# *The Importance of* Nutritional Factors *in the Pathogenesis of* Iron-Deficiency Anemia

*By* CARL V. MOORE, M.D.*

STUDENTS of iron metabolism in the United States, with extremely few exceptions, are agreed that nutrition plays a relatively minor role in the production of iron-deficiency anemia among adults unless blood loss also occurs. It is argued: (a) that iron is excreted in such small amounts that a positive balance is maintained even when the diet is deficient or absorption defective; and (b) that poor nutrition leads to the development of iron deficiency only when requirements are increased by growth, as during infancy and childhood, or by chronic hemorrhage. With poor diet or poor absorption, even the amount of blood lost with normal menstruation is enough to lead gradually to iron deficiency. This belief is strengthened by careful clinical study. Patients with iron-deficiency anemia are not infrequently seen who give no history of chronic hemorrhage or in whom no source of blood loss can at first be discovered. But when one persists—and sometimes weeks or months of observation are required—one can almost invariably demonstrate eventually that occult hemorrhage is occurring intermittently from the gastrointestinal or urinary tracts.

The above concept, however, is not shared by workers in many other parts of the world. They claim that when diets are inadequate for long periods of time, either because of disturbed food production during war or because of persisting food shortages in the most heavily populated areas, iron deficiency develops in adults on the basis of poor nutrition alone. There have been so few data on the absorption of iron from foods and on iron excretion in man that it has been difficult to resolve this difference of opinion, but, in an attempt to do so, Doctor Reubenia Dubach and I have been collecting some of the missing information. On the basis of our experiments, to be reported in detail elsewhere, I should like to analyze the importance of nutritional factors in the production of iron-deficiency anemia.

## ABSORPTION OF IRON FROM FOODS

Most of the information about iron absorption is of little nutritional significance, since it has been obtained from experiments in which inorganic iron salts were fed to patients or animals. The ionizable iron in many foods has been measured on the assumption that only this portion is available for absorption, but when balance studies are done on patients in an attempt to determine the amount retained, the technical difficulties become enormous. Diet and water intake must be rigidly controlled. A relatively large error is involved in the chemical determination of iron in feces, and it is impossible to differentiate between unabsorbed and excreted iron. The few meticulous studies that have been done indicate that from spinach or from mixed diets the per cent of iron absorbed varies from about 11 to 14 per cent, while from beef the absorption may be as high as 21 per cent.[1]

In order to circumvent the difficulties involved in balance studies, we have incorporated radioactive iron into various foods and measured absorption under a variety of conditions with the radioactive technique.[2,3] Radioactive iron has been injected into hens so that the eggs produced contain the isotope. After several weeks, the hens have been killed so

From the Department of Internal Medicine, Washington University School of Medicine, St. Louis 10, Mo.

* Professor of Medicine, Washington University School of Medicine.

The studies reported in this paper were supported in part by Research Grant No. H22 from the National Heart Institute, U. S. Public Health Service.

that their livers and muscle might also be fed. Vegetables have been grown in nutrient solutions to which radioiron was added; they then had a portion of their iron in isotopic form. Foods have been cooked, or prepared as they would be in a normal American diet and fed to fasting subjects. In most experiments, the amount of radioiron incorporated into circulating hemoglobin has been used as the measure of the quantity absorbed, but in some instances the unabsorbed portion recovered in the feces has also been determined. Subjects, for the most part, have been normal healthy students or laboratory personnel, and patients with iron-deficiency anemia.

The most important observation has been that, with few exceptions, the amount of iron absorbed from foods by normal subjects has been 10 per cent or less (Fig. 1). In only two instances was absorption significantly greater than 10 per cent; chicken muscle had been fed in both cases. We next attempted to find out

ABSORPTION OF $Fe^{59}$ FROM FOOD BY NORMAL SUBJECTS

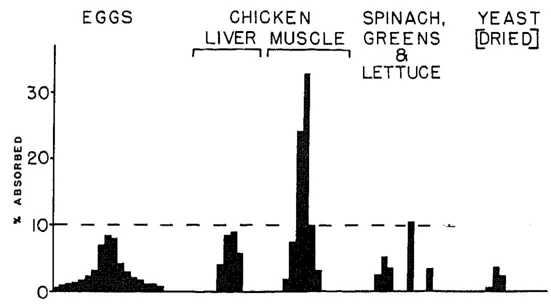


Fig. 1. Each column represents a separate experiment. The dotted horizontal line at the 10 per cent level helps to emphasize the fact that very few subjects absorbed more than this amount.

