THE STOMACH AND ANAEMIA

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The stomach's function is to prepare food for assimilation, and this may involve breakdown of large molecules, conversion of metallic ions into chelates, or combination of molecules found in food with some secreted by the stomach to form a more easily absorbed compound. The mechanical process of kneading the ingested food with the secretions must not be forgotten, though its importance may be exaggerated. Of these processes, the most important in the genesis of anaemia are the production of proteolytic enzymes to break down proteins, including those which form complexes with iron; the production of acid in concentration sufficient to maintain in solution this liberated iron, and the production of the intrinsic factor which combines with vitamin B₁₂ to render it absorbable. These secretory functions are reinforced by the storage and kneading functions, so that in a healthy stomach food is rapidly reduced to an almost homogeneous liquid which is squirted through into the duodenum whenever the stomach contracts.

One would therefore expect that any interference with these functions might contribute to the production of anaemia—an iron-deficiency anaemia should acid and enzymes be absent, a megaloblastic anaemia should intrinsic factor be deficient.

Iatrogenic Deficiencies

The clearest evidence on these deficiencies can be obtained by studying patients whose stomachs have been removed. Unless some attempt has been made to reconstruct the storage component, as by the transplantation of a segment of colon into the place left by the stomach, the food passes straight into the small intestine, which is adapted not for kneading and mixing, but for the completion of digestion and absorption of its product. This failure of storage assures a rapid transit of food through the absorbing zone, so that absorption is likely to be imperfect. Even though in most patients digestion and absorption may appear adequate, when under stress the average, and even without stress the unusual patient, may fail to digest and absorb food in the needed quantity.

Such patients would be expected to suffer from multiple deficiencies. Total gastrectomy should lead to megaloblastic anaemia from intrinsic factor deficiency, and in fact, this usually develops three to five years after operation, about the time when the reserves built up in the liver before operation become exhausted.⁹ Lack of acid and pepsin would reduce the proportion of food iron brought into solution, and this, with rapid transit through the small intestine, reduces the absorption of both iron and protein. Partial gastrectomy, removing only the pyloric part of the stomach, leaves intact the area which secretes intrinsic factor so that among survivors from the operation, megaloblastic anaemia develops at the same rate as would be expected in any population of similar genetic constitution; Maclean⁴² considers that prospective sufferers can be detected at the time of operation, when histological examination of the body mucosa will show an atrophic gastritis.

Recently the iron deficiency which so often follows partial gastrectomy has been studied by Hobbs and Discombe³¹ and Hobbs,³⁰ and, as might be expected, failure of absorption seems to be the principal factor, accounting for about two-thirds of the anaemia, as suggested by Hartfall²⁴ and Dedichen.¹⁶ It also appears that most patients after partial gastrectomy are in critical protein balance;^{37, 49} in such cases response to iron therapy may depend on absorption of protein as much as on iron and Hobbs regards as excellent a rise in haemoglobin level of 2 g. in a month—i.e., about $\frac{1}{2}\%$ daily, compared with figures of 1% to 3% daily which can be obtained in simple iron deficiency occurring in well nourished patients; he points out that little increase over these rates is obtained even when parenteral iron is administered. Owren⁴⁸ showed that in such cases tablets could pass from mouth to colon in about 20 mins. were the patient standing, but disintegrated within the absorbing area if the patient lay down; the importance of posture has further been emphasized by Goldeck and Gudermann²³ and Hobbs.³⁰

So much for the iatrogenic anaemias involving

the stomach; they are now easily treated, and patients need no longer suffer chronic sideropenia, which causes so much lassitude, lack of energy, and loss of weight after partial gastrectomy, and plays some part in the genesis of the dumping syndrome.^{2, 24, 26, 27, 33, 47, 50, 51, 60}

Natural Disorders of the Stomach

There are diseases which may involve the stomach accidentally, or because the stomach is a natural seat of the disease, though it may also manifest elsewhere. Some of these produce anaemia by causing bleeding, and of these the chief is *peptic ulceration*, which produces anaemia not by interference with normal secretion, but by causing loss of blood, which, when it averages 6 ml. daily in a man, or less in a woman, usually causes a negative iron balance. Most iron deficiency in men, and much of that in women, can be traced to chronic bleeding from a peptic ulcer, usually punctuated by episodes of more serious bleeding which are sometimes, but not always, recognized as haematemesis or melaena. It is worth noting that this 6 ml. daily is quite close to the critical level for the detection of occult blood in stools by the usual tests (about 1 to 3 ml.), so that if, as is usually the case, blood loss varies from day to day, it may not always be detected, so that in suspicious cases many tests must be done before a negative result can be accepted. Bleeding from acute ulceration is, fortunately, less common, for it tends to be torrential from the start. Other causes of bleeding may be sought in the gastro-enterological texts.¹

