The Rate of Iron Accumulation in Iron Storage Disease

By WILLIAM H. CROSBY, MARCEL E. CONRAD, JR. AND MUNSEY S. WHEBY

It is generally accepted that the daily requirement for iron in adult humans is about 1 or 2 mg., which can be provided by 10 per cent of a daily dietary intake of about 15 mg. In normal humans the balance of absorption and requirement is nicely controlled so that neither deficiency nor excess of iron develops. Control of the iron balance, which appears to reside in the small intestine, permits increased absorption when requirement is increased, for example after bleeding. When the body's iron store is normally replete the available dietary iron is not absorbed or is absorbed only in sufficient amount to replace any loss. The intestine's ability to refrain from absorbing available, unneeded iron is called the mucosal block after Hahn's suggestion.1 In certain diseases of iron metabolism, control of iron balance is disturbed so that iron in excess of requirement is gradually accumulated. In addition to its occurrence in hemochromatosis, there is iron loading in thalassemia major, sex-linked hypochromic iron-loading anemia, pyridoxine-responsive anemia and in some cases of cirrhosis. Iron overload may be induced by dosing with iron by mouth, by parenteral injections of iron or by transfusion.

Methods for measuring iron absorption with a single dose of radioactive iron involve an experimental situation which only approximates the normal ingestion of dietary iron. These procedures yield a wide range of values suggesting a capriciousness of absorption which does not square with the fine control of iron balance that our bodies obviously possess. Either the methods are fallible or there exist unsuspected means for control of balance by excretion of iron—or both.

In the iron-loading diseases the significant phenomenon is the accumulation of iron, accumulated iron being that which enters the body in excess of that being lost. In the normal state there is no accumulation. During growth or recovery from blood loss anemia, iron accumulates until the normal content of iron is achieved. When transfusions are used for treatment of aplastic or hemolytic anemia, the iron in the transfused hemoglobin is in excess of requirement. In hemochromatosis the iron accumulates because it is absorbed in excess of the amount being lost. Thus a distinction is made between accumulation and absorption.

The rate of accumulation can be determined by measuring the accumulated iron and dividing the amount by the time during which accumulation oc-
curred. We have attempted to measure total accumulation by repeating phlebotomy until iron deficiency developed. The study was performed on a number of patients with various iron storage diseases, and the results provide some interesting insights into the mechanisms and disorders of iron metabolism.

**Materials and Methods**

The diagnosis of iron loading disease was made by demonstrating the existence of excessive iron stores in various tissues: liver, bone marrow and, in some cases, gastrointestinal mucosa. Serum iron was elevated\(^2\) and in some of the patients excessive absorption of radiiron was demonstrated using a whole-body liquid scintillation counter.\(^3\)

Red cell mass was measured by autotransfusion of red cells tagged with Cr\(^{51}\) and observing the degree of isotope dilution.

Phlebotomy was performed by the hospital transfusion service, taking 475 Gm. of blood into a plastic bag plus samples for measuring serum iron, red cell indices and other tests. The total for each phlebotomy was approximately 500 ml. The amount of iron withdrawn was computed from the hemoglobin concentration of the blood, the value for iron in hemoglobin taken to be 0.338 per cent. The patients were bled often enough to maintain a mild to moderate anemia, the rate varying from one to five times weekly.\(^4\) When the patient developed a low serum iron, hypochromia of the red cells and failed to restore his hemoglobin after phlebotomy, he was considered to be iron depleted. In several cases this was confirmed by liver biopsy.

Several of the patients with hemochromatosis, thus stripped of their iron, were thereafter permitted to reaccumulate it for months or years. Then they were phlebotomized again to establish the rate at which iron had accumulated in the interim.

None of the patients were given special diets or supplemental iron. They all ate a freely chosen "standard American diet" which provides about 15 mg. per day of elemental iron. The foibles of this method of clinical investigation are evident, but they should be mentioned. The subject may lose blood by hemorrhage in addition to that lost by phlebotomy. He may select an unusual diet lacking or heavy in iron. The true state of his iron stores may not be reflected by the level of the plasma iron, the appearance of biopsied tissues or the rate of recovery from iron deficiency anemia. Throughout the study we have remained alert to these pitfalls. By questioning and re-examination we have attempted to make an accurate determination.

The rates of accumulation were computed in several ways.