EFFECT OF FOODS ON ABSORPTION OF $Fe^{59}$ FROM EGGS——NORMAL SUBJECTS

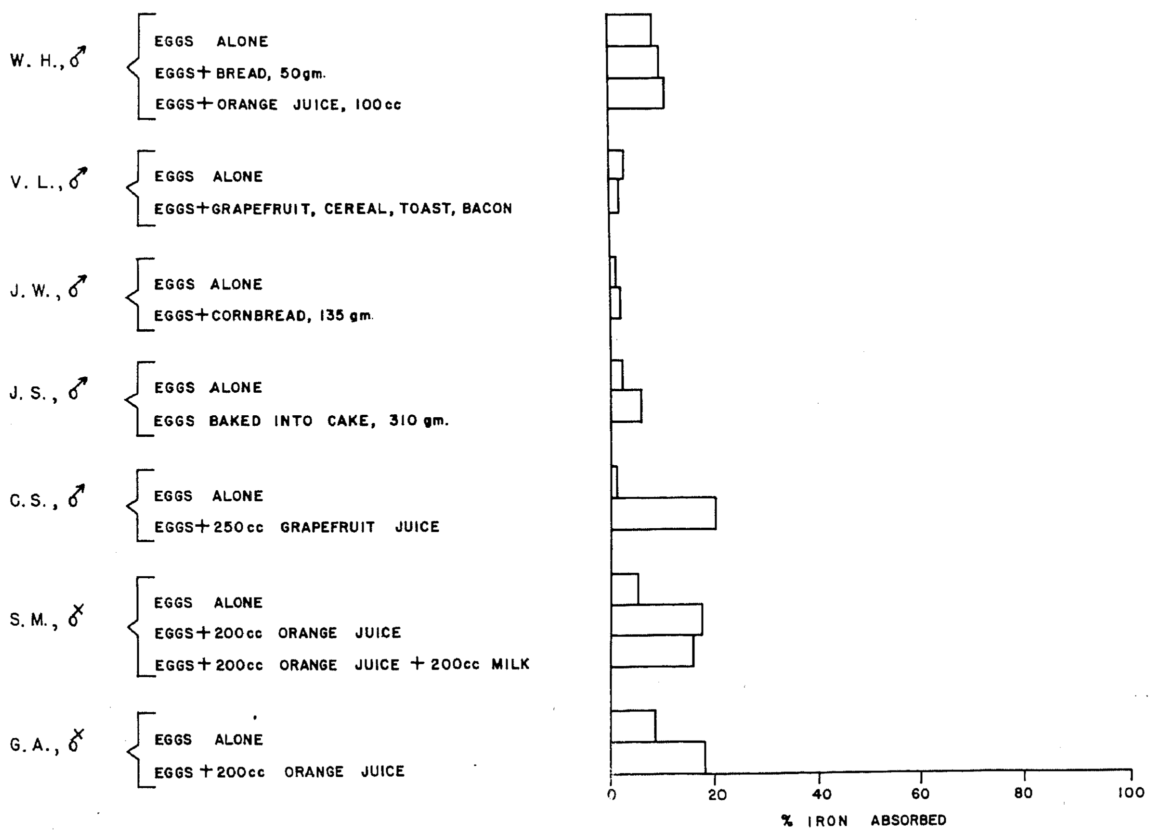


Figure 2.

whether patients with iron-deficiency anemia retained the iron from foods any more efficiently. When eggs were fed, absorption was greater than 10 per cent in only two out of ten experiments. In the few studies so far completed with chicken liver, vegetables, and yeast, however, iron-deficient patients retained more than 10 per cent in the majority of instances.

