PERNICIOUS ANEMIA FROM ADDISON TO FOLIC ACID*

By Russell L. Haden, M.D.

A constantly fatal disease unexplained at autopsy is always intriguing. The mysterious nature of pernicious anemia thus interested Thomas Addison1 when he described the first group of patients in 1849. He said this is a "remarkable form of anemia which has not attracted the attention it really deserves." The anemia was profound and of unknown origin. The patient became progressively weaker with little wasting and finally died without response to any treatment. A postmortem examination did not aid in explaining the problem. No real progress was made in solving the puzzle until the discovery of the beneficial effect of liver feeding in 1926 by Minot and Murphy2 completely altered the outlook of the patient. Further research is slowly unraveling the mystery. Clinicians still think, however, of pernicious anemia as a "remarkable form of anemia."

It is my purpose to discuss historical highlights of this interesting disease from the time of Addison to the discovery of folic acid, and to emphasize some important clinical aspects.

Idiopathic pernicious anemia is a disease of nutrition characterized by macrocytic anemia, histamine-refractory achlorhydria, combined sclerosis of the spinal cord, and a specific response to liver and liver substitutes. The anemia alone may be completely relieved by a single chemical compound, pteroylglutamic acid (folic acid). The clinical picture is variable; the anemia may be minimal; only about three-fourths of the patients have signs of a cord lesion initially; a loss of vibratory sense is usually the earliest and often the only evidence of neurologic involvement; achlorhydria is a constant finding.

It is a disease of older people. In 427 patients studied at the Cleveland Clinic only 5 were less than 30 years of age. In a total number of 579 I have seen, the anemia began in only 1 individual less than 20 years of age. Fifty-two per cent of the patients were between 40 and 60. A very large proportion were over 60 when the diagnosis was made.

Numerous clinicians, beginning with Combe in 1811,3 reported fatal unexplained cases of anemia which we now recognize as pernicious anemia. Thomas Addison, however, first in 1849 and again in 18554 described it as a clinical entity.

Why was the disease so-called? Addison in his original description speaks of it as "a remarkable form of anemia.... Its approach is first indicated by a certain amount of languor and restlessness to which presently succeed a manifest paleness of the countenance.... The symptoms go on increasing.... the patient experiences a distressing and increasing sense of helplessness and faintness.... he dies either from sheer exhaustion or death is preceded by signs of passive effusion or cerebral oppression." All patients in this group were not suffering from true pernicious anemia since 2 recovered and in 3, disease of the adrenal was found at autopsy. Addison said in 1855 that he was trying to throw additional light on this

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* Peter T. Bohan lecture given at the University of Kansas Medical School, March, 1947.
condition when he discovered the disease of the adrenal glands known as Addison's disease. He again emphasized that there was no "discoverable cause whatever."

Addison recognized the anemia only by the pallor of the skin and the thinness of the blood. In 1849, no blood cell counts or hemoglobin estimations had been done. Vierordt did the first red cell count in 1851; Funke discovered hemoglobin the same year; and Welcher published the first extensive clinical article reporting blood counts and hemoglobin estimations in numerous diseases in 1854. Thus, accurate measurements of the blood came after Addison's original communication.

Addison's observations made little impression even in England, and little more was heard of this "remarkable anemia" until it was reported independently by Biermer in Switzerland in 1871. At a meeting of the Medical Society in Zurich, November 6, 1871, Biermer under the title of Progressive Pernicious Anemia described 15 cases of severe anemia. He used the name only in a symptomatic sense, grouping together anemias of widely different etiology. He had previously mentioned similar cases in which he emphasized fatty degeneration of the heart and vessels. Biermer stressed the role of pregnancy. So some cases he described were evidently what we know now as the anemia of pregnancy. His group has been described as a "provisional shelter for a multitude of cases." He did not think of pernicious anemia as a single disease. He again emphasized the finding at autopsy of fatty degeneration of the heart muscle and small vessels.

Biermer's report was published in 1872 in the proceedings of the Medical Society in Zurich. For some unknown reason it quickly excited the interest of clinicians everywhere. Articles on progressive pernicious anemia began to appear rapidly. In England, Addison's original description was not recalled until stimulated by Biermer's work. In 1875, William Pepper in Philadelphia wrote an extensive article of 26 pages on the disease in the American Journal of Medical Sciences. Pepper says, "My present purpose is to offer a contribution to this important study by calling attention to a peculiar form of anemia of obscure and fatal character which has recently been redescribed (i.e. by Biermer) as though it were a new affection under the name of Progressive Pernicious Anemia." He then emphasizes that Addison had previously described the disease as "idiopathic anemia." Pepper's main contribution is his discovery of the extreme hyperplasia of the marrow. He considered pernicious anemia as a primary disease of the bone marrow.

