ABSORPTION *of* IRON
from the Gastrointestinal Tract

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THE ABSORPTION of iron from the upper gastrointestinal tract following large doses of iron produces a prompt and brisk rise in the level of the serum iron.[1-5] Currently it is said that ferrous salts are more readily absorbed than ferric salts[2-7] and that both are less readily absorbed from the gastrointestinal tract of persons with achlorhydria.[2,3,7,9] The presence of free hydrochloric acid is held to be necessary for the conversion of ferric to ferrous iron,[3,7] in which state the iron is absorbed, and to prevent the precipitation of insoluble and nonabsorbable ferric salts.[3,10] A pH of 5 of the gastric content is believed to be the critical level for the conversion of ferric to ferrous iron. The absorption of iron is through the mucosa of the stomach and duodenum[3,5,11] and this corresponds closely to the distribution of ferritin in the gut.[12] However, as a striking exception to part of this hypothesis, it should be emphasized that the absorption of iron from the gastrointestinal tract of persons having Addisonian pernicious anemia is often prompt and adequate.[2,13] More recent studies using the technique of determination of the absorption of radioactive iron from the stomach and upper gastrointestinal tract[6,8] also seem to indicate, but not conclusively, that ferrous iron is better absorbed than ferric.

In the original experiments which led Widdowson and McCance to suggest that there was a limited absorption of iron rather than a colonic excretion,[14,15] the path of iron metabolism was inferred from balance studies. Inferences on the absorption of iron have also been made on the basis of clinical trial, as quoted by Hahn[4] and Heath and Patek.[7] However, over the last several years two additional methods have been extensively used: the study of the serum iron level (as in refs. 1, 2, and 5) and the estimation of the amount of radioactive iron absorbed and appearing in the red cells (as in refs. 5, 6, 8, 11, 13, and 16). Yuile *et al.*[16] state that their results show there is no close relation between the total amount absorbed and the height of the serum iron after the test dose. However, in their results, there is a general trend that higher curves go with greater absorption; and there is little doubt that investigators studying serum levels felt that these rises were of some significance. In a parallel field of study, the comparison of tolerance curves with actual absorption shows that there is a useful general relation for protein,[17] and for fat and vitamin A.[17,18] The probable greater merit of the tolerance curve has been discussed by Althausen *et al.*[17] We have adhered to the view that the height of the curve does give an indication of the functional activity of the bowel involved and this relates to the total absorbed.

In this paper we are reporting studies on the absorption of iron in healthy subjects and in the subject "Tom," in whom the presence

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of a large gastric fistula afforded a unique opportunity.[19]

Method

The serum iron was determined by the method of Kitzes[20] modified to use orthophenanthroline as the color reagent. In our hands this method showed values of 80–125 μg. per 100 cc. in healthy individuals. Duplicates were run on all specimens and they agreed within 5 μg. per 100 cc. Serial determinations on the same person from day to day showed a variation which was within the range of laboratory error. Specimens of serum which were cloudy or lipemic were not utilized; similarly, all those in which the icteric index was over 8 were discarded. The total and free hydrochloric acid values of the gastric juice were determined by the usual method of titrating with *N*/10 sodium hydroxide solution using Topfer's reagent and phenolphthalein indicator. The pH of the gastric content was determined by the Beckman pH meter.

The iron tolerance test was performed as follows:

Iron in the amount of 2 mg. per Kg. was given to the subject after an overnight fast. Specimens of venous blood were withdrawn at the time of the test dose and hourly thereafter for four hours (the curve obtained is referred to as the "iron tolerance curve"). Such a test was performed in seven healthy physicians and laboratory personnel. The healthy subjects were repeatedly studied, and observations were included on the absorption of iron when a dose of 5 Gm. of sodium bicarbonate was given with the test dose of iron.