1. When a patient is being bled repeatedly and his hemoglobin mass remains constant he must provide iron from his stores or his diet in amount equal to that in the shed blood.\(^4\) When the iron stores are empty, all of this replacement iron comes from the diet. A normal subject with his iron stores empty was phlebotomized often enough to keep his hemoglobin concentration at 14 Gm. (His normal is 16 Gm.) Under these conditions he accumulated 5.7 mg. of iron per day.

2. After a patient has been bled sufficiently to produce obvious anemia and iron deficiency and the bleeding is then stopped, he reconstitutes the hemoglobin mass using dietary iron. The rate of growth of the hemoglobin mass reflects the rate of accumulation of iron. A normal subject treated in this fashion was found to absorb 6.2 mg. of iron per day.

3. A patient with iron-loading disease who is neither iron deficient nor anemic has no requirement for iron yet continues to accumulate it. When phlebotomy is used to remove the accumulated iron the patient is deliberately made iron deficient, with hypochromic red cells and low serum iron. To assure the removal of all stored iron, he is left with a hemoglobin deficit and depletion of the normal stores. In computing the amount of abnormal accumulation an allowance is made for the iron represented by the hemoglobin deficit and for the normal storage iron, which is arbitrarily set at 1 Gm.

4. In Case 5 a definite amount of iron had been injected as transfusion. All of the stored iron was later removed by bleeding. Accumulation, in this case a negative rate,
was computed from the difference between the amount injected and the amount recovered. Allowance was made for depletion of normal iron stores and for the hemoglobin deficit which was present when the phlebotomies were discontinued.

**RESULTS**

**Case 1.** An earlier report was published of this 54-year-old officer (b. 1908) who has idiopathic hemochromatosis. During a course of 110 phlebotomies in 1956 we removed 22 Gm. of iron, and left him with a hemoglobin concentration of 7 Gm. Recovery of his red cell mass required approximately 7 months. In 220 days, from December 1956 to July 1957, the circulating hemoglobin increased from 300 Gm. to 821 Gm., requiring the accumulation of 8 mg. of iron per day. In September 1957, to test the state of the patient's iron stores, two units of blood were removed. The serum iron promptly fell from 300 \( \mu g. \), indicating a lack of storage iron. The patient had not been filling his iron storage depots as he expanded the hemoglobin mass. By October 9 his hemoglobin had returned to 16.2 Gm.

Forty months later phlebotomies were begun again. Between January 5 and March 9, 1961, a total of 18 units of blood was removed, containing 1175 Gm. of hemoglobin and 4.0 Gm. of iron. It is estimated that the patient was left with a hemoglobin deficit of 225 Gm. representing 780 mg. of iron. Normal iron stores were empty at the beginning and at the end of the period of 1192 days from October 1, 1956 to March 9, 1961. The net accumulation was 3200 mg. of iron, accumulated at the rate of 2.7 mg. per day. Prior to this course of phlebotomies, on two occasions he absorbed approximately 60 per cent of a test dose of 1 mg. of iron.

Following phlebotomy the patient was studied once again during the period of recovery. Red cell mass was measured on April 7 (1854 ml.) and again on May 9 (2172 ml.) representing an increase of 318 ml., or 95 Gm. of hemoglobin. The 322 mg. of iron required to expand the hemoglobin mass represents an accumulation at the rate of 10 mg. per day.

**Comment.** Over a period of 3 years this patient with hemochromatosis accumulated iron at the rate of 2.7 mg. per day. During periods of iron deficiency the rate of accumulation was 8 to 10 mg. per day. It would appear that the rate of iron accumulation in hemochromatosis can be increased by the induction of iron deficiency.

The first course of phlebotomies in 1957 removed 22 Gm. of iron. Assuming absorption at the rate of 8 mg. per day during the time of vigorous bloodletting, about 2.5 Gm. of iron would have been absorbed during the 11 months of therapy. The hemoglobin deficit at the end of the phlebotomies represents 1.7 Gm. and the normal amount of storage iron, also removed, is 1 Gm. Therefore, when the patient first came to the hospital with hemochrom-

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*Report by pathologist, Major H. C. Hewitt, Jr., dated October 22, 1962:

Review of the four liver biopsies from March 1955, July 1956, January 1957, and the present reveals the following:

The first biopsy has thick, cellular portal tracts and marked iron deposition in liver cells and Kupffer cells. There are no central veins seen. The next two biopsies reveal the same disorganized liver architecture but the iron is decreasing. In July 1956 there is a moderate amount of iron still in hepatic cells while in January 1957 there is no iron in the hepatic cells and only a few iron laden macrophages in the dense portal fibrous tissue.

