Refractory Sideropenic Anemia in Childhood Due to an Error of Iron Metabolism

By ROLF ZETTERSTRÖM AND SIMONE DELAVA

In some earlier reports indications have been put forward that pure hypochromic anemia might develop in the absence of nutritional deficiency or bleeding. In an extensive study on hereditary hypochromic anemia occurring in a district in the northern part of Sweden, Lundholm concluded that the cause of the anemia was an increased demand of iron. When the patients were treated with high doses of iron by mouth the anemia improved. Although this is an indication that defective iron absorption might be the cause of hypochromic anemia, cases with proved complete refractoriness to peroral treatment with iron have never been reported except in association with steatorrhea. In such refractory cases which have been studied with reference to fat absorption it has always been found to be defective.

In this communication, one case with a completely refractory primary sideropenic anemia, and another with poor response to iron therapy will be reported. In both cases there were indications that the anemia was not only caused by poor iron absorption from the gastro-intestinal tract, but to a more generalized disturbance of iron metabolism which was not secondary to infection or other disease. The features of this special type of hypochromic anemia will be discussed with reference to the results obtained when studying the iron metabolism by means of radioiron.

METHODS

Test of the absorption of oral iron: To a ferrous pyrophosphate mixture containing 25 mg. Fe, 2.5 μC. of Fe59 (as ferric chloride*) containing negligible amounts of iron was added. Since the ferrous mixture used will reduce small quantities of ferric iron, it can be assumed that all of the radioactive iron given was in the ferrous state. The solution was given in the morning after the patient had been fasting overnight. No food was allowed for 3 hours after the test dose was given. After the administration of Fe59, feces was collected, quantitatively, for 3 days. Since in the patients studied the radioactivity was almost quantitatively recovered in feces after 3 days the period of collection can be considered to be sufficiently long.

Test of the rate of removal of radioiron from the plasma and of the utilization of intravenously injected iron: 2μC. of Fe59 as ferric chloride with an extremely high specific activity (1 μC. per 5-10 μg. Fe) was diluted with 2 ml. physiologic saline in a Florence flask of 150 ml. and autoclaved. To the solution, 25 ml. of human plasma with a level of unsaturated iron-binding protein that far exceeded the amount of ionized iron, was added with sterile pre-

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We wish to express our gratitude to Professor B. Vahlquist for examination of bone marrow smears and to Dr. R. Bonichsen for discussions concerning methods of radioiron analysis. We are also indebted to Dr. C.-G. Holmberg for the copper determinations, to Dr. K.-G. Paul for the porphyrin determinations, and to Mrs. Franzí Wagenherr for the determinations of serum iron-binding capacity.

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* Supplied by A.E.R.E., Harwell.
cautions. The mixture was then incubated with shaking at 37 C. for 1 hour. Dialysis control proved that all iron had combined with the protein during this time and that no radioactive iron remained in the ionic state. Twenty ml. of the mixture was injected intravenously into the fasting patient. Successive heparinized blood samples were then drawn from another vein. The blood samples were centrifuged immediately and plasma was removed for determination of radioactivity.

To test the utilization for hemoglobin synthesis of intravenously injected iron, blood samples were taken repeatedly during four weeks after the injection. For estimating the radioactivity incorporated in hemoglobin the total circulating hemoglobin was measured with the CO-method as modified for children.

Measurement of the radioactivity in the samples: The total amount of feces was homogenized with water in a Waring blender. Two aliquots of the feces-mixture (10-15 ml. of a total amount of about 2 l.) were ignited with sulfuric acid and hydrogen peroxide. The samples of whole blood for determination of the utilization of radioiron for hemoglobin synthesis were hemolyzed by the addition of a few drops of concentrated aqueous ammonia. Plasma samples and hemolyzed whole blood samples were ignited in the same way as the feces samples. Duplicate determinations were performed.

Standard samples were obtained after a dilution procedure of the stock solution. Radioactivity of the different samples was measured according to the method of Agner, Bonichsen and Hevesy.

The total iron-binding capacity of serum (transferrin or siderophilin) was determined according to Rath and Finch. Serum iron was determined according to Vahlquist.

