Intrinsic factor secretion in gastric atrophy

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EDITORIAL SYNOPSIS The appearance of the gastric biopsy histologically has been correlated with assay of the intrinsic factor and acid content of the gastric juice, and also with vitamin B₁₂ absorption studies. The loss of intrinsic factor parallels the loss of gastric secretory cells. The assay of intrinsic factor proved a better index of secretory capacity of the mucosa than either acid production or vitamin B₁₂ absorption.

The loss of secreting cells from the gastric mucosa results in the decline of acid production and in some cases in loss of intrinsic factor of sufficient degree to impair vitamin B₁₂ absorption (Siurala, Erämaa, and Nyberg, 1960; Glass, Speer, Nieburgs, Ishimori, Jones, Baker, Schwartz, and Smith, 1960; Whiteside, Mollin, Coghill, Williams, and Anderson, 1964). However, since normal vitamin B₁₂ absorption requires only about 1 to 2% of the daily intrinsic factor output (Ardeman and Chanarin, 1965a), impaired absorption of vitamin B₁₂ represents almost complete loss of intrinsic factor secretion. Reduced secretion of intrinsic factor with normal vitamin B₁₂ absorption has been reported in patients with gastric atrophy (Ardeman and Chanarin, 1963; Irvine, 1965). The purpose of this paper is to describe the

findings in a group of patients in whom the appearance of the gastric biopsy was correlated with vitamin B₁₂ absorption studies, direct assay of the intrinsic factor secretion and acid content of the gastric juice.

MATERIALS AND METHODS

Gastric juice was collected by continuous aspiration via a Ryle's tube for one hour after giving an injection of 0.04 mg. of histamine HCl per kilogram of body weight. An injection of chlorpheniramine maleate (10 to 20 mg.) was given before the dose of histamine. The intrinsic factor content of the gastric juice was assayed by the method of Ardeman and Chanarin (1963, 1965a). When one unit of intrinsic factor is taken as the amount that binds 1.0 µmg. of vitamin B₁₂, the normal range of

FIG. 1. The secretion of intrinsic factor over one hour following 0.04 mg. of histamine per kilogram of body weight in patients with gastric atrophy.

FIG. 2. The results of the urinary excretion of ^{57}Co -vitamin B_{12} (Schilling test) using a $1.0 \mu\text{g}$. oral dose as an index of vitamin B_{12} absorption in patients with gastric atrophy.

intrinsic factor secretion after histamine is 2,100 to 18,000 units in one hour (Ardeman, Chanarin, and Doyle, 1964).

The absorption of ^{57}Co -vitamin B_{12} was assessed by the urinary excretion method (Schilling, 1953), using a $1.0 \mu\text{g}$. oral dose.

Gastric biopsies were obtained using a Wood's tube. The results were classified as normal, superficial gastritis, atrophic gastritis, either moderate or severe, depending on whether large numbers of secreting cells remained or whether these cells were only scanty, and gastric atrophy where there was complete loss of parietal and peptic cells.

Twenty-seven patients were studied. They had either iron-deficiency anaemia, Addisonian pernicious anaemia, thyroid disease, megaloblastic anaemia due to folic acid deficiency, myelofibrosis, or they were relatives of patients known to have Addisonian pernicious anaemia.

RESULTS

NORMAL GASTRIC BIOPSY In one hour after histamine these four subjects secreted 4,100, 6,000, 7,000, and 12,000 units of intrinsic factor (mean 7,700). These results are shown in Figure 1. The absorption of vitamin B_{12} tested in two of these subjects was normal (Fig. 2). All had HCl in the gastric secretion (18.0 to 21.5 mEq.).

SUPERFICIAL GASTRITIS Post-histamine intrinsic factor output in one hour was normal in three patients (5,000, 6,700 and 12,100 units in one hour) and was 1,100 units in a fourth patient. The mean secretion in the four patients was 6,200 units. The absorption of vitamin B_{12} was tested in three of the four patients, including the patient with reduced

intrinsic factor output, and was normal in all. All had HCl in the gastric secretion although only 1.7 mEq. was present in the patient with low intrinsic factor output. Hydrochloric acid in the other subjects ranged from 10.5 to 28.0 mEq.

