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Iron absorption in the post-gastrectomy state

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IRON ABSORPTION IN THE POST-GASTRECTOMY STATE

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Introduction

The general metabolism of iron, including its absorption, utilization, and excretion has been studied extensively since 1930. Most of these investigations were very inconclusive until radioactive iron became available. Subsequent research provided a better understanding of iron metabolism in both the normal and abnormal subject. However, despite this gain in knowledge, specific information as regards the physiology and biochemistry of iron kinetics remain unknown.[22]

For the past ten years various articles have appeared in the literature regarding iron deficiency and anemia in patients who have undergone partial gastrectomy for various reasons. Many of these reports have limited themselves to those patients who have had a partial gastrectomy for benign disease, i.e., peptic ulcer, etc. Despite the research and investigation into the reason or reasons for the development of this post-operative iron deficiency and anemia, there has been no general agreement as to its etiology.[17] The possibilities include a decreased intake of iron,[5] diminished or absent gastric acid resulting in impaired reduction capacity of gastric juice and thus malabsorption of iron, [8,9,21] and rapid intestinal transit resulting in a diminished time of exposure of food to that portion of the gastrointestinal mucosa which is instrumental in iron absorption.[2,18] Investigators, in general, are in agreement that the etiology in most cases is

chronic blood loss.[26] However, others flatly state that blood loss is the only etiologic agent involved in the development of post-gastrectomy iron deficiency and anemia.[23,24,26]

This study will present a review of the literature to date regarding the metabolism of iron in the normal and post-gastrectomy patient, and the results of iron absorption studies in a group of patients who have had a partial gastrectomy.

Literature Review

McCance and Widdowson advanced the first widely accepted concept of iron absorption known as the "mucosal block theory". According to this hypothesis, the mucosal cells of the duodenum and jejunum absorb iron in the ferrous form. It is then oxidized to the ferric form and combines with a protein acceptor, apoferritin, to yield ferritin, one of the storage forms of iron. When the mucosal cells become saturated, they form a barrier to further absorption until the available supply is utilized by the body.[16] Iron is subsequently released into the blood stream in the ferrous form, combines with a B-globulin known as transferrin, and is transported to the bone marrow and iron depots.[20]

Numerous experiments have been performed to support the "mucosal block theory". For example, absorption of an oral dose of radio-iron given to iron deficiency anemic dogs was reduced when preceded from one to six hours earlier by a feeding of 100 milligrams

of ordinary iron. It was concluded from this experiment that the mucosa was apparently saturated and absorption subsequently "blocked". These investigators presume that the change in the gastrointestinal mucosa which permits active absorption of iron requires a certain amount of time for mobilization or depletion of the mucosal iron.[14]

In addition, it is believed that the reserve stores of iron, stored as ferritin, has a greater control over iron absorption than does anemia in the presence of adequate iron stores. For instance, individuals with depleted iron stores, as demonstrated by bone marrow hemosiderin determinations, absorb a much larger quantity of iron than do those suffering from an acute episode of anemia with normal iron stores.[3]

The following evidence has been advanced to prove the mucosal block theory false: (1) There is a block to iron absorption when large doses are followed by a test dose but this is only transient. (2) As the size of a test dose increases, the total amount of iron absorbed also increases although the percentage retained becomes less, but no limit to the total amount absorbed was reached. (3) Absorption is greater in many instances when erythropoiesis increases even when tissue iron stores are high. (4) Absorption continues in patients with hemochromatosis even with an increased mucosal iron content. (5) The high ferritin content of the duodenal mucosa does not cause a block to absorption. It has thus been concluded that ferritin may be a mediator of iron absorption but its

concentration in the intestinal mucosa neither controls nor blocks absorption.[22]

The normal adult male has a total iron content which varies from three to five grams, varying with body size. Fifty-five per cent of this iron is present in the circulating hemoglobin, there being 3.38 milligrams of iron per gram of hemoglobin. Ten to twenty per cent of the body iron is present in the bone marrow hemoglobin, myoglobin, and respiratory enzymes, and the remainder is in the body iron stores which includes, primarily, the liver and spleen.[10]