The effect of other foods on the absorption of iron from eggs has also been measured (Fig. 2). The eggs were baked into cake or corn bread, or scrambled and fed along with toast, bacon, cereal, and fruit juice. Greater assimilation could be detected only with relatively large amounts (200 to 250 cc.) of citrus fruit juices. That observation suggested that the ascorbic acid contained in fruit might increase absorption by promoting the reduction of ferric iron in food to the ferrous form. Crystalline ascorbic acid in comparable amounts had a similar effect; when the amount of ascorbic acid was increased to one gram, there was even greater absorption (Fig. 3). Further studies have indicated that: (a) ascorbic acid usually increases the assimilation of food iron even more in iron-deficient than in normal subjects; (b) reducing substances such as cysteine have a similar action; while (c) other organic acids (citric, lactic, tartaric) are without effect.

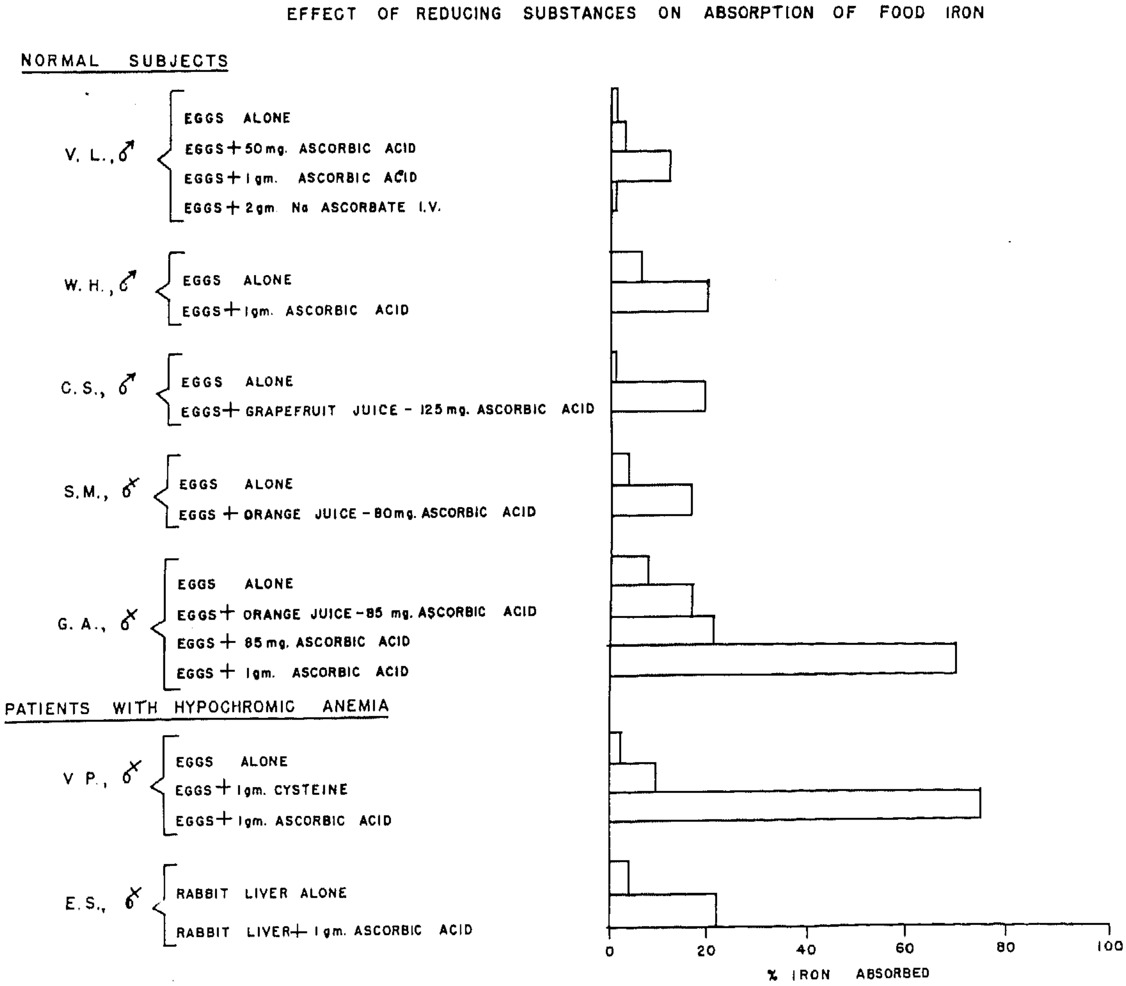


Figure 3.