The final biopsy in addition to having no stainable iron exhibits the striking reappearance of lobular architecture with central veins or viewed another way, the cirrhosis evident in the first three biopsies has disappeared.
Hemochromatosis at the age of 48, he possessed 16.8 Gm. of excess iron. To accumulate such an amount of iron at the rate of 2.7 mg. per day would require 17 years. If the assumption is made that the rate of accumulation was constant, the onset of the disease occurred at 30 to 35 years of age.

Case 2. A 56-year-old officer (b. 1906) was found in 1958 to have cirrhosis with varices, diabetes and, on the basis of liver biopsy and an elevated serum iron, hemochromatosis. From September 1958 until August 1959 the patient was bled 50 liters, losing 22 Gm. of iron. At the conclusion of phlebotomy he was iron deficient and had a hemoglobin deficit of 480 Gm., representing 1.6 Gm. of iron.

Replenishment of the hemoglobin mass required 170 days, until January 1960, the iron accumulating at the rate of 9.4 mg. per day. During subsequent months the patient was not bled. Then, in September 1961, a course of 13 phlebotomies removed 2.8 Gm. of iron, of which 0.5 Gm. represented a postphlebotomy hemoglobin deficit. Total accumulation in his stores was 2.3 Gm. During a period of 400 days, from January 1960 to March 1961, he had accumulated iron at the rate of 5.75 mg. per day.

The patient died with a malignant hepatoma in July 1962.

Comment. This patient with hemochromatosis and cirrhosis was found to accumulate iron at the rate of 5.75 mg. per day. With iron deficiency the rate increased to 9.4 mg. per day. His basic rate of accumulation was higher than that of the first patient. It is possible that the difference is related to severity of the cirrhosis, since cirrhosis itself may be an iron-loading disease.

The first course of phlebotomies removed 22 Gm. of iron, including 1 Gm. of normal storage iron, and 1.6 Gm. of iron, reflecting the hemoglobin deficit at the end of the course. During the time of intense phlebotomy the rate of accumulation is assumed to be 9.4 mg. per day; on this basis the accumulation during that year was 3.3 Gm. Thus, at the beginning of his treatment in 1958 at the age of 52, the total amount of excess iron was 16 Gm.

If one assumes a constant rate of accumulation of 5.75 mg. per day, it would require 8 years to accumulate 16 Gm. This would place the onset of the iron-loading disease at the age of 44.

Case 3. This 62-year-old officer (b. 1900) was found to have hepatomegaly in 1946, diabetes in 1950 and skin pigmentation and cirrhosis with siderosis of the liver in 1952. Between June 1953 and April 1956 he was bled 101 times with a loss of 19 Gm. of iron. Liver biopsy, now for the first time, showed iron depletion and his hemoglobin was 14.8 Gm. per 100 ml.

From April 1956 until May 1959 he underwent 19 phlebotomies with a loss of 4.35 Gm. of iron. During this second course his hemoglobin remained at a level of about 13.5 Gm., representing mild anemia, and his serum iron was about 130 µg., which is low for hemochromatosis. Iron to replace the shed hemoglobin required absorption of 4 mg. per day.

Between May 1959 and July 1961 there were no phlebotomies. At the onset of the third series the patient's hemoglobin was 15.7 Gm., and he absorbed approximately 50 per cent of the 1 mg. test dose of Fe⁵⁹. After the second phlebotomy the hemoglobin concentration fell to 13 Gm. It remained there during the course of 10 blood lettings in 62 days which removed 1.95 Gm. of iron and left him with a hemoglobin deficit of 147 Gm., equivalent to 500 mg. of iron. In the 833 days from the end of the second course of phlebotomies until the end of the third, he had accumulated 1.45 Gm. of iron, which is a normal amount of storage iron, at the rate of 1.74 mg. per day. During the period of iron deficiency subsequent to the bleeding, his red cell volume was measured on October 2
IRON ACCUMULATION IN IRON STORAGE DISEASE

(22.8 ml./Kg.). During the intervening 98 days the hemoglobin mass increased 43 Gm., requiring 145 mg. of iron accumulated at the rate of 1.5 mg. per day. In May his hemoglobin was still 11.5 Gm., but by August it had increased to 15.8 Gm. This increase represents an expansion of the hemoglobin mass by at least 220 Gm., requiring the accumulation of approximately 750 mg. of iron in the 75 days between mid-May and the 1st of August. The rate of accumulation was 10 mg. of iron per day.