Following absorption, the iron is bound by a B-globulin and the resulting compound, transferrin, carries the iron in the blood stream to its various sites of action and storage. Normally, one-third of the transferrin is saturated with iron and the remaining two-thirds is not. There is a significant increase in the iron-binding protein from 200-450 milligrams per 100 milliliters to 450-500 milligrams per 100 milliliters in iron deficiency, but iron absorption cannot be correlated with the level of the total or unbound iron binding protein.[22]

This knowledge is helpful in the interpretation of two basic laboratory tests which are utilized rather extensively for diagnosis and therapeutic evaluation of subjects presenting a hypochromic anemia: serum iron concentration and serum iron binding capacity.

The normal serum iron is usually 80 to 180 micrograms per 100

milliliters.[30] According to Conrad and Crosby, the earliest evidence of iron depletion is a decrease in the serum iron. As the serum iron decreases, the mean corpuscular volume and mean corpuscular hemoglobin decrease and the unsaturated iron binding capacity increases. After this has occurred, there is a decrease in the mean corpuscular hemoglobin concentration.[22] Following partial gastrectomy, Rumball and Hassett noted low serum iron values in thirty-four per cent of 125 patients. It has been noted through study of patients' iron stores and serum iron values that some patients are iron deficient but have a normal serum iron.[26] The serum iron concentration has been considered a factor involved in determining the per cent absorption of iron. Recent work, however, discounts the serum iron level as having any significant effect on the absorption of iron.[11]

Iron deficiency in post-gastrectomy patients is being reported with increasing frequency. The incidence of this complication varies considerably among the numerous studies which have been reported. The more recent studies which have been completed indicate that anywhere from ten to sixty per cent of patients who have had a partial gastrectomy eventually develop iron deficiency. Smith et al report an incidence of iron deficiency of ten per cent in their series of patients.[28] Mason, Atuk, and Leavell reported sixty-two per cent of twenty-four patients had iron deficiency.[19]

The latent iron binding capacity, which represents the unsaturated transferrin, in normal subjects is always less than 300

micrograms per 100 milliliters, and usually less than 250 micrograms per 100 milliliters.[30] In Verloop et al, the latent iron binding capacity of their group of patients was always greater than 300 micrograms per 100 milliliters in the presence of iron depletion.[30] The unsaturated iron binding capacity has been considered a factor in the absorption of iron.[28]

The incidence of anemia following partial gastrectomy varies considerably among the numerous studies reported - from fifteen to seventy per cent. Thus, it is frequently noted that individuals with iron deficiency following partial gastrectomy are not anemic.[1] It has been found that the incidence of iron deficiency and anemia is greatest in pre-menopausal women and lowest in men and women who have had their operations after age fifty.

Anemia, at one time, was considered influential in increasing the absorption of iron but at the present time anemia by itself does not appear to influence iron absorption.[11] For instance, it has been dhown that active absorption of radio-iron in dogs does not take place following an acute anemia period of twenty-four hours.[14]

Estimation of the body iron stores has thus been used to supplement the other tests in determining whether or not a person is not considered a good criterion of early iron depletion but is stated to be the last to return to normal. Iron stores have been calculated by various methods, however, the most practical method is that utilizing sternal marrow. After aspiration of marrow from the sternum, the specimens are stained for hemosiderin and an estimation

of available iron stores is made.[10] Hansen and Weinfeld state that sternal marrow sideroblast counts are more accurate than hemosiderin measurement for diagnosis of iron deficiency since these are present in most types of anemia but reduced in iron deficiency states.[15]

Iron excretion is well controlled by the body and it has been determined, as far as is possible, that the adult male excretes approximately 0.5 to 1.5 milligrams of iron per day. The pre-menopausal woman loses an additional 0.5 to 1.0 milligrams of iron per day through menstrual blood loss.[22]

