<td>Females</td>
<td>No</td>
<td>2</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>(%)</td>
<td></td>
<td>(12.5)</td>
<td>(50.0)</td>
<td>(12.5)</td>
</tr>
</tbody>
</table>

Graded according to the method of Ploem et al. Normal: ± (Rath and Finch grades 1 and 2) or + (Rath and Finch grade 3).

Determination is not possible if less than 15% of the administered 51Cr has left the body at that moment. For this reason three aged test subjects had to be excluded from the study. To promote fecal excretion of 51Cr and nonabsorbed 56Fe, bisacodyl was given as a laxative to all test subjects about 6 hr after ingestion of the test dose.

Iron retention (AR) was determined by whole-body counting on the 14th day after administration of the test dose. The mucosal transfer fraction of iron was determined as the ratio AR/a.

Red cell 55Fe uptake was studied in combination with iron retention on the 14th day. The 55Fe dose was not given intravenously but calculated from the amount of 55Fe in an oral test dose and the 55Fe retention (AR):

\[
{55\text{Fe}}\text{ dose} = AR \times \frac{1}{[100 \times 55\text{Fe administered orally (cpm)}]].
\]

Red cell 55Fe uptake can be calculated by

\[
\text{55Fe uptake} = \frac{55\text{Fe in 1 ml blood}}{\text{55Fe dose}} \times \text{blood volume} \times 100\%.
\]

Blood volumes were determined with the help of a nomogram using sex, weight, and age as parameters. Excluded were test subjects with severe adipositas or leanness according to the Quetelet index (Q = weight/height^2 x 10). Q values were within the following limits: young males, Q = 200-270; young females, Q = 180-250; aged, Q = 195-295. When this method is used for determination of red cell iron uptake, the administered test dose always passes the liver, contrary to a test dose administered intravenously.

Statistical methods. Significance of differences was tested with the nonparametric two-tailed Wilcoxon test for independent samples.

Other methods used. Venous blood was collected on the first day of the study, at about 10:00 a.m., from the fasting subject sitting in upright position. The hemoglobin concentration (Hb) and mean corpuscular volume (MCV) were measured using a Coulter S counter. Erythrocyte sedimentation rate (ESR) was determined according to the Westergren method and serum iron concentration (SI) and total iron binding capacity (TIBC) by the method of Levy and Vitacca.

Bone marrow was obtained by sternal puncture, and gradation of the amount of stainable iron in the RES was performed according to the method of Ploem et al., who considered a grading of ± or + as normal values.

RESULTS

Iron absorption in young adults and in patients with iron deficiency. Iron absorption was studied in young healthy adult males and females and in patients with uncomplicated iron deficiency. The results are summarized in Table 3. No difference could be demonstrated between young males and females with respect to mucosal uptake, mucosal transfer, and retention of iron. The higher values in the female group may be a result of prelatent iron deficiency that was not excluded by bone marrow examination. There was no significant difference in iron absorption between the male (n = 6) and female (n = 14) patients with iron deficiency (p > 0.10).

Much higher values for the mucosal uptake, mucosal transfer, and retention of
iron were found in the iron deficiency than in the control group \((p < 0.01, \text{except that for mucosal uptake in female controls } p < 0.02)\). This demonstrates that iron absorption is regulated on both the luminal and the serosal side of mucosal cells.

**Iron absorption in healthy old aged persons.** Iron absorption was studied in 40 healthy aged subjects, all with sufficient iron in bone marrow stores. The results are presented in Figs. 1 (males) and 2 (females). Mean values for mucosal uptake, mucosal transfer, and retention of iron were higher in old aged males than in young male controls. The difference for the iron retention was significant \((p < 0.05)\). There was no difference between aged females and young female controls with respect to mucosal uptake, mucosal transfer, or retention of iron.

Iron retention values of 50% or greater are usually associated with iron deficiency. These high values were found in four aged males (storage iron was graded as + in all of these cases) and in one female (storage iron ±). Further investigation revealed intermittent blood loss as a result of bleeding from colon polypes in one male. The others showed no signs of actual or recent blood loss. If old males with an iron retention higher than 50% were excluded, the following iron absorption values in this group were obtained: mucosal uptake, 41.0% ± 16.3%; mucosal transfer fraction, 0.61 ± 0.18; retention, 25.3% ± 11.7%. These mean values...
values, although higher than those found in young male adults, were not significantly different.

Iron absorption in young and old patients with iron deficiency. The group of patients with uncomplicated iron deficiency included 14 subjects younger than 60 yr and 6 subjects older than 65 yr of age. As shown in Fig. 3, no difference was found between the mean values of mucosal uptake, mucosal transfer, and retention of iron of young and old patients with a lack of bone marrow iron stores.

Red cell 59Fe uptake was investigated in 12 young adults and 33 aged subjects (Fig. 4). A substantially lower iron utilization was observed in the aged persons than in the young adults ($p < 0.01$). There was no significant correlation between the iron utilization and age or sex within the aged group (Table 4).
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DISCUSSION

The high frequency of iron deficiency in old age might be explained by a decreased ability to absorb iron from the gut. Previous studies recorded a decreased retention of inorganic iron in apparently healthy aged subjects.1,3 The results of these studies are contestable, however, mainly because of an inaccurate choice of test subjects. In studies of iron absorption a careful selection of normals is essential for young as well as for old test persons. Iron deficiency especially should be ruled out because even in prelatent iron deficiency absorption is substantially increased.

