

Pernicious Anemia

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MILESTONES

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George H Whipple

In 1855, Thomas Addison at Guy's Hospital described a lethal, idiopathic anemia that in 1872 was given the name pernicious anemia by Biemer. For decades following, a commonly held view was that pernicious anemia reflected the positive-acting, deleterious influence of an infectious agent or a microbial product. A popular concept was that the injurious agent caused excessive destruction of red blood cells.

Clinical and autopsy studies subsequently established that pernicious anemia was more than a disorder of red blood cells. Besides reduced numbers of blood erythrocytes and low concentrations of hemoglobin, patients were found to have excessive iron deposits in the liver, gastric glandular atrophy and achlorhydria, megaloblastic bone marrow hyperplasia, and profound demyelination and atrophy of sensory axons in the spinal cord. Under the microscope some cells of the body that normally turn over rapidly were found to be increased in size. Large erythrocytic precursors in the bone marrow were recognized early, but with time it became clear that the blood of patients with pernicious anemia contained giant granulocytes and platelets, and that large epithelial cells were present in their gastric and vaginal washings.

Beginning in the early 1900's anecdotal reports suggested to a few investigators that pernicious anemia might be a nutritional deficiency disease. In the 1920's two milestone discoveries were published, one by the pathologist George Whipple and colleagues at the University of Rochester¹, the other by two clinical investigators, George Minot and William Murphy, at Harvard Medical School². Whipple showed that anemia could be the result of a nutritional deficiency. Minot and Murphy developed a special diet that could reverse the pathology of pernicious anemia and cure patients. This was a tremendous breakthrough because 1-2% of adults over age 50, primarily people of northern European ancestry, suffered

from this fatal disease. In 1934, Minot, Murphy and Whipple shared the Nobel Prize in Physiology and Medicine for their discoveries. Their Nobel lectures – available on the Nobel website (www.nobelprize.org) – provide interesting historical information and data about their experiments. These milestone discoveries launched decades of investigations, notably by W.B. Castle³, that uncovered the complex pathophysiological mechanisms underlying pernicious anemia. Castle's discoveries led to new treatments of the disease that were more effective, better tolerated by patients, and more affordable.

The importance of Whipple's work was that it firmly established on a quantitative basis that the properties of food influenced blood formation, a concept not previously accepted. Whipple was originally interested in the metabolism of biliary and blood pigments and had developed a model of chronic anemia in dogs by repeated phlebotomy. When he began to investigate factors that influenced blood regeneration in chronically anemic dogs, Whipple focused on diet. Of the various diets tested, he found that liver and liver extracts were the most effective, although feeding other meats – kidney, muscle, or brain – also stimulated hematopoiesis. The choice of liver was fortunate. As others later pointed out, had Whipple fed iron salts to the dogs, he likely would have observed the same result since the dogs he studied undoubtedly suffered from iron deficiency anemia. Whipple's findings on the effectiveness of liver feeding influenced Minot and Murphy to continue similar clinical studies they had been conducting in patients with pernicious anemia. A key element in the success of those studies was the reliance on blood reticulocyte counts to assess bone marrow responsiveness.

Once it was established that daily feedings of large amounts of liver or concentrated liver extracts induced varying degrees of remission in pernicious anemia, the central question became, "What is the active factor?" Castle³ discovered that daily administration by gastric tube of liquefied stomach contents from a healthy person removed an hour after ingestion

of 300 grams of lean beef stimulated hematopoiesis in patients with pernicious anemia. Administration of gastric juice recovered from histamine-stimulated normal donors was ineffective. Administration of beef digested with pepsin was ineffective. Apparently, there was requirement for interaction between a factor in normal gastric juice and a factor in digested beef. The activity present in beef was designated as extrinsic factor; the activity present in normal gastric juice was designated as intrinsic factor. In retrospect, some of the dietary regimens in the clinical studies that led to the cure of pernicious anemia would probably raise eyebrows in today's Human Subject Committees.

Subsequent chemical analyses showed that extrinsic factor belonged to the cobalamin family of organometallic compounds. When it was shown that the active cobalamin was vitamin B12, therapy with vitamin B12 became standard treatment for pernicious anemia. Intramuscular treatment with vitamin B12 cured patients. To be effective by oral administration, vitamin B12 required the presence of normal gastric juice or massive doses of the vitamin. Later studies showed that intrinsic factor was a vitamin B12-binding protein produced by gastric gland parietal cells. Biochemical studies showed that vitamin B12 played a role in DNA synthesis, hinting at a mechanism that could account for the underproduction of red blood cell precursors in the bone marrow of patients with pernicious anemia.

Although curative treatment for pernicious anemia had been obtained, basic research in the area actually increased and publications continue through today. Uptake of vitamin B12 was shown to take place in the ileum via a specific mucosal receptor for the vitamin B12-intrinsic factor complex. New laboratory tests were developed to screen for pernicious anemia to distinguish it from other megaloblastic anemias. A great deal of effort was directed at understanding the basis for gastric gland atrophy and the loss of the intrinsic factor-producing parietal cells. The discovery of antibodies specific for parietal cells, intrinsic factor and other elements in the vitamin B12-uptake cascade have fostered the concept of pernicious anemia as an autoimmune disorder. Coming full circuit from the notion of a microbial etiology that was in vogue at the start of the 20th century and then discarded, it is now firmly established that *Helicobacter pylori* is a gastric pathogen that produces factors that are toxic for parietal cells.

Pernicious anemia is another example of a disease where an effective treatment came before an understanding of the underlying pathogenic mechanisms. It is another example where a disease, an experiment of nature, provided a powerful tool for biomedical discovery. Once the pathogenic mechanisms of pernicious anemia were understood, they provided critical insights into normal physiological processes, as well as the basis of other diseases. Minot, Murphy and Whipple worked without the highly specific, sensitive and sophisticated tools that are routine in today's biomedical research, yet they succeeded in making seminal discoveries, curing an incredibly complex disease, and launching the field of nutritional deficiency anemias.

References

1. Whipple GH, Hooper CW, Robscheit FS: *Am J Physiol* 1920, 53:236
2. Minot GR and Murphy WP: *JAMA* 1926, 87:470
3. Castle WB: *Am J Med Sci* 1929, 178:748