The modes of iron excretion are as follows: (1) Intestinal excretion, including bile - up to 0.3 to 0.5 milligrams of iron per day. (2) Sweat, maximal loss - 0.5 to 1.0 milligrams of iron per day. (3) Menstrual blood loss - 0.5 to 1.0 milligrams of iron per day. (4) Urine - 0.2 to 0.5 milligrams of iron per day. (5) Dermal loss - unmeasurable, but minimal. These figures are only approximate.[22] As the subject becomes deficient in iron however, his iron excretion decreases to as much as one-tenth that which is found in the normal subject.[23] Pregnancy, lactation, infection, unaccounted blood loss and other conditions will necessarily increase this loss of iron.[22]

Iron absorption occurs primarily in the first part of the duodenum.[12] An examination of the gastrointestinal mucosa has revealed that iron absorption is limited almost exclusively to the first sixty to seventy centimeters of the jejunum and above.[20]

Following partial gastrectomy, a certain percentage of the subjects eventually appear with either an absence of iron stores without co-existent anemia or an iron deficiency anemia. Jejunal biopsy specimens have shown the small intestinal mucosa to be normal in the majority of post-gastrectomy subjects even in the presence of an iron deficiency anemia.[19]

Many factors have been considered in the absorption of iron in both the normal and post-gastrectomy subject.

The role of hydrochloric acid in the absorption of iron continues to be debated. Chados et al believe that dietary iron is ionized, reduced to the ferrous form, and absorbed more efficiently at an acid pH. However, Moore states that achlorhydria has no apparent effect on iron absorption. He added hydrochloric acid to the food of normal subjects and noted no increase in iron absorption.[22,23]

Most authorities believe that ascorbic acid is effective in promoting the absorption of iron in both the normal and iron deficient subject.[4,7,17,23] Brise and Halberg believe that its action is mainly due to its reducing action within the gastro-intestinal lumen, preventing or delaying a formation of insoluble or less dissociated ferric compounds.[7] Succinic acid has also been ascribed as effective in promoting increased absorption of iron. This increased absorption is related to the amount of succinic acid given with the oral iron dose. Brise and Halberg believe that the promoting effect on iron absorption was due to a direct action on the

transfer of iron across the mucosal cells as the result of increased intracellular mucosal metabolism.[6]

A facilitating role of bile is suggested by a study in the iron deficient dog. In a study by Wheby et al, cholecystectomies were performed on two dogs, one normal and one iron deficient. They cannulized their common bile ducts in such a way that bile from one dog could be diverted into the duodenum of the other. They then performed iron absorption studies on the two dogs using Fe^{59}. It was found that bile from the normal dog did not suppress iron absorption in the iron deficient dog nor did bile from the iron deficient dog stimulate iron absorption in the normal dog. However, a facilitating role of bile in the iron deficient dog was suggested, for when bile was excluded from the duodenum of this dog, absorption of iron decreased by about one-half.[31]

Partial gastrectomy does not seem to impair the absorption of iron salts given to fasting patients. And no change in absorption of this iron is seen when it is given with a light meal in these cases. It is noted that in the presence of iron depletion, there is no significant increase in iron absorption in these subjects which is significantly the opposite finding in iron deficient subjects who have not had a partial gastrectomy - these subjects show a marked increase in iron absorption under these conditions.[2,25]

When iron salts are administered to post-gastrectomy patients with a full meal, a small but significant impairment of absorption is noted.[2,29] Pirzio et al added radioactive iron to various foods

in such a way that it would be metabolized similar to the iron found in this food naturally. It was found that iron deficient subjects without partial gastrectomy absorbed more of this iron than did normal subjects or those who had a partial gastrectomy and iron deficiency anemia. The lower absorption of iron observed when given with or a short time after a meal can be explained both by a chemical interaction of food components on iron (formation of insoluble or undissociated iron compounds or phosphates and phytates) and by a reduction of the concentration of iron by the bulk of the meal and by gastric and intestinal juices.[7]