Disorders of the Gastric Secretions

These might involve any or all of acid production, enzyme production, and intrinsic factor production; and they might be either primary or secondary to some other lesion. It is, for example, clear that iron deficiency anaemia in young people may be associated with achlorhydria, but that normal secretion of acid sometimes returns when the deficiency is corrected,^{7, 41} though this did not occur in the patients of Lees and Rosenthal.³⁹ Superficial gastritis is much commoner in patients with iron deficiency than in normal controls, but is not always accompanied by achlorhydria.¹³ If we exclude the consequences of recovery after a corrosive poison, the only lesion which produces complete absence of all these secretions seems to be that which leads ultimately to pernicious anaemia; a process which continues over many years, perhaps most of the patient's life, to its final stage, a degeneration of the body mucosa to a state in which it is not to be distinguished, from the simplest mucosa of the small intestine full of goblet cells; coincidentally

the muscular components of the stomach become atrophic.^{17, 21, 35, 43, 63}

In 1930, Magnus and Ungley⁴⁴ concluded that pernicious anaemia was invariably associated with gastric atrophy. In 1955, however, Joske, Finkh and Wood⁵⁵ showed that in about 60% of cases of clinically typical pernicious anaemia, there was present an inflammatory atrophic gastritis with survival of body chief and oxyntic cells; and Robertson, Wood and Joske⁵³ record the development of pernicious anaemia in a man not less than five years after he was found to have complete gastric atrophy.

The Oxford school, trying to assess gastric secretion, have encountered similar anomalies. Retief⁵² showed that of the patients who secrete no free acid in Kay's³⁶ augmented histamine test meal, about half have subnormal vitamin B₁₂ absorption; Callender and Denborough⁸ studied the relatives of patients with pernicious anaemia and found many with achlorhydria and lowered serum vitamin B₁₂ levels, but without overt disease. During the period of progressive atrophy the secretions continue to diminish, though very slowly—volume, acid, pepsin, intrinsic factor—but they may not all diminish at the same rate; there is a little evidence which suggests that reduction in acid secretion may precede the others, and that, as first suggested by Faber,²⁰ in some cases loss of intrinsic factor may occur before there is any histologically recognizable abnormality in the body mucosa.⁴⁵

Hypovitaminosis B₁₂

We now know that vitamin B₁₂ is necessary for the continued well-being of many cells. Not only are erythroblasts and immature granulocytes affected by its absence, but also the oral epithelium and some neural cells, particularly those mediating protopathic sensation (sub-acute combined degeneration) and those in the central area of the retina, for tobacco amblyopia can be the presenting symptom of pernicious anaemia.^{25, 40} Some degree of mental deterioration is usual and psychoses are not rare.²²

We should therefore cease to regard pernicious anaemia as a disease entity,¹² and consider it as a symptomatic epiphenomenon of hypovitaminosis B₁₂ induced by a progressive gastric atrophy; the hypovitaminosis can be completely asymptomatic, or it may affect any or all of certain tissues, thus producing symptoms.

Tissue Affected	Symptom Complex
Oral epithelium	Glossitis, in early stage red and inflammatory later atrophic.

Tissue Affected	Symptom Complex
Retina	Tobacco amblyopia. Retrobulbar neuritis.
Afferent sensory nerves	Sub-acute combined degeneration of the spinal cord.
Cerebral hemispheres	Psychoses, almost any type; frequently depression (uncommon). Loss of sense of well-being, forgetfulness (common).
Bone-marrow	Megaloblastosis; ectopic haemopoiesis. Anaemia.

Symptoms are not necessarily produced as soon as vitamin B₁₂ stores are depleted or exhausted; a few patients with very low serum vitamin B₁₂ levels, but without anaemia or any other lesions attributable to hypovitaminosis B₁₂, have been encountered.^{38, 46} We do not know what other factors are needed to produce symptoms, but we do know that glossitis, sub-acute combined degeneration of the spinal cord,³⁴ degeneration of the retina,²⁵ and gross psychological disturbances,²² and combinations of these⁶ can develop in the complete absence of anaemia or of megaloblastic change.