Comment. The reason for the variability of the rate of iron accumulation in this case has not been established. However, the patient did on one occasion demonstrate a rate approximating that of the first two patients, that is, 10 mg. per day. Gastrointestinal blood loss was suspected to be the cause of the variability and the patient was found to have a large hiatus hernia. Repeated examinations of his feces failed to reveal evidence of bleeding, but these tests were performed in the summer of 1962 when the patient was accumulating iron at a maximal rate.

Case 4. The patient, a 28-year-old officer (b. 1938), has a diagnosis of hereditary, hypochromic iron-loading anemia and was the subject of an earlier report. From November 1956 to June 1957 he was subjected to a series of 43 phlebotomies which removed 5.8 Gm. of iron, and left him iron deficient and with a deficit of 150 Gm. of hemoglobin. The iron represented by this deficit plus the normal storage iron amounted to 1.5 Gm. With allowance for this it is estimated that the patient had 4.3 Gm. excess iron.

During the first 50 days after cessation of phlebotomy, the patient reconstituted his hemoglobin mass at a rate requiring the accumulation of 5 mg. of iron per day. Thereafter the rate slowed. The hemoglobin returned to its original level in 6 months which required an over-all rate of iron accumulation of 2.7 mg. per day. During the first phase of recovery the serum iron was less than normal, 60 μg. per 100 ml. During the second, slower phase the serum iron was at normal or higher levels, 140 to 160 μg., even though the patient was still iron deficient and anemic.

After the patient had recovered to the original level of hemoglobin, a year elapsed and then in January 1959 he was subjected to a second series of phlebotomies. About 1.1 Gm. of iron was recovered, but at the end of the phlebotomies there was a hemoglobin deficit of 75 Gm.; therefore, the total iron removed from his stores was 850 mg. which had been accumulated at the rate of 2.4 mg. per day. In May 1961 when the patient was once again iron replete he absorbed 35 per cent of an oral test dose of Fe59.

Comment. This disease of iron metabolism permits the accumulation of excessive iron, yet it is different from hemochromatosis. In this patient the rate of accumulation was not increased by iron deficiency except for the short time when the patient’s serum iron was less than normal. During the period of recovery from the induced iron deficiency anemia, this patient reacted differently from those with hemochromatosis. His plasma iron concentration became elevated well before the hemoglobin mass was reconstituted, indicating that iron turnover was increasing. In this disease there is evidence of excessive quantities of nonhemoglobin iron in the erythrocytes and the recycling of this “siderocyte iron” causes the increased turnover of plasma iron. It is also noteworthy that the rate of recovery from the iron deficiency anemia was slower after the plasma iron became elevated. Since the patient’s diet was the only source of iron, this means that the absorption of iron was decreased. Does it also mean that the concentration of plasma
iron governs the “mucosal block” of iron absorption in the gut? There is some experimental evidence to the contrary but the question is not yet settled.

Although this is evidently a genetically determined disease it is suspected that the onset may be delayed until the second or third decade of life. In the case of this patient, assuming the excess 4.3 Gm. of iron was accumulated at a constant rate of 2.4 mg. per day, it may be calculated that the iron loading began 5 years before the first course of phlebotomies.