Since a large number of experiments were performed on the subject "Tom," the test was modified. The dose of iron was given at least three hours after his early morning meal (4–6 a.m.). Specimens of gastric juice were obtained prior to the introduction of iron and at half-hour intervals for two hours after the introduction of the iron. An initial blood sample was not obtained. Two hours after the iron was introduced into the stomach a specimen of venous blood was obtained for determination of the serum iron. This was taken as an index of the absorption of iron. On 26 occasions at the end of the two-hour period, the subject's stomach was emptied and the total iron remaining in the stomach was determined by an appropriate modification of the Kitzes method. Levels of pH of the gastric contents above 5 were not encountered spontaneously, so that in one group of experiments the free hydrochloric acid was neutralized with sodium bicarbonate. In these experiments, after the initial specimen of gastric juice had been obtained, 5 Gm. of sodium bicarbonate was placed in the stomach with the dose of iron. A second dose was introduced an hour later. This was adequate to maintain pH greater than 5 for two hours, and there was no titratable free acid.

TABLE I

Rise in Serum Iron Level (μg. per 100 cc.) in Two Hours Following Administration of 2 mg./Kg. Iron by Mouth

	Serum iron levels following similar dose of various iron preparations			
Subject	Ferric	Ferric + bicarb.	Ferrous	Ferrous + bicarb.
D.B.	8	18	27	30
	7		50	
			125	
			49	
			90	
			120	
M.G.	178	22	139	75
			69	
A.M.	35	14	115	65 N*
	63		70 N	72
P.C.	18	82	82	120
	0		80	
	25		75	
R.D.	30 N	30 N	70	30
	62 N		45	
			110	
C.R.	71 N	182	120	22
	30 N		112	
	67			
W.G.	135	65	56 N	126
	15 N		77	
Average	51	59	84	67
	53		79	

* N = nausea.

Results

(1) *Healthy Subjects*

When a series of "iron tolerance" tests were performed on several subjects, there was vari-

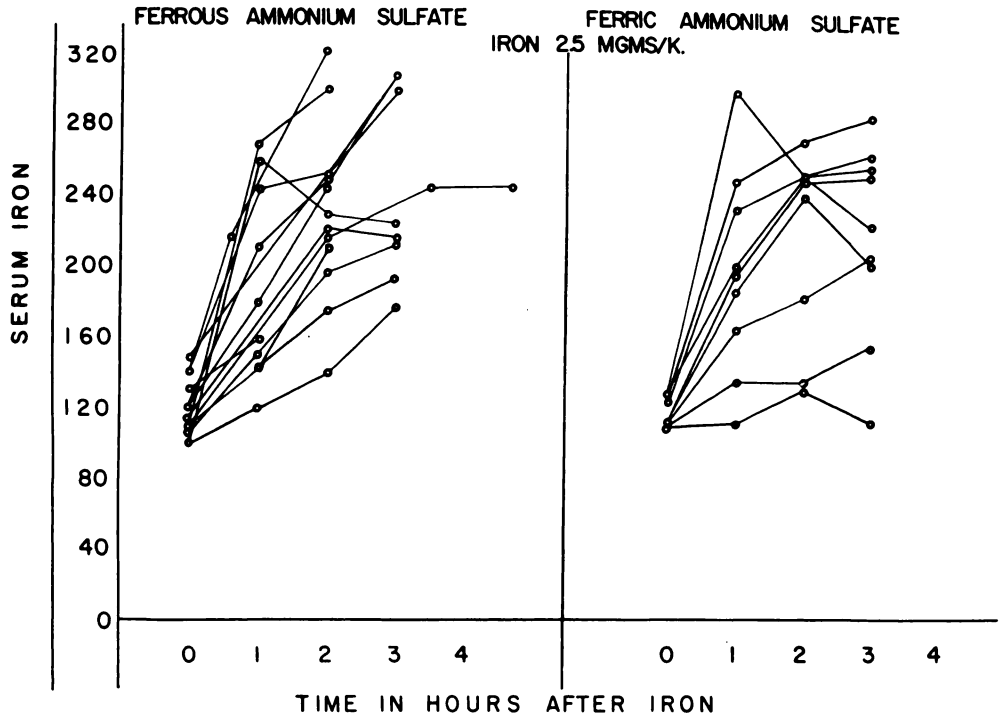

Fig. 1. Iron tolerance curves using ferrous and ferric ammonium sulfate in repeated observations on seven healthy subjects.

ation in the height of the tolerance curve from time to time (Table I and Fig. 1). When the levels of serum iron at two hours were compared, it was found that the level following ferrous iron was 192 μg. per cent; that following ferric iron was 166 μg. per cent; and no difference resulted from the simultaneous administration of bicarbonate (see Table I). This difference could be due to chance (P = 7%). The same comparison (ferric versus ferrous), using the actual or calculated rise in serum iron level over two hours, showed a more significant difference (P = 2%), the changes being 79 μg. and 53 μg. respectively. There were several experiments during which the subject complained of nausea. In such experiments, the serum iron change was less than when nausea was absent, and the slightly greater number of such low values when ferric iron was used accounted for a part of the difference between the two sets of results.