A preliminary attempt has also been made to evaluate the importance of gastric hydrochloric acid on the absorption of iron from food. For many years it has been thought that individuals with hypochlorhydria or achlorhydria probably assimilate food iron poorly. In such patients, however, we have not been able to increase absorption of the radioiron by adding 60 cc. of 0.1 *N* HCl to cooked eggs, or by adding enough 1 *N* HCl to reduce the pH of the mixture to 1.5 before it was given by stomach tube. On the other hand, ascorbic acid in a dose of 250 to 1000 mg. did increase absorption very significantly, even though it had comparatively little effect on gastric acidity.

Of related interest are observations recently completed on the absorption of iron from bread baked with flour which had been enriched with radioactive iron.[4] The four iron preparations used most commonly in the enrichment program (ferrous sulfate, reduced iron, ferric orthophosphate, and sodium ferric pyrophosphate) were added to flour and baked into bread under conditions which closely similated those employed in the baking industry. The amount absorbed by 28 of 32 healthy young men and women varied from 1 to 12 per cent (Fig. 4). The remaining four subjects retained from 26 to 38 per cent of the radioactivity fed, but there was reason to suspect that their iron stores were suboptimal in each instance. The only three patients with iron-deficiency anemia included in the study assimilated 45 to 64 per cent of the iron taken. The addition of 1 gram of ascorbic acid to the bread eaten by six of the healthy subjects increased the absorption of iron two to three times.

From the above observations, one may conclude that the food iron absorbed by healthy men and women probably does not average more than about 10 per cent of that in the diet, and in many individuals the amount is probably less. The diet of adults in the United States contains approximately 12 to 15 mg. of iron per day. The amount of iron absorbed from food per day, therefore, probably varies from about 0.6 to 1.5 mg. Poor diet, infection, diarrhea, or steatorrhea[5] would decrease this amount even further, while iron deficiency would probably result in some increase.

THE ABSORPTION OF FOUR RADIOACTIVE IRON PREPARATIONS FROM ENRICHED BREAD

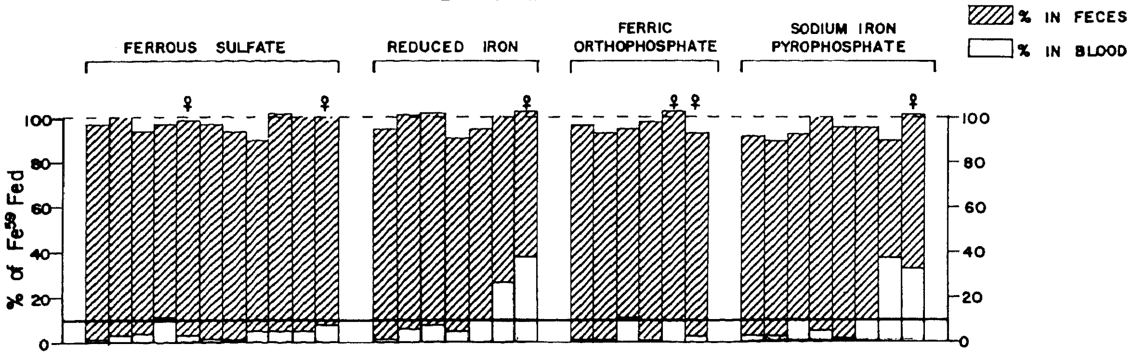


Fig. 4. The subjects were healthy medical students. Each ate four slices of bread enriched with one of the radioactive iron preparations. In many of the experiments, the sum of the radioactivity in the blood and that recovered from feces does not equal 100 per cent. The unaccounted for portion represents a combination of the following three factors: absorbed iron not synthesized into hemoglobin, error of determination, and failure of the subject to make absolutely quantitative collection of feces.