Case Reports

Case 1

B.-M.T., a girl, 7 years old, was admitted to the Pediatric Clinic, Karolinska Sjukhuset on March 26, 1952 because of anemia. She is the only child of healthy parents. Family history was irrelevant. The girl had developed normally and there was no history of any serious disease or hemorrhage. Her diet has not been deficient in any respect. September, 1951, half a year before admission, a moderate anemia was diagnosed on routine examination at school. The hemoglobin level was 8.5 Gm. per 100 ml. Treatment with high doses of iron perorally was without effect. Since the blood values also failed to normalize after folic acid treatment the child was admitted for investigation.

On admission, she was well nourished and appeared quite normal except for a slight pallor. Weight 21 Kg., height 114 cm. The tongue was normal as was also her hair. There was slight koilonychia. No murmurs could be heard over the heart. Liver and spleen were not enlarged. There was no lymphadenopathy.

Laboratory investigations: The hemoglobin level was 8.9 Gm. per 100 ml. and there were 5.0 m. red cells per cu.mm. There were about 2 per cent reticulocytes. The mean red cell diameter according to Price-Jones was 6.4 micra and there was moderate anisocytosis and poikilocytosis. The number of white cells was 4,300 per cu.mm., the differential count showed slight relative lymphocytosis. The number of thrombocytes was normal or slightly decreased (165,000-295,000 per cu.mm.). The serum iron level was very low (20 µg. per 100 ml.). There were no signs of hemorrhagic disease, prothrombin time was normal as was bleeding and clotting time. Clot retraction was normal. There was normal concentration of hydrochloric acid in the gastric juice. Roentgenograms of the oesophagus and the gastrointestinal tract failed to reveal any abnormalities. Sedimentation rate normal.

Treatment and course: During the first weeks in the hospital the girl was treated with iron and copper perorally. There was, however, no improvement. The child was then treated with iron intravenously and during two weeks, in all received 350 mg. iron as colloidal saccharated iron (Intrafer®). After this treatment there was neither significant rise in the hemoglobin level, nor was there a reticulocyte peak. One day after the third injection of the iron preparation (100 mg. Fe) the serum iron level was almost normal (65 µg. per 100 ml.). A few days later, however, the level was very low again. After this treatment the girl was
REFRACTORY SIDEROPENIC ANEMIA IN CHILDHOOD

Table 1.—Case 1. Principal hematologic data

<table>
<thead>
<tr>
<th>Date</th>
<th>Hemoglobin, Gm. per 100 ml.</th>
<th>Red cells, millions per cu.mm.</th>
<th>MCHb, Gm.</th>
<th>Reticulocytes, per cent</th>
<th>Mean red cell diameter, microns</th>
<th>White cells, per cu. mm.</th>
<th>Serum iron, Gm. per 100 ml.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1952</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>III, 28</td>
<td>8.9</td>
<td>5.0</td>
<td>18</td>
<td>2.2</td>
<td>3.600</td>
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<tr>
<td>III, 29</td>
<td>7.9</td>
<td>4.6</td>
<td>17</td>
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<td>IV, 7</td>
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<td>4.7</td>
<td>19</td>
<td>1.4</td>
<td>3.100</td>
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<td>4.5</td>
<td>24</td>
<td>1.2</td>
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<tr>
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<td>10.6</td>
<td>4.5</td>
<td>20</td>
<td>1.3</td>
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<td>3.600</td>
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<tr>
<td>II, 27</td>
<td>9.7</td>
<td>4.8</td>
<td>20</td>
<td>1.3</td>
<td>6.9</td>
<td>3.600</td>
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<td>21</td>
<td>1.4</td>
<td>1.600</td>
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<td>20</td>
<td>3.5</td>
<td>5.200</td>
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<tr>
<td>VI, 10</td>
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<td>3.7</td>
<td>23</td>
<td>1.7</td>
<td>2.700</td>
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</tr>
</tbody>
</table>

Marked anisocytosis and poikilocytosis present.
The differential count usually showed a slight relative lymphocytosis.