(2). Fistulous Subject

As in the healthy subjects, the absorption of iron varied widely from day to day (see Table II). There was no steady drop in the level of serum iron obtained as the experiments proceeded; that is, it did not appear that a saturation of the iron-absorbing capacity was occurring. There were lower values of the two-hour serum iron with ferric salts (P = 4%). The two-hour serum iron levels were essentially the same when the pH of the gastric contents remained low, near pH 2, as when the pH stayed between 5 and 8 from the administration of sodium bicarbonate (Table III and Fig. 2). Only insignificant amounts of iron remained in the stomach at the end of two hours.

Comment

The data suggest that the absorption of iron is not related to the pH of the gastric contents. The findings in regard to the differential absorption of ferrous versus ferric iron indicate that ferrous iron is probably absorbed a little bit better than ferric iron. Although the difference is statistically important, the difference is certainly not very large and is probably not of clinical importance. It is most

TABLE II*

Date	2-hour serum iron	pH gastric juice: Before iron	½ hour after iron	1 hour after iron	1½ hours after iron	2 hours after iron
Ferrous Ammonium Sulfate						
10-29-52	185	2.1	—	2.6	—	—
10-30-52	257	1.4	1.8	1.3	1.7	—
10-31-52	185	1.2	1.8	1.5	1.8	—
11-3-52	195	1.0	1.5	1.4	—	—
11-12-52	175	1.4	1.2	1.2	1.3	—
11-14-52	156	1.3	2.1	1.7	—	—
11-17-52	132	1.7	1.8	2.2	2.3	—
11-24-52	147	1.7	6.2	1.1	6.8	—
11-25-52	140	1.3	3.3	2.9	6.0	—
11-26-52	235	1.5	5.9	3.5	2.2	—
12-1-52	90	1.8	6.7	7.4	7.9	—
12-10-52	223	6.3	5.7	8.5	6.8	6.6
12-11-52	185	5.1	5.4	5.4	7.2	—
12-12-52	175	8.2	7.3	6.3	7.0	—
Ferric Ammonium Sulfate						
11-6-52	145	1.5	1.4	1.5	—	—
11-10-52	150	1.2	1.4	1.5	1.5	—
11-13-52	125	1.5	1.3	1.2	—	—
12-3-52	160	2.8	2.1	3.7	5.1	—
12-4-52	130	1.7	2.6	7.2	7.5	—
12-8-52	145	1.6	2.4	7.4	8.3	—
12-9-52	215	—	—	—	—	—
12-15-52	155	8.2	6.4	2.6	4.2	—
12-17-52	210	7.1	7.0	7.6	—	—
12-18-52	160	7.6	6.6	8.3	7.2	—
12-19-52	200	7.1	7.9	8.6	7.9	—
12-22-52	187	6.3	7.0	8.9	8.3	—
12-23-52	92	8.0	6.5	8.4	7.9	—

* The 2-hour serum iron is the serum iron (μg. per 100 cc.) 2 hours after ingestion of 1 mg./Kg. of iron. All observations on same subject ("Tom"). The pH as measured by the photoelectric method is given in pH units at the stated time after the test dose of iron was administered.