Baird and Wilson believe that iron deficiency and anemia may be associated with a decreased capacity of the upper gastro-intestinal tract, leading to more rapid passage of the contents into the lower jejunum and ileum where iron absorption is less efficient.[2,18] Hauge found that after suppressing intestinal passage with spasmolytic drugs, the rise in serum iron was greater and took place later.[17]

Stevens et al states that patients with partial gastrectomies are unable to increase dietary iron absorption in the presence of iron deficiency. These patients are unable to repair their iron deficiency by increased assimilation of iron from the diet. Thus, impaired absorption is important in the perpetuation of an iron deficiency state.[29]

However, Smith and Mollett believe that there is no gross impairment of iron absorption after partial gastrectomy, and that

malabsorption of iron alone is unlikely to be the cause of anemia.[28]

Moore believes that iron deficiency is rarely, if ever, due to poor nutrition alone. It is his belief that bleeding is the major factor in the pathogenesis of iron deficiency anemia.[26]

Methods and Materials

Two groups of patients were used in this study of iron kinetics: (1) The control group consisted of subjects who had a subtotal gastrectomy with Billroth II gastroenterostomy of at least five weeks duration. They had no history of anemia, blood loss, or malabsorption syndrome. The following laboratory determinations were performed on these subjects and found to be within normal limits: red blood cell count, white blood cell count, packed cell volume determination, differential count, reticulocyte count, and hemoglobin determination. The mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, serum iron and latent serum iron binding capacity were also determined. These are tabulated in Table I with the values considered as normal in this study. (2) The study group consisted of subjects who had a subtotal gastrectomy with Billroth II gastroenterostomy of at least five weeks duration. In addition, they had an iron deficiency anemia. These subjects did not have a history of blood loss. Their hemoglobin determinations and mean

corpuscular volumes were below the lower limits of normal. Their red blood cell count, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration may or may not have been within the limits of normal. In addition to the studies performed on the control group, these subjects had the following studies performed: Bone marrow aspiration and determination of iron stores, which were deficient or absent. Blood urea nitrogen which was within the limits of normal. Total serum protein determination with serum electrophoresis which may or may not have been within normal limits. A bromsulphalein test which was within the limits of normal. See Table I.

Table I

Lab Studies	Normals	W.B.	A.M.	E.C.	J.T.	J.Z.	O.T.
RBC-mil/cmm	4.6-6.2	4.02	5.25	4.16	4.59	4.81	4.75
WBC--cmm	5000-10000	7100	7700	6500	24400	4900	4900
PCV--%	40-54	40	44	36	36	*	38
Retics.--%	0.5-1.5	1.2	0.6	*	*	1.5	0.6
Hb. gm/100 ml	11.8-15.0	12.6	13.8	11.8	11.2	10.9	11.6
MCV--micra^3	82-92	99	84	87	78	81	80
MCHC--uugm	25-31	31	26	27	24	21	24
MCHC--%	32-36	32	31	35	31	28	30
SI--ugm/100 ml	60-200	47	73	95	34	21	29
SIBC-ugm/100 ml	300	191	169	200	*	394	312
BUN-mg/100 ml	9-19	20	*	18	15	12	12
TSP-gm/100 ml	6.5-7.6	7.8	7.4	6.1	*	6.5	7.1
Alb.-gm/100 ml	3.0-4.4	4.7	4.1	3.9	*	4.1	3.2
Glob-gm/100 ml	2.1-4.4	3.2	3.3	2.2	*	2.4	3.9
B-glob.-%	6-12	*	*	*	*	*	13.2
BSP-reten.45"	5	*	*	*	3.5	1.5	7.5

* Determination not done

Each subject in the two groups, following the initial laboratory studies, was given approximately a twenty-five microcurie test dose of ferrous citrate isotope Fe^{59}.*

The liquid isotope was measured with a micropipette and placed in a gelatin capsule which was immediately administered to the subject who was in a fasting state. One hundred and twenty milliliters of water was given with the capsule. The subject was maintained in the fasting state for two hours after which he was placed on a general diet.