The Genesis of Gastric Atrophy

This progressive gastric atrophy seems to be inborn and genetically controlled. The mode of inheritance is not yet certain, but it may be as a unit character-difference with fairly complete single-dose expression (Mendelian dominant) masked clinically by early death or by failure to develop the usual clinical consequence of malabsorption of vitamin B₁₂—that is, megaloblastic anaemia. The genetic factor is very much more common in North Europeans than in other ethnic groups, and in general, the further north you go and the less sun you see, the commoner is pernicious anaemia; in Great Britain the incidence varies between 0.6 in the south to 2.46 per 1,000 in the north,⁵⁶ and estimates of the causative atrophic gastritis range between 0.5% of all women, 1% of all normal adults, and 5% of all people over 40.⁶³ In Austria or Italy the disease is much less common; in Spain rare; in Central Africans so rare that only about five cases have been recorded¹⁴ and it is almost unknown among those of Mongolian race.

The mechanism of this progressive atrophy is completely unknown; it is interesting to note that in a case of 'juvenile' pernicious anaemia, though there was a complete absence of intrinsic factor, the body mucosa was histologically normal and normal secretion of acid and pepsin occurred,⁴⁵ so it is possible that some failure of production may occur at an early age. A few people, basing their views on the observation that the serum of patients with pernicious anaemia inhibits the

activity of intrinsic factor,⁵⁸ suggest that the lesion may be due to auto-antibodies, acting on the intrinsic factor itself or on the cells which secrete it.

The Relationship of Simple Achlorhydric Anaemia to Pernicious Anaemia

In the course of this progressive atrophy, iron deficiency often appears, especially when the patient is a woman who loses blood regularly and sometimes excessively; reduction in the secretion of acid and enzymes renders the absorption of iron less satisfactory. The clinical pattern of this iron deficiency is characteristic; the patient is in the fourth or fifth decade of life, and has usually grey hair, a smooth tongue sometimes sore, often cracks at the corners of the mouth, and complains of dyspepsia and lack of appetite. Occasionally there is true dysphagia with a pharyngeal web (Plummer-Vinson or Patterson-Kelly syndrome). Paraesthesiae are common.

This syndrome constitutes the *idiopathic hypochromic anaemia* of Faber^{18, 19} and Witts^{61, 62} in its most severe form. Davies^{14, 15} studied the gastric lesion in such cases, and was able to demonstrate all degrees of secretory failure, suggesting that many cases of idiopathic hypochromic anaemia will progress to pernicious anaemia if they live long enough—and most haematologists can find among their own patients some who illustrate this progress. There is little doubt that idiopathic hypochromic anaemia in its classical form is a stage in the development of hypovitaminosis B₁₂ in the anaemic form (i.e. pernicious anaemia), though it is an inconstant stage whose appearance probably depends on the time when achlorhydria develops, on the relation between disappearance of acid and intrinsic factor from the gastric secretion, and, above all, on the occurrence of excessive menstrual bleeding and on the time of the menopause; if gastric atrophy develops so slowly that the menopause is past before achlorhydria is complete, then one would expect to see pernicious anaemia without coincidental iron deficiency, just as one would if the iron deficiency had been adequately treated. For similar reasons one would expect the age of onset of pernicious anaemia to vary widely, and in fact, though occasional cases may appear before the age of 40, it becomes commoner with advancing age, especially in women, possibly because women live longer and so give the disease a better chance to manifest.¹³

Achlorhydria and Iron Absorption

Genuine achlorhydria, that is, achlorhydria which persists even when large doses of histamine, covered by an anti-histamine drug, are adminis-

FIG. 1.—Concentration of ferric and ferrous ions present in aqueous solutions of different pH. Abscissa—pH; ordinate—concentration of iron ions (expressed as moles per litre on the right and as grammes or milligrammes per litre on the left).

The dotted horizontal line is at a concentration of 100 mg. per litre: the bars above and below at 300 and 30 mg. per litre indicate the probable range encountered in practice.

Vertical line at pH 7, the neutral point.

Note.—Vertical scales are logarithmic.

tered, is so rare that it has been thought to occur only in patients with pernicious anaemia and in those who are fated to develop it.¹⁰ The association of severe hypochlorhydria with iron deficiency is probably due to two factors: first, lack of acid and pepsin delay the digestion of food iron, much of which is combined with protein as ferritin and haemosiderin; and second, most food iron is in the ferric state which is almost completely insoluble at pH 3 or more, a degree of acidity never exceeded in the achlorhydric stomach. Further, even powerful reducing substances find it difficult to reduce ferric iron, insoluble and complexed with protein, to the much more soluble ferrous iron (Fig. 1). Medicinal iron, especially if initially in the ferrous state and maintained thus with large doses of reducing agent, remains dissolved even at pH levels as alkaline as pH 8.