Treatment: Folic acid, 1952, Feb.-March.
Iron and copper perorally, 1952, April.
Iron intravenously (350 mg. Fe**, 1952, April.
Iron perorally (275 mg. Fe** per day), 1952, May to 1953, October.
Cortisone (12.5 mg. 4 times a day), 1954, April.
Vitamin B₁₂ (30 μ Gm. twice), 1954, May.

sent home to continue the peroral iron medication (about 275 mg. Fe** a day). This treatment was continued for one and one-half years, but there was no change in the sideropenic state.

The hematologic and the therapeutic data during the observation period are given in table 1. From this table it is clearly seen that the sideropenia was completely resistant to peroral treatment with iron. Very often a leukopenia was found. Treatment with cortisone and with vitamin B₁₂ was without effect. Periodically the child was tired, suffered from headache, and had anorexia. Occasionally there was also mild dysphagia of the type seen in the Plummer-Vinson syndrome. Blood transfusion was found to be the only effective therapy during periods with marked sideropenic symptoms.

Special investigations: Examination of the bone marrow: Repeated bone marrow punctures during the follow-up of the patient showed a highly sideropenic picture. There was increased erythropoiesis in the marrow with an increased number of proerythroblasts and early basophilic normoblasts. Occasionally there was hypersegmentation in the myeloid series. The bone marrow changes remained unaltered after treatment with folic acid or vitamin B₁₂.

Investigations to exclude a hemolytic component: The total serum bilirubin level was normal (0.50 mg. per 100 ml.), and there was normal fecal excretion of stercobilin (mean daily output 38 mg.). Osmotic resistance was normal. Paper electrophoresis of a hemoglobin sample from the patient (for method cf.[11]) revealed the same migration as hemoglobin from normal individuals.

Porphyrin metabolism: No abnormalities were detected. The daily urinary excretion of coproporphyrin was 15 μg. No uroporphyrin or other porphyrins were found in the urine.

Copper metabolism: The serum copper level was normal (105 μg. per 100 ml.) and there was minute urinary excretion of copper (5 μg. per day).

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Liver function tests: The serum protein level was 6.5 Gm. per 100 ml. and the electrophoretic pattern was normal. Bromsulphalein excretion test normal.

Renal function: No impairment could be demonstrated.

Intestinal function: The fat absorption coefficient (i.e., the percentage of ingested fat absorbed) was normal (91 per cent).

Heredity: Hematologic examination of the father revealed no abnormalities. The mother had a slight hypochromic anemia with a low serum iron level (32 μg. per 100 ml.).

Clinical summary of Case 1: A moderate hypochromic anemia was diagnosed in a 7 year old girl and the patient was under observation for more than two years. The child exhibited typical general sideropenic symptoms. There were no evidences of occult bleeding. The concentration of hydrochloric acid in the gastric juice was normal and there were no symptoms of steatorrhea. The bone marrow showed changes typical of long-standing sideropenic anemia. The anemia failed to respond to peroral treatment with high doses of iron for almost one and one half years, and there was no reticulocyte peak or rise of the hemoglobin level after intravenous iron therapy.

Results of the studies on the iron metabolism in Case 1: The fact that the treatment of the patient with 275 mg. Fe++, daily during one and one half years was without effect on the anemia and the low serum iron level seems to indicate that there is an incapability to absorb iron from the alimentary tract. This suggestion finds support from the observation that the peroral test dose of radioiron was quantitatively recovered in feces. After the administration of 225,000 counts, 237,000 counts were found in feces over the following 3 days. Another observation indicating the refractoriness to peroral iron is the finding that a single dose of 750 mg. Fe++ by mouth did not cause any significant rise of the level of serum iron within 6 hours. The serum iron level before the load was 20 μg. per 100 ml. and during the following 6 hours the highest value observed was 35 μg. per 100 ml. In ordinary iron-deficiency anemia the administration of such a dose causes a peak of the serum iron level which may exceed 500 μg. per 100 ml.12

Figure 1 shows the rate of disappearance of intravenously injected labeled ferric-siderophilin from the circulating plasma. If the rate of decrease in radioactivity is expressed in terms of the half-time of disappearance (T½) (i.e., the time in minutes when 50 per cent of the radioactivity injected is removed from the plasma), this value was found to be 8 minutes. In normal subjects, Wasserman, Rashoff, Leavitt, Mayer and Port13 have found that the half-time of disappearance ranges from 70 to 140 minutes, with an average of 90 minutes. Furthermore, in two cases of severe hypochromic anemia with low serum iron levels, Wasserman et al.13 found a decreased half-time (30 and 60 minutes respectively). Thus, there was, in the patient studied, an extremely rapid half-time of removal far exceeding that earlier observed in hypochromic anemia.

