Recognizing, treating and understanding pernicious anaemia

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In 1824, James Combe of Edinburgh reported a case of severe pallor in a man who also had diarrhoea, thirst, and passed a great deal of urine.[1] Although Combe is sometimes credited with having been the first to describe what became called pernicious anaemia, it was not until Thomas Addison provided a clinico-pathological description that this anaemia began to be recognized as a distinct entity,[2] which the French physician Trousseau dubbed 'Addisonian anaemia'.

Addison described a condition with an insidious clinical course and a curious type of dingy pigmentation found at postmortem examination. This was not the classical lemon colour of the skin that is now recognized clinically, but a darker, sometimes mottled discolouration that pervaded most tissues, including the gums. It is difficult to recognize pernicious anaemia as we know it today from this description, and although the paper was entitled 'Anaemia: disease of the supra-renal capsules', it did not actually contain a description of the patient's blood, and reported minimal involvement of the suprarenal glands. The earliest description of the disease in mainland Europe was by Michael Anton Biermer, a German physician who also noted the condition's insidious course and, because it was untreatable at the time, first referred to it as 'pernicious' anaemia.[3]

Until the liver was recognized to be important in haematopoiesis, the treatment of pernicious anaemia was unsuccessful and arbitrary. Sir William Osler's textbook suggested that some patients had benefited from diet and others from sunlight, but he even suggested trying Fowler's Solution – an arsenical preparation developed by Sir James Kingston Fowler, a fashionable physician of the Middlesex Hospital – which may well have dispatched patients more quickly than their disease.

Research into blood substitutes and ways of improving haematopoiesis was stimulated by the massive loss of life from blood loss during the First World War, when transfusion services had proved inadequate. This may have stimulated George Whipple, who had an established interest in liver diseases, to investigate the liver's role in haematopoiesis. While director of the Hooper Foundation for Medical Research at the University of California, he conducted a series of experiments to assess the effects of various treatments for acute anaemia in exsanguinated dogs.[4] After moving to the University of Rochester School of Medicine and Dentistry in New York State, Whipple began assessing the effects of treatments for anaemia caused by chronic blood loss. Whipple, Hooper and Robscheit studied the effects on haemoglobin and blood regeneration of a variety of treatments – iron pills, bread and other foods, and even arsenic and germanium dioxide[5] – among which only raw liver showed real promise.[6]

Serendipity is said to have played a role in this discovery (Theo Chalmers, personal communication). Whipple had noted that blood regeneration was poor in dogs fed cooked liver following chronic blood loss. Had it not been that a lazy laboratory technician had given the dogs raw liver, the much more dramatic response might not have been discovered at that point in history.

Two Boston physicians, George Minot and William Murphy, who learned of Whipple's discovery while visiting him, decided to try raw liver as a treatment for pernicious anaemia. At a meeting of the Association of American Physicians in Boston on 4 May 1926, Minot and Murphy described their results in 45 patients who had been given a high-protein diet for between six weeks and two years. Their daily diet contained 120–240 grams of liver and 120 grams of muscle meat. This caused rapid symptomatic improvement and a coincident elevation of the red cell count. At the same meeting William Murphy, Reginald Fitz and Robert Monroe reported the haematological changes in detail. These showed that, within a period of four to ten days of starting the diet, the formation of new young red cells (the reticulocyte count) had increased from 1% to an average of 8%, jaundice had lessened (because

fewer red cells were being destroyed), and haemoglobin concentration and the red cell count had increased.

Minot and Murphy published their results in detail in the *Journal of the American Medical Association* in 1926.[7] They reviewed the previous literature critically and described previous attempts to treat the disorder by diet and other means, referring, in particular, to the above work of Whipple, Hooper and Robscheit-Robbins, and reported the clinical improvement they had observed in many cases. They also presented detailed records of the improved red blood cell counts, which had usually occurred within a month of starting therapy.

In spite of these dramatic results, they adopted a modest and cautious approach to their discovery:

> *'It is possible that this series of cases eventually may be proved to be unusual in that there happen to be treated a group that would have taken a turn for the better under other circumstances. Also, time may show that the special diet used, or liver and similar food, is no more advantageous in the treatment of pernicious anaemia than any other nutritional diet. Let this be as it may, that at the present time it seems to us… that it is wise to urge pernicious anaemia patients to take a diet of the sort described.'*[7]

Fruit and iron had also been part of the diet, and it appears that, at this stage, Minot and Murphy were not entirely sure that the liver was a crucially important factor.

The discovery was soon confirmed by many physicians throughout the world, however, and Minot, Murphy and Whipple were awarded a joint Nobel Prize in 1934, becoming the first American recipients of the Nobel Prize for physiology and medicine. In his Nobel Prize Lecture, Minot properly emphasized that '…to determine the effect [of liver feeding] it was considered essential that data should be obtained in a large number of cases to be appropriately compared with controls.'[8]

As it happens, Minot – a diabetic – would not have survived to do his research and receive recognition for it had the Canadians Banting and Best not discovered insulin a few years earlier.[9] Indeed, had it not been for the fact that a laboratory attendant fell behind in cleaning up after a polyuric depancreatized dog, Oscar Minkowski would not have found the floor wet with urine, checked for glycosuria, and discovered the critical connection between pancreatectomy and diabetes – diabetes at that point not being the subject of his experiment on the dog. Again, serendipity, without which Banting and Best might not have been in time.[10]

Because a diet of raw liver is not easy to take, extracts of liver were developed for intramuscular injection, and this became part of the standard management of pernicious anaemia until the 1950s. It was not until 1948 that the anti-pernicious anaemia factor was isolated from liver and kidney by Smith[11] and by Rickes *et al.*,[12] who named the factor vitamin B_{12}. They showed that the administration of a few micrograms could prevent relapse in the disease. Dorothy Hodgkin and her co-workers went on to use X ray crystallography to elucidate the structure of Vitamin B12 (now called cobalamin); work for which she, too, was awarded a Nobel Prize.[13]

Understanding of the pathogenesis of pernicious anaemia increased over subsequent decades. It had long been known that the disease was associated with defects in the gastrointestinal tract: patients suffered from chronic gastritis and lack of acid secretion (achlorhydria). Indeed, dilute hydrochloric acid was at one time used in the management of pernicious anaemia. It is now known that transport of physiological amounts of vitamin B_{12} depends on the combined actions of gastric, ileal and pancreatic components. The gastric moiety was discovered and named 'intrinsic factor' by William Castle in 1930.[14] Castle had demonstrated the presence of intrinsic factor after managing to persuade some patients to eat predigested meat or liver aspirated from the stomachs of normal subjects' This work helped to show that normal stomachs secreted a substance that promoted effective absorption, which was absent from the stomachs of patients with pernicious anaemia. A further important advance was made in the early 1960s by Doniach with the recognition that pernicious anaemia is an autoimmune disease.[15]

The development of effective treatment for pernicious anaemia illustrates the complementary roles of clinical and postmortem observations, physiological and clinical research – and serendipity.

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