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Effect of gastric juice on iron absorption in patients with gastric atrophy

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The influence of gastric juice on iron absorption has been studied extensively in recent years. The absorption of haemoglobin iron is unaffected by achlorhydria (Biggs, Bannerman, and Callender, 1962) but inorganic iron is better absorbed in the presence of normal gastric juice (Goldberg, Lochhead, and Dagg, 1963; Cook, Brown, and Valberg, 1964). It has been shown that the administration of hydrochloric acid to patients with achlorhydria will increase iron absorption (Jacobs, Bothwell, and Charlton, 1964) but it has also been suggested that other gastric juice constituents also play a part. Koepke and Stewart (1964) and Murray and Stein (1967) have produced evidence from experiments in dogs and rats that the stomach secretes an absorption-promoting factor which is increased in some conditions associated with high iron absorption. Davis, Luke, and Deller (1966), on the other hand, demonstrated an iron-binding protein in normal gastric juice which was absent in patients with high iron absorption. They suggested that this substance, which they call gastroferrin, inhibits inorganic iron absorption and that variations in its secretion provide a physiological mechanism for regulating the uptake of iron from the body.

The object of the present study was to see whether normal human gastric juice influences the absorption of inorganic iron in human subjects with gastric atrophy when given together with a standard meal under conditions in which gastric *p*H is maintained at neutrality. Clear evidence was produced that gastric juice promotes iron absorption even when the local effect of acid is eliminated. No inhibitory effect was observed.

METHODS

SUBJECTS WITH GASTRIC ATROPHY Sixteen patients with fully treated pernicious anaemia volunteered to have three successive iron absorption tests. They were all haematologically normal at the time of the tests and were taking no haematinics other than regular injections of vitamin B_{12}. Haemoglobin concentration in this group was in the range 13·5 to 17·1 g per 100 ml. All patients had been shown to have a histamine-fast achlorhydria.

IRON ABSORPTION TESTS Iron was administered as ^{59}Fe labelled ferric citrate (RCC IFS 2P) with an activity of 5μCi added to a standard meal consisting of 200 ml tinned cream of chicken soup with 2 oz of minced breast of chicken. The total iron content of each meal was 4·2 mg, most of this being derived from the soup and only a few micrograms being added with the radioactive isotope. The soup was heated to 40°C before administration in all cases. All the test meals were given in the morning after an overnight fast and nothing was taken by mouth for the following two hours. This particular test meal had a number of advantages over those consisting of more solid items. A constant composition in terms of protein, carbohydrate, and iron content thoughout the tests was easy to ensure and mixing and incubation with gastric juice before administration was more efficient. Iron absorption was measured by whole body counting using a modified scintiscanner and a profile integration technique (Owen, Kirkman, Williams, and Jacobs, 1967). The 100% activity was measured three to four hours after the oral dose was given and retention was measured after 14 days. The second and third doses of radioactive iron were given at 14 and 28 days after the first dose and after absorption from the preceding doses had been measured. All the patients were given the first dose of iron after the soup had been mixed with 200 ml water. The freshly stimulated gastric juice used in subsequent tests was obtained during histamine infusions in normal subjects or patients with duodenal ulcer and was free of blood and bile. Fifteen patients received a second dose in which iron-containing chicken soup was mixed with 200 ml fresh, neutralized gastric juice before administration. For the third dose 13 patients were given 200 ml of iron-containing soup which had been incubated with 200 ml fresh acid gastric juice for one hour at 37°C before neutralization with 12·5 M NaOH solution. Three patients who did not have the third test were given 200 ml soup mixed with 200 ml fresh acid juice. The buffering capacity of the soup was such that the *p*H on administration was 3 to 4. In all the other tests the *p*H of the meal on administration was 6 to 8.

RESULTS

Iron absorption expressed as a percentage of the radioactivity given in each case is shown in Fig. 1, and the mean value in each group is shown in Table I. The iron absorption in individual tests is

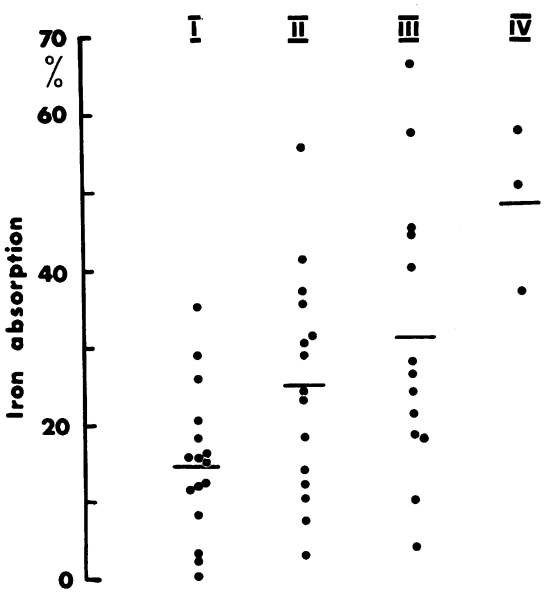

FIG. 1. *Iron absorption in patients with gastric atrophy showing the effect of I, 200 ml water; II, 200 ml neutralized gastric juice, III, 200 ml acid gastric juice incubated with the test meal for one hour before neutralization; and IV, 200 ml acid gastric juice.*