Figure 2 shows the utilization of intravenously injected radioiron (as ferric-siderophilin) for hemoglobin production. As is clearly demonstrated from this figure the rate of incorporation of injected iron is much slower than in normal subjects. In cases of uncomplicated hypochromic anemia, Dubach, Moore and Minnich14 found a still more rapid rate of utilization (in the cases studied 100 per cent of the injected dose of radioiron was incorporated within the red cells in 10 days). A slow rate of appearance of radioiron in hemoglobin after intravenous
injection was found by Dubach et al.\textsuperscript{14} in patients with fever or with untreated pernicious anemia. In hypoplastic anemia the rate of incorporation of radioiron into hemoglobin was extremely low.

Figure 2 also shows that the rate of incorporation of radioiron into hemoglobin increases after treatment with cortisone. During such a treatment the iron utilization was found to be within the normal range. There was not, however, any improvement of the anemia when the patient was under cortisone therapy. Earlier, Loeb, Moore and Dubach\textsuperscript{15} reported that cortisone increases the utilization of intravenously injected radioiron in patients with chronic bone marrow failure. In such cases, however, the cortisone treatment induced a reticulocyte peak and a rise in the hemoglobin level.

The total iron-binding capacity of serum (TIBC) and its saturation was determined twice. In April, 1954, the value for TIBC was 320 \( \mu \text{g.} \) per 100 ml. with a serum iron level of 20 \( \mu \text{g.} \) per 100 ml. When the determinations were repeated in June, 1954, the TIBC was found to be 329 and the serum iron level 35 \( \mu \text{g.} \) per 100 ml. The value for TIBC is, therefore, within the normal range for the age of the patient as found by Smith, Schulman and Morgenthau\textsuperscript{16} (mean 340), and by Hagberg\textsuperscript{17} (mean 353). The observation that the TIBC is normal is another finding which indicates abnormal iron metabolism. Smith et al.\textsuperscript{16} and Hagberg\textsuperscript{17} have constantly found elevated TIBC in iron deficiency anemia, the level usually

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{fig1}
\caption{Rate of Disappearance of Intravenously Injected Radioiron from Plasma in Case 1. Fe\textsuperscript{59} was injected in tracer dose as ferric-globulinate. The curve for the disappearance in normal subjects is calculated from the values given by Wasserman et al.\textsuperscript{13}}
\end{figure}
reaching 500 μg. per 100 ml. The reduction in plasma iron in the presence of a normal concentration of iron-binding protein indicates that the per cent saturation of the protein with iron was decreased from the normal of 35 per cent to a value of about 7 per cent.

The urinary loss of iron amounted to 0.1–0.2 mg. per day. Thus, since the excretion in the urine was normal, there was no indication of abnormally high urinary iron excretion.

Since the mother of the patient had a low serum iron level it was suspected that there was inheritance for abnormal iron metabolism. However, of an oral test dose of radioactive iron she absorbed 15 per cent, thus the absorption from the alimentary tract was within the normal range.

*Case 2*

In Case 1 there was an abnormality of iron metabolism resulting in complete refractoriness to treatment with iron by mouth as well as intravenously. Another case which exhibited features of the same type but not to the same extent will be reported in brief.

P. U., a boy, almost 3 years of age, was admitted because of anemia. Birthweight 3,080 Gm. He had always been pale and there was periodic anorexia. There was no history of nutritional deficiency or hemorrhage. He had suffered from repeated mild throat infections, however.