Following administration of the isotope, each stool specimen passed by the subject was collected until less than one per cent of the administered dose was excreted in a twenty-four hour period for two consecutive days. These stools were tested for the presence of occult blood by means of the standard Hematest tablets.

Five milliliter blood specimens were collected approximately every other day following administration of the test dose until a plateau had been reached in regard to radioactivity.

The radioactivity of the stools and blood specimens was quantitated in a Picker scintillation well counter. Each specimen was counted three times and an average value obtained. The radioactivity of the stools and blood was compared with the standard and expressed as a per cent of the total dose given. It was assumed that the radio-iron not collected in the stools was absorbed.

* Abbott Radio-Ferrous (Fe^{59}) Citrate Sterile Solution.

Results

(1) Control group. Three male patients ranging in age from 38 to 76 years comprise this group. One subject in this group, E. C., had a hemoglobin value below 13.8 grams per 100 milliliters, the lower limit of normal in this study. However, the remainder of his hemogram was satisfactory. See Tables I and II.

Table II

Pt.	Age	Post-op Period
W. B.	76	14 Years
A. M.	38	6 Weeks
F. C.	75	17 Years

The quantity of radio-iron collected in the stools and blood in these three patients is listed in Table III. The average amount of absorption of radio-iron in this group was 75.21 per cent.

Table III

Pt.	Total Dose Fe^{59}	Radio-active iron recovered			Fe^{59}
		Feces - %	Blood - %	Total - %	Absorbed - %
W. B.	25 uc	39.49	19.00	58.49	63.51
A. M.	25 uc	8.33	1.80	10.13	91.67
E. C.	25 uc	29.56	0.50	30.06	70.44

The time required for the radioactive level to reach a peak in the peripheral blood varied from 12 to 18 days, with an average of 15 days.

The quantity of radio-iron measured in the peripheral blood at peak concentration varied from 0.50 to 19.00 per cent. See Graph I.

(2) Study group. This group consisted of three male patients ranging in age from 22 to 75 years. See Table IV.

Table IV

Pt.	Age	Post-op Period
J. T.	75	5 Weeks
J. Z.	22	2 Years
O. T.	75	20 Years

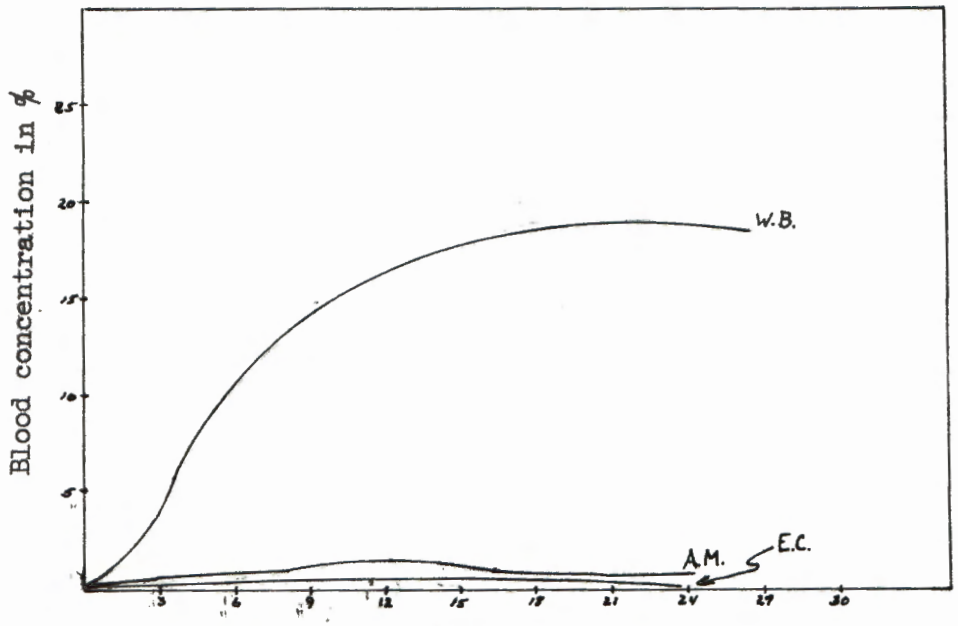
The quantity of radio-iron collected in the stools and blood in these three patients is listed in Table V. The radio-iron assumed to have been absorbed was nearly equal in each subject, the average amount being 49.05 per cent.