## Excretion of Iron

Because conservation of iron is so tenacious and because the amount excreted is so small, many people have mistakenly assumed that no iron whatever is lost from the body except as shed blood. The error of this assumption becomes obvious from the following considerations. All cells in the body contain iron. When leukocytes and epithelial cells are discharged in body secretions, when erythrocytes appear in urine, when cells are desquamated from the skin or the mucosa of the intestinal tract, and even when hair grows, some iron is lost. Attempts to estimate this amount and to determine in addition how much is excreted in other ways has proved a very difficult task. The metal is so ubiquitous that it has been almost impossible to differentiate between ex- span of the erythrocytes. Every fecal specimen on every subject contained a detectable amount of radioactivity; the amount averaged 0.01 per cent of the dose per day for normal subjects (Fig. 5). Three iron-deficient patients excreted much smaller amounts, while one young woman with a hemolytic (sickle cell) anemia excreted more. No significant increase in fecal radioactivity was detected

THE AVERAGE DAILY RADIOIRON EXCRETION AND THE CALCULATED TOTAL IRON EXCRETION OF TEN HUMAN SUBJECTS

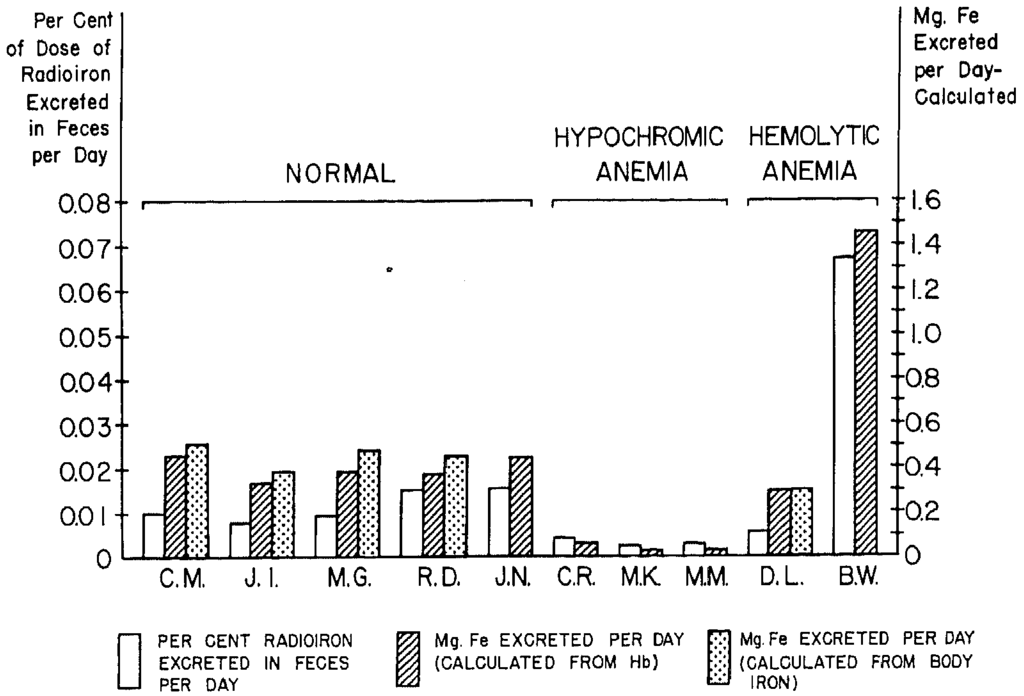


Fig. 5. (Reproduced by permission of the *Journal of Laboratory and Clinical Medicine.*)

creted iron and that present because of contamination or because it wasn't absorbed. Radioiron has provided a partial, but not a complete, solution to the problem.