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**Fig. 2.** Utilization of Intravenously Injected Radioiron for Hemoglobin Synthesis in Case 1. Fe59 was injected in tracer dose as ferric-globulinate. Cortisone was given in a dose of 25 mg., 4 times a day. The treatment was started 12 hours before the injection of radioiron and was continued for 18 days. The curve for normal subjects is calculated from the values given by Dubach et al.14

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Table 2.—Case 2. Studies of iron metabolism before treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron</td>
<td>10 μ Gm. per 100 ml.</td>
</tr>
<tr>
<td>Total iron binding capacity</td>
<td>402* μ Gm. per 100 ml.</td>
</tr>
<tr>
<td>Per cent absorption of an oral test dose of radioiron</td>
<td>5</td>
</tr>
<tr>
<td>Per cent utilization for hemoglobin synthesis of intravenously injected radioiron after 15 days</td>
<td>52</td>
</tr>
</tbody>
</table>

* Normal mean value for age, 387 μ Gm. per 100 ml.

On admission, he was drowsy and had moderate pallor. The hemoglobin level was 4.9 Gm. per 100 ml. and there were 2.7 million red cells per cu.mm. MCHb was 18 μg. There were 4 per cent reticulocytes. Marked anisoctosis and poikilocytosis and slight polychromasia were noted. The mean red cell diameter according to Price-Jones was 6.2 micra. Normal white cell count, differential count and thrombocytes. The bone marrow was extremely sideropenic. The fat absorption coefficient was 86 per cent. Studies of iron metabolism on admission are listed in table 2.

The child was first treated with iron by mouth but with very slow improvement. For that reason the treatment was continued by the intravenous route and 350 mg. iron was administered over one month period. During this treatment there was a slow progressive rise of the hemoglobin level. The average daily increase was 0.07 Gm. per 100 ml., and far below the usual daily rise, after treatment of iron-deficiency anemia by this means. Brown, Moore, Reynolds and Smith have reported that the average daily rise after intravenous therapy of hypochromic anemia varies from 0.11 to 0.26 Gm. per 100 ml. per day. There was no reticulocyte peak. Two months after treatment was started the hemoglobin level was 9.8 Gm. per 100 ml. and the MCHb was 25 μg. After another month (the child had been treated with iron by mouth during this period) there was no further increase of the hemoglobin level. At that time the serum iron level was still very low (25 μg. per 100 ml.).

Summary and discussion of Case 2: The patient exhibited the features of a marked hypochromic anemia. There was no history of nutritional deficiency nor was there any evidence of occult bleeding. As shown by the oral test dose of radioiron there was poor iron absorption. The utilization of intravenously injected radioiron was relatively slow. The total iron-binding capacity of the serum was normal for age. Studies of the iron metabolism and the slow response to peroral as well as intravenous treatment with iron might indicate that there is, also in this case, a disturbance of iron metabolism of the same type, although not so pronounced, as in Case 1.

Comment

According to Hawkins the following criteria must be satisfied before a diagnosis of hypochromic anemia refractory to peroral treatment with iron can be established. A potent iron preparation must have been taken and tolerated for an adequate period and the presence of hemorrhage, chronic infection, and other diseases must be excluded. In Case 1 all these criteria are established.

True refractoriness to peroral treatment with iron in hypochromic anemia has been considered to occur only in association with steatorrhea. The normal fat absorption coefficient seems, however, to exclude steatorrhea as the cause of defective iron absorption.

In Case 1 not only the absorption of iron is defective. Also, other signs of a disturbance of iron metabolism as manifested by a decreased rate of utilization of intravenously injected iron for hemoglobin synthesis are present. Furthermore,
the normal concentration of the iron-transporting protein in the serum, in spite of
the extremely low serum iron level, is another factor pointing to abnormalities
in the regulation of iron metabolism. The lack of increase in siderophilin con-
centration and the low rate of utilization of intravenously injected radioiron is
the same finding as seen in anemia of infection.\textsuperscript{21} It has, however, been shown that
when iron deficiency is severe, injected iron may be utilized for hemoglobin pro-
duction in the normal way despite the presence of inflammation.\textsuperscript{27} Therefore, the
disturbance of iron metabolism is more profound than in the anemia of infection.