Table V

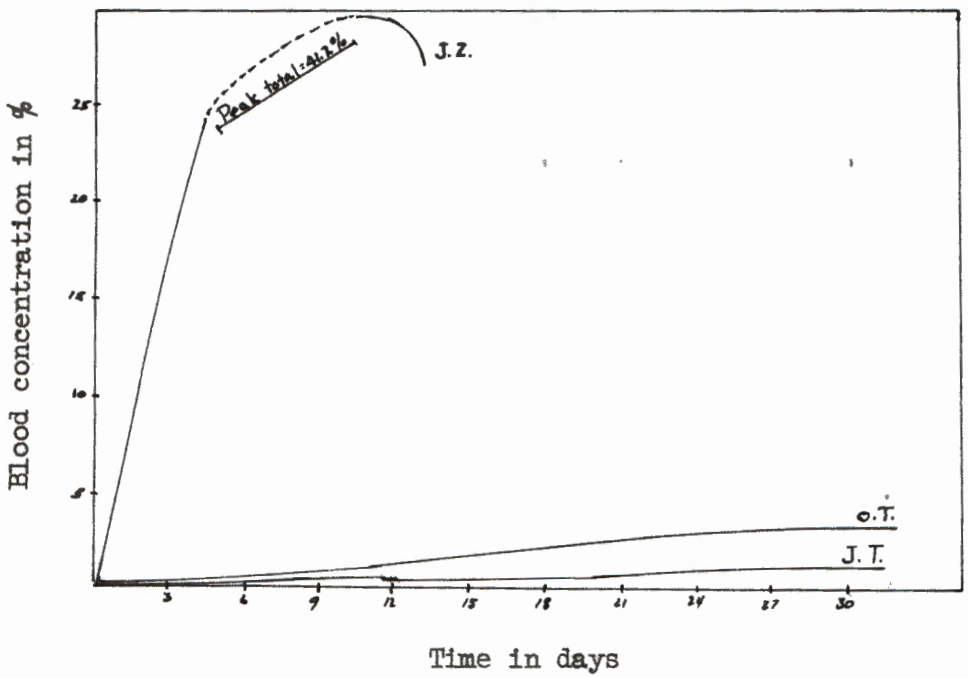
Pt.	Total Dose Fe^{59}	Radio-active iron recovered			Fe^{59}
		Feces - %	Blood - %	Total - %	Absorbed - %
J. T.	25 uc	51.60	0.49	52.09	48.40
J. Z.	25 uc	50.30	41.20	91.50	49.70
O. T.	25 uc	50.95	2.40	53.35	49.05

The time required for the radioactive level to reach a peak in the peripheral blood varied from 15 to 30 days, with an average of 25 days. The quantity of radio-iron in the peripheral blood at peak concentration varied from 0.49 to 41.00 per cent. See Graph II.

Graph I



Graph II



Discussion

It has been assumed that the quantity of orally administered radio-iron not collected in the stools was absorbed. With this assumption, it is noted that each of the six subjects absorbed over 45 per cent of the administered radio-iron. It is thus apparent that partial gastrectomy of the Billroth II type did not inhibit the absorption of tracer doeses of inorganic iron under fasting conditions. However, the difference in the average percentage of absorption in the two groups, 75.21 per cent in the control group and 49.05 per cent in the study group is quite apparent. This suggests there may be some relationship between an apparent lower absorptive capacity and the presence of an iron deficiency anemia in the study group.

