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Mechanisms in Pernicious Anaemia

Since the discovery of the specific therapeutic effect of vitamin B_{12} pernicious anaemia has become one of the least pernicious of diseases. Anaemia itself may be minimal or absent, though the characteristic haematological changes will be observed—including macrocytosis, megaloblastic change, and multilobed neutrophils. Such patients may come with a complaint of sore tongue or with neurological and occasionally psychiatric disturbances. Thus the term pernicious anaemia may seem less appropriate than it was before the advent of liver and vitamin B_{12} treatment, but it remains in use because it still serves to designate a specific disease.

The clinical, haematological, and biochemical features of pernicious anaemia have been reviewed,[1] and more recently some of the outstanding problems have been discussed.[2] Little is known about the origin of the gastric atrophy which is the fundamental pathological lesion and eventually leads to failure of production of intrinsic factor, the substance required for the absorption of vitamin B_{12} from food. Furthermore the role of antibodies directed against gastric parietal cells and against intrinsic factor itself remains to be clarified.[3]

Though pernicious anaemia is largely a disease of middle-aged or elderly people, the greater incidence of the disease in related people than in the general population has long suggested that genetic factors are concerned. The relatives are also specially prone to achlorhydria, chronic gastritis, and a reduced ability to absorb an oral dose of radioactive vitamin B_{12}. In the general population the incidence of achlorhydria, chronic gastritis, and circulating antibodies to the gastric parietal cell rises steadily after middle age. These findings have led to the suggestion[3] that people who develop pernicious anaemia have a genetic liability to extensive gastritis, which culminates in complete gastric atrophy and secretory failure.

What of the autoimmune aspects? It has been postulated[4] that pernicious anaemia is the result of a genetically determined defect in immunological tolerance for antigens in the stomach. This defect is thought to give rise to lymphocytes and plasma cells capable of destroying gastric cells by direct cellular action (delayed hypersensitivity) and also capable of producing circulating antibodies against parietal cells and against intrinsic factor itself. But these roles of the antibodies remain speculative. While immune reactions may be the primary cause of the gastric atrophy, they could equally well be a consequence of injury to cells in the stomach from other causes, the altered mucosal cells being rendered antigenic.[3] In these circumstances the antibodies may perpetuate and intensify the local tissue damage without themselves initiating the changes.

The antibodies found in the serum are unlikely to be of pathological significance. Probably of greater importance are the antibodies produced locally in the stomach. Antibodies to intrinsic factor have been detected in gastric juice,[5 6] and it has been suggested that antibodies produced locally

in the stomach cause the final failure in the secretion of intrinsic factor.[7] The gastric atrophy is probably the result of excessive exfoliation[8] and is reversible, since treatment with corticosteroids can induce regeneration of mucosal cells with a return of secretory function.[9 10] The situation is perhaps analogous to that in autoimmune haemolytic anaemia.

Why does the absorption of vitamin B_{12} require the mediation of intrinsic factor? And how is vitamin B_{12} transported from the lumen of the gut into the cells of the terminal ileum and thence into the blood stream for distribution to the tissues? This apparently complex mechanism remains one of Nature's mysteries. The vitamin B_{12} released from food during digestion becomes bound to intrinsic factor (a glycoprotein secreted by the parietal cells of the stomach), and the intrinsic-factor-B_{12} complex is carried to the ileum by peristalsis. There it attaches to specific receptors on the brush border of the lining epithelial cells.[11] The complex is thought to fit into the ileal cell receptors by molecular complementarity as a key fits into a lock, but the exact nature of the receptor is unknown. The present evidence[11] suggests that vitamin B_{12} becomes detached from intrinsic factor when it passes into the ileal cell, but little is known about its pathway through the ileal cell and into the subepithelial capillaries of the portal system. In the blood vitamin B_{12} becomes bound to a specific carrier protein, transcobalamin II, an α-1 globulin.

How does vitamin B_{12} function in the body? Though cyanocobalamin and hydroxocobalamin are therapeutically effective forms of vitamin B_{12}, they do not function as such in the body. Like the vitamin B_{12} derived from food, they must be converted intracellularly into metabolically active forms that function as co-enzymes. Two co-enzyme forms are recognized—namely, methyl-B_{12} and 5′-adenosyl-B_{12}. And through its co-enzyme forms vitamin B_{12} has widespread biochemical ramifications.[12-15] In vitamin B_{12} deficiency methyl-malonic acid accumulates and is excreted in increased amounts. The measurement of urinary methyl-malonic acid after a valine load appears to be a good test for deficiency of this vitamin.[16]

The molecular biology of vitamin B_{12} is gradually revealing itself, though for man much is still unknown.[12] We are particularly ignorant about the way in which deficiency of vitamin B_{12} produces neurological lesions and how it affects the metabolism of nerve and brain tissue. Its role in haemopoietic cells, as well as in other proliferating cell systems, such as epithelium, is only beginning to be understood. We need to define more precisely the biochemical basis underlying megaloblastic haemopoiesis.

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Restless Legs

Patients who suffer from "restless legs" have been known to physicians for centuries, but the clinical syndrome was most clearly defined by K. A. Ekbom in 1944[1] and reviewed in greater detail in 1960.[2] Recognition is easy if the physician knows of its existence. Though it is not uncommon, its causation remains obscure. Ekbom[2] found that 5% of normal people suffered the symptoms to some degree. Though often stated to be commoner in women than men and in older than younger people, they are familiar to schoolboys and students and may affect both sexes and all age groups.

The essential feature of the condition is an intolerable creeping, internal itching, sensation, often defying description, occurring in the calves and lower legs, sometimes in the thighs, usually bilaterally, and developing towards the end of the day when the patient is either seated or—and particularly—in bed. So unpleasant is this sensation that the patient is compelled to keep moving his limbs, and this movement will bring relief. But many have to get out of bed and walk round or wave their legs on the edge of the bed, perhaps several times during the night, so that loss of sleep is a serious consequence to both the patient and his spouse. This disorder must not be confused with nocturnal myoclonus, when without previous discomfort a patient's limbs jerk violently just as he is dropping off to sleep.

Some patients cannot remain seated for any length of time. Others find that the symptoms are made particularly severe by long car, sea, or plane journeys, especially if motion sickness remedies such as the cyclazine group have been taken. It is the extreme unpleasantness of the symptoms, coupled with immobility and relief by movement, that characterizes the condition.

Theories of aetiology have been many and varied, ranging from disorders of the peripheral nerves, through vascular causes, to hysteria.[2] These patients are neurologically and electromyographically normal, and D. G. F. Harriman, D. Taverner, and A. L. Woolf found no abnormality after in-vivo staining of the intramuscular terminal nerve endings.[3] The association of symptoms with warmth, rest after exercise, or vibration and their relief by muscular movement suggest some vasomotor factor, and indeed some patients say they get relief from vasodilators, hot baths, or (paradoxically) cold sponging. Ekbom[2] recorded a greater than normal incidence after gastrectomy, and it is reported again at page 774 of the *B.M.J.* this week by Drs. N. K. Banerji and L. J. Hurwitz, who draw attention as well to an association with diabetes and uraemia. Also in this issue (page 796) Dr. J. D. Spillane records eight consecutive cases of patients who all suffered

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