The isotope has been injected intravenously in tracer amounts into normal subjects and patients with hypochromic or hemolytic anemias.[6] Five-day fecal collections have then been made at intervals up to 150 days; this long period was used because most of the injected radioiron was promptly synthesized into hemoglobin and we wanted the collection periods to be greater than the 120-day life at or near the 120th day after the injection had been given. It is difficult, however, to calculate from these figures what the fecal excretion of all body iron—inert as well as radioactive—would be. Two calculations were made: one from the ratio of total hemoglobin iron to radioactive hemoglobin iron; the other from the ratio of estimated total body iron to the injected dose of the isotope (Fig. 5). Fecal excretion calculated in these ways for normal subjects varied from 0.3 to 0.5 mg. per day. For iron-deficient patients the value was about one-tenth as much. While these calculated values are admittedly estimations, one can be reasonably certain that they do not vary from true figures by more than 100 per cent. One cannot differentiate with this method among the following three possible sources of fecal iron: (a) true excretion; (b) desquamated mucosal cells; and (c) iron delivered to the duodenum via the bile and not completely absorbed.

Some of the injected radioiron was also found regularly in sweat for at least 320 days, the longest time after administration that a collection was made. The amount was small, but definitely measurable. We were not able to determine whether it came from sweat glands by a process of true excretion or from desquamated epithelial cells. Calculations indicated that under normal conditions the total iron lost from dermal surfaces is certainly less than 1 mg. per day and probably not more than 0.5 mg. It is of interest that radioactivity could also be detected in hair clippings obtained several months after the injection of radioiron and washed with dilute HCl to free them from surface (sweat) contamination.

To the above values must be added the small amount of iron found in urine. From these figures, one can estimate that the adult male loses or excretes between 0.5 and 1.5 mg. of iron per day; the median value of 1 mg. is probably not in error by more than 20 to 25 per cent. Menstrual blood flow of 35 to 70 cc. every 28 days in a normal woman with a hemoglobin value of 12 grams would account for an additional average loss of 0.5 to 1 mg. per day.

## Importance of Nutrition in the Pathogenesis of Iron-Deficiency Anemias

Even though the data presented for the absorption of iron from food and for the excretion of iron are admittedly incomplete and provide approximations only, they do permit a better evaluation of the importance of nutritional factors in the pathogenesis of iron deficiency than has previously been possible. If the adult male absorbs an average of 10 per cent of the iron in a diet that contains 12 to 15 mg. per day, he retains 1.2 to 1.5 mg. Since he excretes only about 1 mg. or less of iron per day, he maintains a positive balance rather easily. The adult woman, however, during the years of menstruation and child bearing tends to eat less and loses additional amounts. A mother furnishes her fetus during gestation with about 300 to 500 mg. of iron, or between 1 and 2 mg. per day throughout the duration of her pregnancy. The volume of menstrual blood is normally approximately 35 to 70 cc. If the hemoglobin value of that blood is 12 grams per 100 cc., then 14 to 28 mg. of iron would be involved. Spread evenly over a 28-day menstrual cycle, this equals 0.5 to 1 mg. per day. Iron balance in a young woman, therefore, is precarious, so that poor diet or poor absorption may lead to iron deficiency even though menstrual loss remains normal. Frequent pregnancies or any increase in menstrual flow make her all the more susceptible. Almost nothing is known about iron excretion in children, but the infant and the growing child need iron to increase their blood volume, their myoglobin volume, and the respiratory enzymes required by all cells. Since the body of an infant contains about 0.5 gram and that of an adult 3 to 5 grams of iron, there must be a net gain during the first twenty years of life of 2.5 to 4.5 grams; this net gain averages 0.12 to 0.22 gram per year or about 0.35 to 0.6 mg. per day. In all probability, therefore, the positive iron balance maintained by normal children during their most active growth must be slight, so that poor diet or poor absorption could readily produce iron deficiency.

It is much more difficult, however, for iron deficiency to develop in the adult male or the post-menopausal woman on a purely nutritional basis without any associated blood loss. The calculations in Table I, based on two hypothetical patients, demonstrate that if these two persons excreted 1 mg. of iron per day and absorbed none at all, six and four years, respectively, would be required before they would become deficient enough to have only 7.5 grams of hemoglobin per 100 cc. These figures ignore the evidence that as patients become iron-deficient they excrete smaller amounts of the metal. Any iron contained in

TABLE I.