The peak concentration of radio-iron varied considerably among the three subjects in the control group: W.B. had a peak concentration of 19 per cent. In sharp contrast is the peak concentration of 0.50 per cent of E.C. and 2.4 per cent of A.M.

The relatively high concentration of radio-iron exhibited by J.Z. indicates a rapid and complete incorporation of the absorbed iron into the circulating hemoglobin without any significant incorporation of the absorbed iron into the iron stores.

Most of the absorbed radio-iron should appear in the circulating hemoglobin in 14 to 20 days unless it becomes incorporated into relatively inaccessable iron compounds with slow rate of turnover.[13]

This is substantiated by Moore who states that the iron used for hemoglobin synthesis comes primarily from the plasma.[22]

The very low concentration of radio-iron in the blood of E.C. may have some relationship to his diminished rate of erythropoiesis. It was noted on bone marrow examination in this patient that he had a very hypoplastic marrow and erythroid hypoplasia.

The low peak concentration of 1.8 per cent in A.M. may be due to three factors: (1) The incorporation of a large percentage of the absorbed radio-iron into the iron stores; (2) retention of this iron in the mucosal cells; and (3) pooling as non-heme iron in maturing erythrocytes.[13,27]

The peak blood concentration of radio-iron likewise varied considerably among the three subjects in the study group. J.Z. had a peak concentration of 41 per cent in contrast to the peak concentration of O.T. and J.T. who had 2.4 per cent and 0.49 per cent respectively.

The very high concentration of absorbed radio-iron J.Z. again indicates rapid incorporation of the iron from the plasma into hemoglobin with a minor portion going to the iron stores.[22]

The low peak concentration exhibited by O.T. may be associated with pooling of the absorbed iron in the mucosal cells and other iron stores,[22] or in slowly maturing erythrocytes.[27]

The low peak concentration of radio-iron in J.T. might be partially on the basis of chronic infection. This patient had a consistently elevated white blood cell count and temperature during

the test. Balfour et al report that chronic infections, in spite of anemia, show no utilization of iron whether it may be absorbed or not.[3]

The results of measuring blood concentrations of absorbed radio-iron are too inconstant for interpretation.

Conclusion

This group of post-gastrectomy patients did not exhibit a complete inhibition of absorptive capacity for radioactive iron under fasting conditions. However, there was a marked difference in the absorption exhibited by the two groups. Despite the presence of iron deficiency and anemia in the study group, these patients are apparently unable to increase their absorptive capacity for iron and are, subsequently, unable to correct this pathology. A reduction in the time allowed the administered iron to be in contact with that portion of the gastrointestinal mucosa principally involved in iron absorption may be a factor in this condition. This time element may be related to several factors: (1) Size of the gastric remnant; (2) size of the stoma; (3) quantity of contents regurgiatated into the duodenal stump; and (4) gastrointestinal motility.

The peak blood concentrations of the absorbed radio-iron is very inconstant in both the post-gastrectomy patients without iron deficiency and in the post-gastrectomy patients with iron deficiency

and anemia. This great variation in the manner and speed with which the absorbed radio-iron is dealt with does not allow one to judge the utilization of iron by this measurement.

Summary

A review of the literature regarding the metabolism of iron in both the normal and post-gastrectomy patient has been presented in detail.

Also, a group of six patients with partial gastrectomies was studied with a tracer dose of radioactive iron. The purpose was to elicit the etiology or etiologies for the development of iron deficiency and anemia which frequently develop in post-gastrectomy patients.

The study group, both individually and as a group, absorbed a significantly smaller amount of the administered tracer dose of radio-iron than did the control group, individually or as a group. In addition, the blood levels of absorbed radio-iron are very inconstant.

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