In Case 1 there was a very rapid removal of intravenously injected radioiron
from the plasma. In subjects with normal iron stores the rate of removal has been
considered to be an index of red cell production. A rapid removal usually is con-
sistent with an intense erythropoiesis.\textsuperscript{13} In the patient studied, this cannot,
however, be the only cause since there was a slow rate of utilization for hemo-
globin synthesis. It seems more logical to assume that the rapid disappearance
of the radioiron given intravenously was due to a high rate of exchange between
plasma iron and iron in the depots. Finch, Wolff, Rath and Fluhart\textsuperscript{23} have
found that the distribution of intravenously injected radioiron is influenced by
the size of the iron stores and that less radioiron appears in circulating erythro-
cytes when the stores are increased, probably due to the low specific activity of
the iron circulating through the marrow. Thus, the slow rate of incorporation
of the radioiron in hemoglobin, as observed in Case 1, might indicate that the
iron stores are filled despite a low serum iron level. The lack of increase in con-
centration of the iron-transporting globulin in serum also is in agreement with
this hypothesis.\textsuperscript{24}

One can only speculate as to the cause of the abnormal iron metabolism in the
reported cases. According to Granick,\textsuperscript{25} absorbed iron in the mucosa combines
with apoferritin to form ferritin that is capable of releasing it to the blood when
there is need for iron. A defect in releasing ferritin iron from the mucosa to the
plasma might account for the refractoriness to peroral iron. It might also be
assumed that the release of iron from the depots to the blood serum is disturbed.
This assumption is also in accordance with the lack of response to intravenous
therapy with saccharated iron in Case 1. Earlier the existence of abnormal iron
metabolism has been considered. From studies of iron metabolism Walden-
ström,\textsuperscript{6} concluded that there sometimes occurs an essential sideropenia in which
the low serum iron level must be regarded as purely regulatory. In such patients,
the incapacity to maintain a normal serum iron level is demonstrated by the
tendency to a relapse of the low values shortly after the iron administration.\textsuperscript{27}
The chronically low serum iron level is considered to lead to a starvation of the
bone marrow and result in a hypochromic anemia. The finding that cortisone
treatment in Case 1 increased the rate of incorporation of intravenously injected
radioiron in circulating erythrocytes is difficult to interpret. However, it has been
observed that cortisone influences iron metabolism.\textsuperscript{29}

It seems reasonable to assume that different degrees of the disturbance of iron
metabolism as manifested in Case 1 might exist. In the second case the funda-
mental abnormality seem to be the same, although not to the same degree as
revealed by the response to therapy.
Two cases of essential hypochromic anemia in childhood are reported. One of the cases which developed a mild Plummer-Vinson syndrome was completely refractory to peroral as well as intravenous iron therapy. In both cases the iron metabolism has been studied by means of radioiron.

The following characteristics were found: The serum iron level was extremely low but the iron binding capacity was normal. The absorption of iron from the alimentary tract was defective and intravenously injected radioiron was utilized for hemoglobin synthesis at a slow rate. There was a rapid plasma iron turnover.

The hypothesis is offered that the cause of the anemia resided in an abnormality in the regulation of iron metabolism.

SUMMARY IN INTERLINGUA

Es reportate duo casos de anemia hypochromic essential in juveniles. Un del casos disveloppava un leve forma del syndrome de Plummer-Vinson e esseva complemente refractori a therapias a ferro, tanto oral como etiam intravenose. In ambe casos le metabolismo de ferro esseva studiate per medio de ferro radioactive.

Le sequente caracteristicas esseva constatate: Le nivello del ferro seral esseva extremely tasse, sed le capacitate a ligar ferro esseva normal. Le absorption de ferro ab le vias digestive esseva defective, e le ferro del injectiones radioactive esseva utilisate lentemente in le synthese de hemoglobina. Le processage plasmatic de ferro esseva rapide.

Es formulate le hypothese que le causa del anemia in iste casos esseva a cercar in un anormalitate del regulation del metabolismo de ferro.

REFERENCES

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