MODERATE ATROPHIC GASTRITIS The post-histamine intrinsic factor output in one hour was normal in one patient (3,300 units) and reduced in the other three (1,200, 700, and 400). The mean secretion was 1,400 units. The absorption of vitamin B_{12} was normal in three subjects producing the larger amounts of intrinsic factor. The fourth patient, who produced 400 units of intrinsic factor, had a Schilling test result of 10%. All these patients had hydrochloric acid in the gastric juice although it was reduced in amount in two out of the three cases in which it was titrated (9.1, 0.07, and 0.2 mEq.).

SEVERE ATROPHIC GASTRITIS All but one of these seven patients had a reduced secretion of intrinsic factor (100, 200, 200, 400, 400, 1,000, and 2,000 units in one hour). The mean secretion was 600 units. The absorption of vitamin B_{12} was tested in five patients and was normal in three (32, 23, and 11.4%) and reduced in two (5.0 and 9.0%). The absorption was improved in the patient with a 5% excretion by the addition of intrinsic factor. In the patient who excreted 9.0%, a further Schilling test with carbachol increased the urinary output to 13.0%. All these patients had normal serum vitamin B_{12} levels. Four patients had a histamine-fast achlorhydria. Acid was present in two others.

GASTRIC ATROPHY WITHOUT PERNICIOUS ANAEMIA Two observations on the intrinsic factor content of the gastric juice in one patient gave values of 100 and 200 units in one hour. The absorption of vitamin B₁₂ was reduced (9.5% excretion) and this increased to 13.0% when repeated with intrinsic factor. The serum vitamin B₁₂ level was normal and has remained normal over the past 12 months. Acid was absent from the gastric juice.

GASTRIC ATROPHY WITH PERNICIOUS ANAEMIA The amount of intrinsic factor secreted in one hour was zero in six patients and 100 units in the seventh. The absorption of vitamin B₁₂ was abnormal in all. All had a histamine-fast achlorhydria.

DISCUSSION

The loss of secreting cells from the gastric mucosa is paralleled by a decline in the total output of intrinsic factor. In some respects the assay of intrinsic factor offers a better index of the secreting capacity of the gastric mucosa in such patients than either acid production or vitamin B₁₂ absorption. Thus appreciable quantities of intrinsic factor may still be present after acid production has failed. This was the case in most of the patients with a severe degree of atrophic gastritis, *i.e.*, those patients in whom the biopsy showed only small numbers of parietal cells.

While the assay of the intrinsic factor content of the gastric juice appears to be a better index of the state of the gastric mucosa than measurement of the acid production, it also proved to be better than the vitamin B₁₂ absorption test. Thus all the four patients with a moderate degree of atrophic gastritis had normal vitamin B₁₂ absorption. Nevertheless the intrinsic factor secretion was reduced in three of these patients. This difference is even more striking in the group with the more severe degrees of atrophic gastritis where almost all the patients had reduced intrinsic factor secretion but only two a subnormal Schilling test. In one of these vitamin B₁₂ absorption was improved after carbachol.

Although we do not believe that cholinergic drugs stimulate intrinsic factor output in man (Ardeman *et al.*, 1964; Ardeman and Chanarin, 1965b), the improved vitamin B₁₂ absorption achieved in some patients with gastric atrophy given carbachol (Whiteside *et al.*, 1964) is probably due to more rapid passage of the vitamin B₁₂-intrinsic factor complex to the distal gut.

Loss of secreting cells from the gastric mucosa is associated with a marked reduction in the volume of gastric juice produced, and it is possible that in

some tests only a small proportion of the total amount of secretion produced is aspirated. Thus, although one patient with severe atrophic gastritis excreted only 100 units of intrinsic factor, the total volume of gastric juice was only 15 ml. A further test on the same patient, using a different gastric stimulant, however, produced a volume of 35 ml. and an intrinsic factor content of 700 units.

SUMMARY

There was a good correlation between the decline of intrinsic factor output and the loss of gastric secreting cells as judged from the appearance of gastric biopsy specimens. The secretion of intrinsic factor was reduced in 10 out of 11 patients with atrophic gastritis although most of these still absorbed vitamin B₁₂ normally.

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CORRECTION

In the list of contents for Gut, 6, no. 6, 1965, the title of the article by W. C. Watson was printed incorrectly. It should read 'Malabsorption of small doses of castor oil in patients without steatorrhoea'.