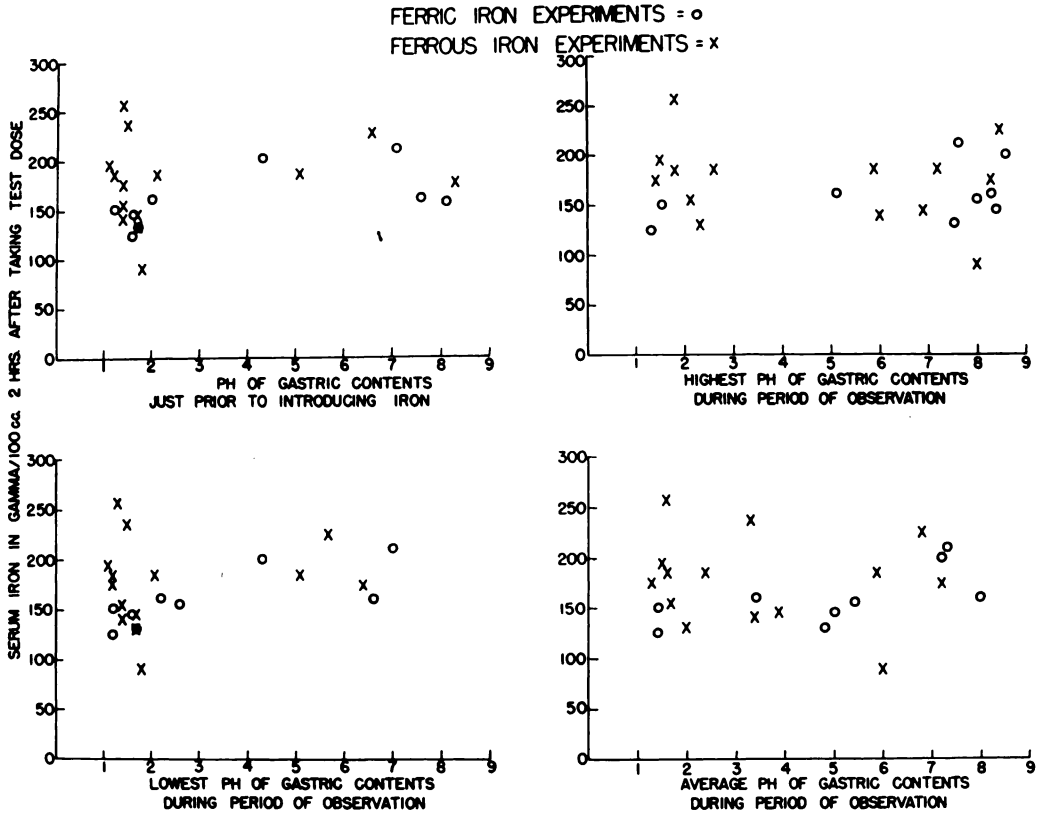

Figure 2.

likely that the failure to absorb iron is a manifestation of lowered absorptive capacity of the upper small intestine, rather than a defect in the hydrochloric acid secretion. An analogous situation is seen in sprue,[17] where the studies of the absorption of a great variety of substances show that a failure to absorb iron is included in the reduced absorptive capacity of the upper small intestine.

TABLE III

Serum Iron Level Two Hours After Administration of Iron to the Fistulous Subject, "Tom." Results in Each Column are in Chronological Order

	Ferrous iron	Ferrous iron plus bicarb.	Ferric iron	Ferric iron plus bicarb.
	185	223	145	155
	257	185	150	210
	185	175	125	160
	195	205	160	200
	175	177	130	187
	156	150	145	92
	132	—	215	—
	147	—	68	—
	140	—	63	—
	235	—	90	—
	90	—	103	—
	68	—	70	—
Average	164	186	122	167

In addition, a large proportion of the older age population are said to show no hydrochloric acid in their stomach, yet these people do not have a comparable amount of iron deficiency anemia.[21]

Summary

Iron-absorption studies were performed on a series of healthy persons and one subject with a gastric fistula. The data indicate that the absorption of iron is not necessarily related to the acidity of the stomach and that the absorption of iron is probably related to the absorptive capacity of the upper gastrointestinal tract.

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Resumen

Absorción del hierro del tracto gastrointestinal

Se realizaron estudios de la absorción del hierro en una serie de personas sanas y en un indivíduo con fístula gástrica. Los datos indican que la absorción de esta substancia no está necesariamente relacionada con el grado de acidéz estomacal y que más bien se encuentra en relación con la capacidad de absorción de la parte alta del tracto gastrointestinal.