Calculation of Time Required for Development of Iron Deficiency on Nutritional Grounds Alone in Two Hypothetical Patients (see text)

| | Adult male Hb. 15 Gm./100 cc. Bl. vol. 5000 cc. | | Post-menopausal woman Hb. 14 Gm./100 cc. Bl. vol. 4000 cc. | |
|---|---|---|---|---|
| A. When Normal | | | | |
| Total Hb. iron | 2500 mg. | | 1900 mg. | |
| Storage iron | 1000 mg. | | 500 mg. | |
| Total | | 3500 mg. | | 2400 mg. |
| B. After development of Fe deficiency (Hb. of 7.5 Gm./100 cc.) | | | | |
| Total Hb. iron | 1250 mg. | | 950 mg. | |
| Storage iron | 0 | | 0 mg. | |
| Total | | 1250 mg. | | 950 mg. |
| Deficit in Hb. and storage iron (with this degree of hypochromic anemia) | | 2250 mg. | | 1450 mg. |
| Time required to produce deficiency if no iron is absorbed and 1 mg. excreted per day | | 2250 days (6.3 yrs.) | | 1450 days (4 yrs.) |

the deficient diet, furthermore, would tend to be assimilated with greater than normal efficiency unless there were a serious absorptive defect in the intestinal tract. Both factors would considerably delay the appearance of iron-deficiency anemia. One is forced to admit, however, the theoretical possibility that men or post-menopausal women who consume very deficient diets or who have absorptive defects could, over a period of many years, develop iron deficiency on a nutritional basis alone. On the other hand, it seems far more likely that patients with inadequate diets or poor absorption also lose small amounts of blood that go undetected. In this country, at least, there is not a single, well-documented published instance in which iron-deficiency anemia has been shown to develop in an adult in the absence of blood loss. The bleeding may be slight and intermittent, so that diligent search is required for its detection. With such hemorrhage, even though small in amount, inadequate iron intake or absorption then becomes of major importance in the pathogenesis of hypochromic anemia.

## Summary

Nutritional factors are of major importance in the production or prevention of iron-deficiency anemia. Healthy persons probably maintain a positive iron balance by a narrower margin than was formerly believed. Approximately 5 to 10 per cent food iron seems to be assimilated by normal adults; daily retention on a diet containing 12 to 15 mg. of iron, therefore, may be estimated to be about 0.6 to 1.5 mg. The amount of iron lost from the body each day, in all ways except as blood, seems to be between 0.5 and 1 mg. The added requirements of children and young women to compensate for growth needs and menstrual flow place them in a precarious state of iron balance, so that poor diet or poor absorption can readily lead to the production of hypochromic anemia. In adult men or post-menopausal women, however, nutritional factors appear to be of less importance in the pathogenesis of iron deficiency. If purely nutritional iron deficiency ever occurs in these people, many years would be required for its production. It is more likely that occult, intermittent bleeding, often difficult to detect, must also be present along with inadequate diet or malabsorption before severe degrees of iron deficiency develop.

## References

1. McMillan, T. J., and Johnston, F. A.: The absorption of iron from spinach by six young women, and the effect of beef upon the absorption. *J. Nutrition* 44: 383, 1951.
2. Moore, C. V., and Dubach, R.: Observations on the absorption of iron from foods tagged with

radioactive iron. *Tr. A. Am. Physicians* 64: 245, 1951.
3. Dubach, R., and Moore, C. V.: To be published.
4. Steinkamp, R., Dubach R., and Moore, C. V.: Studies in iron transportation and metabolism VIII. Absorption of radioiron from iron-enriched bread. *Arch. Int. Med.* 1955 (in press).
5. Badenoch, J., and Callender, S. T.: Iron metabolism in steatorrhea. The use of radioactive iron in studies of absorption and utilization. *Blood* 9: 123, 1954.
6. Dubach, R., Moore, C. V., and Callender, S. T.: Studies in iron transportation and metabolism IX. The excretion of iron as measured by the isotope technique. *J. Lab. & Clin. Med.* 1955 (in press).