However, there are plenty of cases of iron deficiency without gastric atrophy, and even without hypochlorhydria. Nine patients out of ten with iron deficiency are anaemic because they have been bleeding, and these patients usually have a fairly normal gastric mucosa; even among elderly women iron deficiency without gastric atrophy is more common than is anaemia with gastric atrophy, and their stomatitis is as likely to be due to deficiency of riboflavin or other B vitamins as to vitamin B₁₂ deficiency. It must be remembered that the age of onset of simple achlorhydric anaemia (perhaps, more correctly,

sideropenic pre-megaloblastic hypovitaminosis-B₁₂—*Domine defende nos!*) is the same as that of simple iron deficiency due to menopausal disturbances of menstruation, and that the oral and gastro-intestinal symptoms accompanying it are probably manifestations of deficiency of gastric secretion and of vitamin B₁₂ thrown into prominence by the stress of iron deficiency.

The Effect of Iron Deficiency

The days are past when we could believe that the only significant effect of iron deficiency was to produce anaemia; the occurrence of koilonychia, cheilosis and digestive disturbances, and the subjective sensations of lassitude and tiredness, often with palpitations, all suggest that other mechanisms may be involved, the more so because even minor degrees of iron deficiency seem to cause complaints out of proportion to their severity. My first proof of this was when a mild attack of the bloody flux caused a male colleague to develop koilonychia without anaemia or evidence of iron deficiency among the red cells, and I was able to cure this by injecting only 240 mg. iron; soon afterwards Reimann⁵⁰ showed that chronic iron deficiency in infancy and childhood affected the rate of growth and the development of sexual characteristics; Waldenstrom,⁶⁰ Jasinski,³² and Henderson²⁹ have shown that *sideropenia* or *anaemia* (masked sideropenia) gives rise to a complex of symptoms differing only slightly from those of gross iron deficiency anaemia, and Hobbins has found that it is involved in the maintenance of weight after partial gastrectomy. Beutler and his colleagues³ have shown that sideropenia is accompanied by tissue enzyme deficiencies, and that some of the symptoms of iron deficiency are more likely due to tissue deficiencies of iron than to the anaemia.⁴

Conclusion

What, then, are the practical consequences of this alteration in our attitude to pernicious anaemia, to this widening of our horizon which shows us that anaemia is only one of many possible consequences of a progressive atrophic gastritis? First, we shall have to review many patients with neurological disorders or confusional states which might conceivably be ascribed to hypovitaminosis-B₁₂, and since anaemia may be absent, this investigation must involve either an augmented histamine test meal, determination of the absorption of radioactive vitamin B₁₂, a gastric biopsy, or a determination of the serum vitamin B₁₂ level. Of these, only the last is practicable on a large scale, and the proportion of positive is likely to be small, if Sewell's (private communication) preliminary results are any guide; how

ever, if the deficiency is missed the patient usually suffers greatly, so it seems that the estimation of serum vitamin B₁₂ will soon become an essential part of the investigation of the patient with the more obscure neurological disorders.

It could be argued that a therapeutic test would suffice, but this is hardly wise in the more chronic disorders in which improvement appears to be little more than an arrest of progress.

Treatment

The treatment of hypovitaminosis B₁₂ is fortunately simple and cheap; it consists in the regular injection of adequate quantities of the pure vitamin. Each individual dose should be fairly small, for much of a large dose is excreted in the urine; initially, half a dozen to a dozen injections each of 200 µg. spread over a fortnight or a month will not merely relieve the symptoms and most of the signs, but leave stores for several months deposited in the liver; thereafter 200 µg. every three or four weeks should suffice.

There is no justification for treating the ordinary patient with oral preparations. It is true that daily oral administration of 100 µg. or more of the pure vitamin will in most cases produce adequate response and even normal blood levels,^{11, 28} but there are many patients who respond less satisfactorily and inadequately treated patients may develop severe neurological disturbances. The much recommended compounds of vitamin B₁₂ with hog gastric mucosa or intrinsic factor (Bifacton, Cycloplex) should *never* be used, for many patients treated with them become refractory to these preparations and relapse even though taking large doses,^{5, 38, 54, 55, 57} and the vitamin B₁₂-peptide complex of Heathcote and Mooney has been found by some to produce sub-optimal levels of vitamin B₁₂ in the serum.⁵⁹

In any case, regular visits to the doctor for an injection give the patient a chance of consultations at regular intervals, and it is quite possible that these regular consultations give the patient a better chance of prolonged survival than those for whom such a consultation is an important event—for patients with pernicious anaemia are all middle-aged or elderly, and simple medical advice may be very useful.

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