**Case 5.** The patient is a 42-year-old male officer (b. 1920) who had transfusion siderosis. In 1943, while on Cau-dalvalle, he developed a sprue-like disease with diarrhea, weight loss and severe anemia. During the years 1944 and 1945 he received 130 transfusions containing approximately 32.5 Gm. of iron (250 mg. per unit). Then, following folie acid therapy, he substantially recovered from his anemia and required no further transfusions. However, in 1958 during a routine examination he was found to have a mild anemia and was admitted to hospital for study. His hemoglobin was 11.5 Gm. and red cells were normocytic. Platelets and leukocytes were normal. Reticulocyte count was 2 per cent and the marrow showed mild normoblastic hyperplasia. The half-life of Cr-51-tagged red cells was 22 days with red cell mass of 19 ml. per Kg. Serum iron was 245 μg. per 100 ml. with no unsaturated binding capacity. Liver biopsy showed “severe siderosis with early perirenal scarring and chronic inflammation.” Repeated tests of feces for hemoglobin were negative. On March 28, 1958 the patient was begun on a course of phlebotomies; 500 ml. per week proved to be the limit of blood loss consistent with keeping the hemoglobin level above 9 Gm. The last of 102 units was removed on February 8, 1960. During the course the serum iron had gradually fallen. Not until it finally went below 100 μg. in December 1959 did the total iron-binding capacity begin to rise. In February the serum iron was 20 μg., total iron-binding capacity 395 μg. and hemoglobin 5.9 Gm. per 100 ml. The hemoglobin concentration in the 102 units of blood averaged 9 Gm. per 100 ml.; the total contained 4.6 Kg. of hemoglobin and 15.5 Gm. of iron. The bone marrow showed almost no stainable iron.

During the 157 days from February 8 until July 15, 1960, the patient’s hemoglobin mass expanded 240 Gm., requiring accumulation of 810 mg. of iron. The rate of accumulation during this period of iron deficiency anemia was 5.2 mg. per day. In December 1962 the bone marrow contained a normal amount of stainable iron and in the liver an occasional parenchymal cell contained a few small granules.

**Comment.** During his period of anemia in 1944, the patient received 32.5 Gm. of iron. Twelve years later we recovered 15.5 Gm. of iron including 1 Gm. of normal storage iron and 800 mg. represented by the hemoglobin deficit which was present at the end of the phlebotomies. The net recovery of excess iron was 13.7 Gm. Of the 32.5 Gm. of iron given in the transfusions, 18.8 Gm. were not recovered, the equivalent of 75 units of blood. Assuming a constant decrement between 1945 and 1958, the patient had lost 4.0 mg. of iron per day. The actual loss of iron undoubtedly was greater because even in the presence of iron storage disease, whether induced by ingestion or injection of iron or by transfusion, the mucosal block is unable to prevent absorption of some portion of ingested iron. In this patient 4.0 mg. per day is the measure of negative iron balance and represents that which he lost in addition to the amount equal to that absorbed from his diet.

The rate of accumulation of iron during the postphlebotomy period of iron deficiency was 5.2 mg. per day, about the same rate that was found in the
iron-deficient normal subject studied in a similar way. This patient with transfusion siderosis evidently had no intrinsic disorder of iron balance.

Case 6. A 31-year-old female (b. 1931) developed normocytic anemia in 1958. There were few reticulocytes; the leukocyte and platelet counts were normal. Examination of the marrow revealed virtual erythroid aplasia with M:E ratio of 50:1. When the patient was admitted to Walter Reed General Hospital in 1960, she had received approximately 60 blood transfusions. Her red cell mass at this time was 7 ml per Kg. of body weight and the T/2 of Cr-51-tagged red cells was 27 days. Cr-51 activity in her feces indicated a daily blood loss of 1.5 ml. Peroral biopsy of the upper jejunum revealed "heavy deposition of iron pigment in the tunica propria of the tips of the villi" (fig. 1). She continues to require monthly blood transfusions.

Comment. It has been recognized for many years that in iron storage disease there are iron-laden macrophages which appear in the tips of the intestinal villi and cross the epithelial cortex into the lumen carrying the iron with them.9 The macrophages may pick up the iron in other parts of the body and carry it to the villi.10 In a sense this comprises an iron-excretory mechanism. A similar mechanism exists in the glandular epithelial cells of the body. In hemochromatosis11 and other kinds of iron storage disease,12 these epithelial cells become laden with stainable iron. These are deciduous cells and when they are desquamated the iron is lost with them.

DISCUSSION

Hemochromatosis usually reveals itself in the middle years of a patient's life, by which time the accumulation of iron amounts to about 20 Gm. It is not known when the accumulation begins, whether the absorptive fault extends over the patient's entire life or whether it is of relatively brief duration. In the present study the rate of iron accumulation was measured in several patients with well established hemochromatosis. By making an assumption that the rate of accumulation remains constant throughout the duration of the disease, a hypothetical time of onset could be established. Ten to 17 years would have been required to accumulate the quantities of iron which were removed from these patients. However, one must question the assumption that the rate of iron accumulation remains constant. It is possible that the intestinal lesion which permits the absorption of unneeded iron may develop gradually rather than abruptly so that the rate of accumulation increases over a period of years. It is possible that excretory mechanisms for iron, as suggested by Cases 5 and 6, may serve to compensate for mild or early cases of the disease; in such cases iron absorption may be increased with little or no accumulation. Thus, the subclinical evidence of disease which is frequently encountered in members of the families of patients with full-blown hemochromatosis13,14 may represent a mild or partial lesion of a genetically determined disorder of intestinal mucosa.

