Gastric intrinsic factor

The demonstration, by W. B. Castle and his collaborators some 40 years ago of a haemopoietic substance in the gastric secretion absent in pernicious anaemia was the starting point of a chain of observations that has continued to the present time.

Intrinsic factor (IF) has now been obtained in a relatively pure state from human gastric juice and from hog pyloric mucosa. It is a mucoprotein with a molecular weight of about 60,000 and contains about 13% of carbohydrates. Each molecule binds one molecule of vitamin $\text{B}_{12}$, that is, 1 mg of IF binds 25 $\mu$g of vitamin $\text{B}_{12}$. In man, as well as in the guinea pig, cat, rabbit, and monkey, IF arises from the gastric parietal cell but surprisingly in the rat and mouse its source is the chief cell. Substances that stimulate secretion of hydrochloric acid in man also stimulate that of intrinsic factor. These include histamine and gastrin and their analogues, and insulin. Cholinergic drugs such as carbachol are not effective. The early and rapid rise in intrinsic factor secretion preceding that of acid has suggested that the stimulus to secretion has washed out preformed IF from the parietal cell. If, however, histamine is infused over a longer period the IF level is maintained above base line levels indicating a continuous stimulus to increased production.

The normal stomach produces far more intrinsic factor than is required for vitamin $\text{B}_{12}$ absorption. Indeed, only about 1% of the normal daily output is required to achieve maximum absorption of a 1·0 $\mu$g dose of vitamin $\text{B}_{12}$. Impaired vitamin $\text{B}_{12}$ absorption implies loss of at least 99% of IF secreting capacity.

The large excess of intrinsic factor that is available under normal circumstances implies that stimulants to gastric secretion are not likely to influence vitamin $\text{B}_{12}$ absorption. The exception to this rule probably occurs after partial gastrectomy. Deller et al (1961) first pointed out that there was a significant increase in the amount of vitamin $\text{B}_{12}$ absorbed after partial gastrectomy when the $\text{B}_{12}$ was given with a meal rather than in the fasting state. This was confirmed by Turnbull (1967), who also noted that a similar increment in absorption took place when histamine (40 $\mu$g per kg) was substituted for the meal. This suggests that after gastrectomy a stimulus is required to produce adequate IF from the gastric remnant. Rune (1966) has suggested that food has an effect on gastric secretion similar to that of an augmented dose of histamine. In the light of these observations it is necessary to re-examine $\text{B}_{12}$ absorption in post-gastrectomy patients. The frequency of $\text{B}_{12}$ malabsorption after partial gastrectomy when the test is performed in the fasting state is 30%. This may prove to be too high an estimate, particularly when the frequency of megaloblastic anaemia due to vitamin $\text{B}_{12}$ deficiency in this group is likely to be of the order of 5 to 6%.

The production of IF may be suppressed by IF antibody. This antibody also prevents the attachment of vitamin $\text{B}_{12}$ to IF, presumably by combining with the vitamin $\text{B}_{12}$-binding site. Both Bar-Shany and Herbert (1967) and Goldberg et al (1967) studied infants born to mothers with pernicious anaemia. Intrinsic factor antibody had crossed the placenta and was present
in the infant’s serum, and, in one child, in the gastric secretion. Intrinsic factor could not be demonstrated in the gastric juice of either of these infants till about 1 to 3 months of age when IF-antibody had largely disappeared. Thereafter IF appeared in the gastric juice in normal amount. Intrinsic factor is always present in gastric secretion collected on the first day of life from normal infants. This mechanism may be important in pernicious anaemia and suppression of such antibody may, in part, account for the improvement in vitamin B₁₂ absorption in steroid-treated pernicious anaemia patients.

Most of the vitamin B₁₂ present in food is available for absorption. Intrinsic factor binds firmly and rapidly to dietary vitamin B₁₂. In vitro the reaction between IF and B₁₂ in solution is complete in a few seconds. In vivo much of the reaction occurs in the stomach but can also take place in the gut. Like all biochemical reactions an equilibrium is achieved between free IF, free B₁₂, and the complex and indeed IF-bound B₁₂ readily exchanges with labelled vitamin B₁₂ in the environment. The reaction is unaffected by change in pH and once bound to vitamin B₁₂ IF becomes relatively resistant to proteolytic digestion. This is particularly important because the complex must survive exposure to proteolytic enzymes in its long passage to the ileum.

Some intrinsic factor normally persists in the small gut probably adsorbed on the villous cells. Total gastrectomy in the rat is not followed by an abrupt cessation of vitamin B₁₂ absorption but by a gradual decline over 24 hours. Booth et al (1957), in their study of vitamin B₁₂ absorption in rats, demonstrated transient uptake of some vitamin B₁₂ presumably bound to intrinsic factor in the upper gut and a return of this material to the lumen to be reattached lower down the gut. This phenomenon occurs in man, and vitamin B₁₂ attachment to jejunum was demonstrated by Doscherholmen et al (1960) in one patient who died two hours after taking an oral dose of labelled vitamin B₁₂. This transient binding of IF-B₁₂ to jejunum is also the explanation of the observation of Gazet and McColl (1967) that vitamin B₁₂ introduced to an isolated jejunal loop at operation was partially retained there. However, absorption of vitamin B₁₂ does not take place from the jejunum even when left in that site for up to 12 hours. Absorption only follows the release of vitamin B₁₂ to the lumen and its reattachment lower down the gut.

The large body of evidence on the effect of small gut resection on vitamin B₁₂ absorption points unequivocally to the ileum as the only site of IF-mediated B₁₂ absorption in man. Once the ileum is reached the fate of IF is less certain. The complex attaches to ‘receptors’ on the brush borders and microvillus membranes of the cells lining the villi. That there are specific receptors for attachment of IF-B₁₂ in the ileum is implied in the fact that only this particular segment of gut is capable of vitamin B₁₂ absorption, that the amount of vitamin B₁₂ that can be absorbed at one time through the agency of intrinsic factor is strictly limited to about 20 μg, and, most important, ileal absorption of vitamin B₁₂ may fail as an isolated gut abnormality in congenital vitamin B₁₂ malabsorption (Gräbeck-Imerslund), a disorder transmitted as a recessive characteristic. This disorder is associated with albuminuria and suggests a failure of protein transport across a membrane involving both villous cell and renal tubule. This, indeed, is the only evidence that IF-B₁₂ may enter the villous cell.
Thereafter our information about IF is even less certain. It is likely that there is slow separation of IF from B\textsubscript{12} so that the latter reaches the portal blood in highest amount only some eight to 12 hours after the oral dose.\textsuperscript{80} That IF is left behind is suggested by normal vitamin B\textsubscript{12} absorption in a small group of otherwise healthy thyroid patients who have IF antibodies in serum, and by the failure to identify IF after cannulation of both lymphatics and portal blood during B\textsubscript{12} absorption.\textsuperscript{31,32}

I. CHANARIN

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