The selection of "healthy" aged subjects is important. Aged test subjects should be chosen in such a manner that deviations from normal can be ascribed to aging itself and not to pathologic processes. In our study subjects with any kind of blood loss were excluded. For practical reasons bone marrow iron stores were not assessed in young controls. It is very unlikely that healthy young men suffer from iron deficiency, but the mean iron absorption values in female controls might be slightly increased because of inclusion of some menstruating women with prelatent iron deficiency.

In this study not only iron retention but also mucosal uptake and mucosal transport of iron were investigated. In patients with uncomplicated iron deficiency mean values were significantly higher than in male and female controls. No differences were found between males and females with iron deficiency.

The separate steps of iron absorption were also studied in 40 healthy aged subjects. In the aged the absorption of a physiologic dose of inorganic bivalent iron was not decreased as compared with young adults of the same sex. Consequently iron deficiency in old age should not be interpreted as caused by a physiologically lowered iron absorption, and no time should be wasted with mere symptomatic iron therapy.

Table 4. Red Cell *%Fe Uptake (%) in Healthy Old Aged, With Subdivision Into Smaller Groups According to Sex and Age

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males 65-71 yr</td>
<td>66.2 ± 15.7</td>
<td>40-84</td>
<td>10</td>
</tr>
<tr>
<td>Males 72-83 yr</td>
<td>66.3 ± 16.8</td>
<td>40-92</td>
<td>11</td>
</tr>
<tr>
<td>Females 65-69 yr</td>
<td>66.8 ± 16.5</td>
<td>43-88</td>
<td>6</td>
</tr>
<tr>
<td>Females 70-77 yr</td>
<td>64.5 ± 12.3</td>
<td>40-74</td>
<td>8</td>
</tr>
</tbody>
</table>
We also could not demonstrate a difference in iron absorption values between younger and older patients with iron deficiency. Thus if adequate treatment of iron deficiency anemia in old age does not improve hemoglobin concentration sufficiently, the cause will probably not be poor absorption; more likely is an inaccurate diagnosis, incorrect use of the prescribed medication, or use of slow-release iron preparations in patients with accelerated passage through the stomach.

Our study was confined to the absorption of inorganic iron presented as Fe\(^{2+}\) and therefore may not have detected alterations in the absorption of heme iron. There is no reason, however, to suggest that the absorption of organic iron alters with age as a result of a higher incidence of chronic gastritis. Even in patients with achalasia gastrica the absorption of heme iron and inorganic Fe\(^{2+}\) is completely normal, while there is practically no absorption of inorganic Fe\(^{3+}\).\(^{15}\) Heinrich et al.\(^{16}\) gave normal subjects a test dose of 0.56 mg Fe\(^{2+}\) and found a mean retention of 30%. From a dose of the same amount Fe\(^{3+}\) retention was only 12%. We have compared the retention of 1 mg Fe\(^{2+}\) with that of 1 mg Fe\(^{3+}\) in ten healthy aged subjects acting as their own controls.\(^{9}\) Mean retention was 28.0% for Fe\(^{2+}\) and 12.5% for Fe\(^{3+}\) (p < 0.01), which compares very well with the results recorded by Heinrich et al. in younger test subjects.

We were puzzled by the finding of a very high iron absorption in five of our normal aged subjects with normal iron stores in whom an iron retention of 50% or more was found. Those high values are usually associated with iron deficiency. Increased iron absorption in an individual with normal iron stores may be the first sign of blood loss: more iron is needed in erythropoiesis, while mobilization of storage iron is not fast enough. Further investigation revealed intermittent blood loss, however, in only one case. Moreover, we found in a number of the healthy aged a higher than normal amount of storage iron, as shown in Table 2. This finding has also been reported by others\(^{5,6}\) and is in agreement with the finding of higher serum ferritin values in old age.\(^{17}\) An increased amount of iron, as found in other tissues such as the appendix and the pituitary gland,\(^{18,19}\) is probably related to an increase of connective tissue.\(^{20}\) If hemoglobin concentration and iron absorption do not change, an increase of storage iron in the elderly can be explained by a decreased muscle volume and red cell volume.

Our iron absorption study did not permit combination with ferrokinetic studies. Red cell iron uptake, however, could be calculated as the percentage of \(^{55}\)Fe retained from an oral test dose and recovered in the erythrocytes. Red cell iron uptake was markedly decreased in old age (mean 66%) compared to young adults (mean 91%). The latter value agrees very well with the red cell iron uptake (mean 92.9%) in young adults found by others using a similar method.\(^{21}\) Since transferrin iron apparently does not go directly to the reticuloendothelial cell, one could postulate an increased degree of ineffective erythropoiesis in old age. This would be in agreement with the experience that an increased number of overt abnormalities in red cell production is seen in the aged.\(^{22}\) The decreased iron incorporation into red cells might also be a result of an increased dilution of tracer iron with storage iron. We found, however, no correlation between red cell iron uptake and iron stores in our aged test subjects. Because the test dose in this study was given orally it might be suggested, too, that in the aged, part of the iron is retained in the liver.
Red cell iron uptake may underestimate effectiveness of erythropoiesis because it includes the $^{57}$Fe that returns to the plasma from extravascular sources and from ineffective erythropoiesis. Further investigation of ferrokinetics in old age, especially of ineffective erythropoiesis and tissue iron turnover, will be necessary, combined with determination of mean red cell lifespan. Apparently it is justified to interpret the results of ferrokinetic studies only if they are matched to values of normal subjects of the same age.

ACKNOWLEDGMENT
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