In the three present patients with hemochromatosis the rate of iron accumulation was found to be different during the periods when they were not iron deficient. This may represent differences in severity of the intestinal fault which permits absorption of unneeded iron, or it may represent dif-

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Fig. 1.—Duodenal biopsy performed after 60 blood transfusions for erythroid aplasia. Most of the villi contained iron-laden macrophages. Material indicated by the arrow in the opening at the villous tip gave a positive reaction for iron. Prussian blue, safranine counterstain X75 and 300.
IRON ACCUMULATION IN IRON STORAGE DISEASE

In Case 2 the rate may have been increased by the complication of cirrhosis which can, itself, be an iron-loading disease. In Case 3 the rate may have been diminished by gastrointestinal bleeding, but this was not demonstrated. In all three, however, the rate of accumulation increased to about 10 mg. per day when iron deficiency was added to the hemochromatosis. This appears to be significant for at least two reasons. (1) It indicates that iron accumulation in iron deficiency depends upon some mechanism other than that which is at fault in hemochromatosis. (2) It demonstrates that at least two-thirds of the iron in a "standard American diet" is available for absorption; by so doing it sets a limit on the quantity of iron with which the body has to cope in hemochromatosis. Theoretically, if the iron excretory mechanism (the iron-laden deciduous cells and macrophages) were capable of unloading these 10 mg. of iron the patients would be in iron balance and no accumulation would take place. Conversely, the fact that iron does accumulate in hemochromatosis indicates that the amount absorbed exceeds the capacity of the excretory mechanisms. These mechanisms are evidently active, in view of the prominence of iron-laden deciduous cells in the descriptions of the pathology of hemochromatosis. It is proposed that in iron deficiency these active excretory mechanisms become inactive. The iron-loaded deciduous cells are no longer present. At the same time the mucosal block to the absorption of iron is removed, completely or in part. In hemochromatosis where there is already a defect of the mucosal block, the difference in the rates of accumulation with and without iron deficiency may depend largely upon the capacity of the excretory system.

The rate of iron accumulation in hemochromatosis exceeds the normal with or without iron deficiency. Measurements in the iron-deficient normal subject and in Case 5 indicate that iron deficiency permits the accumulation of 5 to 6 mg. of iron per day in contrast to the 9 to 10 mg. in hemochromatosis. The patient with hemochromatosis evidently lacks a barrier to iron accumulation which in the normal human even iron deficiency does not remove. Whether this is a difference of degree or kind remains unknown.

**SUMMARY**

1. By means of phlebotomy to recover and measure accumulated iron and by determining the rate of replenishment of hemoglobin after induction of iron-deficiency anemia, it is possible to compute the rate at which iron is accumulated by absorption from the diet. Normal humans are presumed to be in iron balance and absorb iron only to replace what is lost; under these conditions they accumulate none. During recovery from induced iron deficiency a normal human accumulated iron at the rate of 5 to 6 mg. per day.

2. Patients with hemochromatosis were found to accumulate iron at the rate of 1.5 to 5 mg. per day. With iron deficiency the rate increased to 8 to 10 mg. per day. Because of uncertainty concerning the manner of onset of
iron accumulation in hemochromatosis, whether gradual or abrupt, it is not possible by extrapolation to establish the time of onset in these patients. However, at the rates of accumulation established in this study there was an insufficient excess of iron to permit a conclusion that such rates had existed throughout the patient’s life. If the disease began early, the initial or interim rates were less than those found. If the disease began and continued at the rate found, its onset was 10 to 17 years prior to this study.

3. In a patient with hypochromic iron-loading anemia the rate of accumulation was about 2.5 mg. per day. It was not appreciably increased by iron deficiency except when the deficiency was severe and the plasma iron was quite low. While this patient was iron deficient the plasma iron became abnormally high even before the hemoglobin mass was completely reconstituted.