TABLE I

IRON ABSORPTION IN PATIENTS WITH GASTRIC ATROPHY

Test Meal		*Number of Patients*	*Mean Absorption*[1] (±SE)
I	Soup + 200 ml water	16	14·5 ± 2·18
II	Soup + 200 ml neutralized gastric juice	15	24·6 ± 3·72[2]
III	Soup incubated with 200 ml acid juice before neutralization	13	30·9 ± 5·18[3]
IV	Soup + 200 ml acid juice	3	48·2 ± 14·28

[1]Percentages.
Significance of difference from I
[2]$P < 0.05$.
[3]$P < 0.01$.

shown in Table II. In 15 subjects paired observations are available for basic absorption (I) and absorption with neutralized gastric juice (II). Evaluation of the differences shows them to be highly significant ($t = 3.65$, $P < 0.005$). In 13 subjects the difference between basic absorption (I) and absorption after preincubation with gastric juice (III) shows a similar degree of significance ($t = 4.29$, $P < 0.005$). The addition of neutralized gastric juice to the test meal thus results in an increase in absorption and there is an even greater increase when the meal is incubated with acid gastric juice before neutralization. This effect could not be due to changes in the gastric *p*H or that of the meal at the time of administration. In

TABLE II

IRON ABSORPTION IN INDIVIDUAL PATIENTS USING DIFFERENT TEST PROCEDURES[1]

Subject	*Type of Test*[2]			
	I	*II*	*III*	*IV*
1	11·7	30·2	—	36·7
2	15·3	30·9	—	57·5
3	11·1	13·7	—	50·4
4	25·4	23·8	65·7	—
5	34·9	41·1	40·2	—
6	28·7	28·7	57·2	—
7	20·3	55·4	45·0	—
8	15·4	35·4	18·3	—
9	15·0	37·0	44·0	—
10	11·0	12·0	4·0	—
11	3·0	7·0	10·0	—
12	Nil	18·0	26·0	—
13	2·0	10·0	18·0	—
14	12·0	23·0	28·0	—
15	8·0	3·0	24·0	—
16	18·0	—	21·0	—

[1]Percentages.
[2]Tests as in Table I.

the three cases in which the meal was given with unneutralized gastric juice, absorption was considerably increased.

DISCUSSION

In iron-deficiency anaemia impaired iron absorption is found in those subjects with gastric atrophy (Goldberg *et al*, 1963; Jacobs, Lawrie, Entwistle, and Campbell, 1966a). A similar impairment is found in anaemic rats after gastrectomy (Rieber, Conrad, and Crosby, 1967) and this is due to loss of a factor in the gastric secretion (Murray and Stein, 1967). The effect of gastric juice appears to be at least partly due to the presence of hydrochloric acid (Jacobs *et al*, 1964) and the effect of administration of acid gastric juice in the three subjects in group IV confirms the effect observed by Cook *et al* (1964).

Results of the other tests show that this is not the only factor involved. The test meals were all administered at neutral *p*H and the presence of complete achlorhydria in the recipients indicates that gastric juice can promote iron absorption irrespective of the *p*H in the gastrointestinal lumen. A similar study on five patients by Cook *et al* (1964), using neutralized gastric juice and a test meal consisting of bread, gave inconclusive results. Studies *in vitro* have shown that gastric juice contains substances that combine with iron at low *p*H to form complexes that remain soluble after neutralization and that this maintains iron in a form suitable for absorption (Jacobs and Miles, 1968). If the increase in iron absorption produced by neutral gastric juice is due to the formation of such complexes then the greater effect of preincubating the juice at acid *p*H before neutralization might be

due to the increased complexing known to occur *in vitro* under these conditions. In addition the peptic digestion of protein is likely to provide additional ligands for complex formation, an effect which would not be apparent if the test meal contained no protein.

Koepke and Stewart (1964) found a substance in the gastric juice of anaemic dogs that stimulated iron absorption in normal dogs. Murray and Stein (1968) have claimed a similar effect for gastric juice from iron-deficient and haemochromatotic patients on iron absorption in rats. They suggest that the gastric mucosa responds to iron deficiency by an increased secretion of the absorption-promoting factor and that this is a physiological mechanism for the regulation of iron absorption. Similar experiments using iron-deficient patients as donors of gastric juice and normal human volunteers as recipients showed no stimulation of iron absorption by 'anaemic' gastric juice (Jacobs, Rhodes, and Eakins, 1967). It seems unlikely that the iron-deficient gastric mucosa will increase its secretion of this specific factor when it is known that acid, pepsin, and intrinsic factor secretion are all reduced in these circumstances (Jacobs, Rhodes, Peters, Campbell, and Eakins, 1966b; Stone, 1968). Our results do not support the suggestion (Davis *et al*, 1966; Luke, Davis, and Deller, 1967) that normal gastric juice contains an inhibitor of iron absorption.

SUMMARY

When inorganic iron is given to patients with complete achlorhydria absorption is increased by the simultaneous administration of neutralized normal gastric juice. Gastric juice potentiates iron absorption even when the effect of acid is eliminated.

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