4. A patient with transfusion siderosis who had recovered from his anemia was phlebotomized to remove the accumulated iron. When iron deficiency finally developed the total amount of iron which had been recovered was less than half of the 32.5 Gm. given in the transfusions some years before. It was computed that during those years the patient was losing iron at a rate of about 4.0 mg. per day. The rate of iron accumulation during his recovery from the induced iron deficiency was the same as the normal: 5 to 6 mg. per day.

5. The ability to lose iron which is in excess of requirement is implicit in the demonstration of iron-laden deciduous cells such as the glandular epithelium of the stomach and duodenum and macrophages in the intestinal villi.

6. In hemochromatosis there is a failure of the intestinal mucosal block to prevent absorption of unneeded iron. When absorption exceeds the capacity of the iron excretory mechanisms, iron accumulation occurs. In iron deficiency the excretory mechanisms become less active so that the rate of iron accumulation is further increased.

**Summario in Interlingua**

1. Per medio de phlebotomia (que recovra e mesura le accumulate ferro) e per determinar le intensitate del replenation de hemoglobina post le induction de anemia a carentia de ferro, il es possibile calcular le intensitate con le qual ferro es accumulate per absorption ab le dieta. Humanos normal se trova supponitamente in balancia de ferro, i.e. illes absorbe solmente le quantitates de ferro que illes ha perdite; sub iste conditiones illes accumula nulle ferro. Durante le restablimento ab un artificialmente inducite carentia de derro, un subjecto normal accumulava ferro con un intensitate de 5 a 6 mg per die.

2. Esseva trovate que patientes con hemochromatosis accumula ferro con un intensitate de 1,5 a 5 mg per die. In carentia de ferro, ille intensitate montava a inter 8 e 10 mg per die. A causa del incertitude concernente le maniera del initiation del accumulation de ferro in hemochromatosis (i.e., si illo es gradual o si illo es abrupte), il non es possibile establir per extrapol-a-
Iron accumulation in iron storage disease

The initiation of ferro accumulation in tal patientes. Ta-
mente, a base del intensidades del accumulation de ferro establite in le presente
studios, le excesso de ferro non esseva sufficiente pro supportar le conclusion
que tal intensitates habeva existite in omne periodos del vita del paciente. Si
le morbo comenciava a un multo juveme etate, le intensidades initial e interime
del accumulation de ferro esseva inferior a illos trovate in le investigation. Si
le intensitate trovate in le investigation esseva characteristic del morbo ab su
inìicio e durante su curso, le declaration del morbo occurreva 10 a 17 annos
ante le investigation.

3. In un patiente con hypochromic anemia a cargation de ferro, le inten-
sitate del accumulation de ferro esseva circa 2,5 mg per die. Isto non esseva
augmentate appreciabilemente per carentia de ferro, excepte quando le car-
entia esseva sever e le nivello de ferro in le plasma esseva multo bassse.
During que iste patiente se trovava in stato de carentia de ferro, le ferro del
plasma montava a nivellos anormalmente alte mesmo ante que le massa de
hemoglobina esseva completemente reconstituite.

4. Un patiente con siderosis transfusional, qui se habeva restablite ab su
anemia, esseva subjicite a phlebotomia con le abjectivo de eliminar le accumu-
late ferro. Quando finalmente carentia de ferro se disveloppava, le quantitate
total de ferro recovrate esseva minus que un medietate del 32,5 g administrate
in le transfusiones plure annos previemente. Esseva calculate que durante le
intervallo le patiente habeva perdite ferro con un intensitate de approxima-
tivemente 4,0 mg per die. Le intensitate de su accumulation de ferro durante
su restablimento ab le artificialmente inducite carentia de ferro esseva identic
con illo in subjectos normal, i.e., 5 a 6 mg per die.

5. Le capacitate de perder ferro que excede le requirimentos del corpore es
implicite in le demonstration de ferrifere cellulas decidue, tal como le epithehio
glandular del stomacho e del duodeno e le macrophagos in le villos intestinal.

6. In hemochromatosis, le bloco intestino-mucosal non succede in prevenir
le absorption de non-requirite ferro. Quando le absorption excede le capacitate
del mechanismos de excretion de ferro, le consequentia es accumulation de
ferro. In carentia de ferro, le mechanismos excretori deveni minus active, de
maniera que le intensitate del accumulation de ferro es augmentate addition-
almente.

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