Many papers on the subject were published between 1875 and 1878. In 1878, Eichhorst's extensive monograph of 375 pages entitled "Progressive Pernicious Anemia" appeared. All cases previously reported were reviewed. Eichhorst mentioned Addison's work but gave him little credit. "Addison," he said, "considered the anemia due to fatty degeneration of the internal organs while we now know that the anemia is primary and the fatty degeneration is secondary." Eichhorst described as pernicious anemia cases of anemia which we now exclude. The term designated only a group of fatal anemias and included such conditions as true aplastic anemia, leukemia, and other bone marrow diseases as well as severe anemias due to infection and toxemia. Eichhorst did not have our present concept of pernicious anemia as a single specific entity. The name he used, however, has persisted. Interest stimulated by these early papers has never abated.
Pernicious anemia is defined as a macrocytic anemia—the red cells are characteristically large. Eichhorst mentions macrocytosis but reports no measurements or even counts in his own cases. He does say the number of red cells was about one-tenth or one-twenty-fifth of normal. The first blood count in a patient with pernicious anemia seems to have been done by Sørensen in 1874 when he counted the blood with Malassez’s apparatus and found only 470,000 red cells. Sørensen also emphasized the large size of the cells. The diameter of red cells had been measured from the time of Leeuwenhoek. A monograph on the dimensions of red blood corpuscles by Mänassein had appeared in 1871. Eichhorst concluded that the diameter of the cells is almost always increased. Laache in his book on the anemias published in 1883 has a long discussion of pernicious anemia and emphasizes the large size of the red cells and the increased color index. The decrease in number of red cells, the increase in size, and the increase in hemoglobin content were thus established very early as characteristic findings.

Earlier workers used the red cell diameter as a measure of size. With the development of the hematocrit the cell volume was found increased also and a more sensitive indicator of macrocytosis. Capps, in his work on volume index, found this always increased in pernicious anemia. In our series of 579 patients all showed a macrocytosis if untreated except in the rare instance with a coincident iron deficiency. Other clinical conditions will also produce a macrocytosis but seldom so marked as in a pernicious anemia. Examples are liver disease, intestinal obstruction and nutritional deficiency such as sprue. Ehrlich considered the presence of megaloblasts in the peripheral blood as diagnostic of pernicious anemia. He insisted that these were pathologic nucleated red cells and not simply very young cells. Although Ehrlich and others believed that the diagnosis of pernicious anemia should not be made without the finding of megaloblasts in the blood, this view is no longer held. A diagnosis should never be made of untreated idiopathic pernicious anemia in the absence of a macrocytosis of the red cells.

The presence of an achlorhydria refractory to histamine stimulation is an essential finding. All clinicians now accept the fact that idiopathic pernicious anemia should never be diagnosed if free hydrochloric acid be present on gastric analysis.* The achlorhydria has been a most important factor in the final solution of the origin of the disease. Addison and Biermer knew nothing about achlorhydria.

How did it become recognized that this was a necessary part of the symptom complex? Test meals were not done until relatively late in clinical medicine. Cahn and von Mering first studied the acid in healthy and diseased stomachs in 1886. During the next ten years many articles on the subject appeared in England, on the continent, and in this country. It was soon noted by numerous investigators that when no free hydrochloric acid was found the patients were frequently anemic, and that the anemia belonged in the group already designated as pernicious. As late as 1900, however, Faber and Bloch could collect only 33 cases of pernicious anemia on whom a test meal had been done. Martius and von Lubarsch, in the first monograph on achylia gastrica in 1897, reported both pernicious anemia and

* Wilkinson and Israël, Waldenström and others report that achlorhydria occurs in approximately 1 case of 100. Eds.
secondary anemia associated with achlorhydria. Achlorhydria was not then considered as a necessary part of the clinical picture. The first large group of patients with pernicious anemia on whom test meals had been done were reported by Levine and Ladd in 1921. In 107 patients only 3 were found to have free acid. In 2 of these 3 patients the diagnosis was questioned. In the light of present day knowledge all would be questioned. One, for instance, had had several operations and a persistent diarrhea following an intestinal resection. This patient probably had a symptomless obstruction of the small bowel with a macrocytic anemia. Recently Goldhamer in a report on the gastric acidity during remission in pernicious anemia, mentions 1000 patients at the Simpson Memorial Institute as having had a test meal without finding free hydrochloric acid in a single one. In our series of 579 patients a test meal was done in 546. Free acid was found but once. This patient had a typical clinical and blood picture of pernicious anemia with subacute combined sclerosis. A technical error was not excluded. The test meal was not repeated because the patient died soon after the original examination. No special studies were done to exclude other causes for a macrocytic anemia. Recently we have studied 2 patients with a macrocytic anemia and a normal gastric analysis. Both were found to have a benign chronic intestinal obstruction. These 2 patients also had signs of a subacute combined sclerosis.

A possible relation of the stomach to pernicious anemia through impaired nutrition was recognized long before test meals were done. Immerman in 1877 described pernicious anemia as a disease of nutrition due to faulty absorption of food. Austin Flint in 1860 said, "Nor is it difficult to see how fatal anemia must follow an amount of degenerative disease reducing the amount of gastric juice so that the assimilation of food is rendered wholly inadequate to the wants of the body." The English physician, Samuel Fenwick, especially emphasized this point of view. His book, "Atrophy of the Stomach," was published in 1880. Here he recognized severe anemia as occurring with atrophy of the stomach. In Chapter 3 on "The Relation of Gastric Atrophy to Other Forms of Idiopathic Anemia" he remarked that the cases of atrophy of the stomach with anemia reported by him were identical with those described by Addison as idiopathic or pernicious anemia. He quoted Addison's description to emphasize the similarity. Fenwick thought, however, that the anemia was produced by interference with nutrition. He pointed out that the digestive powers of the stomach were so impaired that the usual postmortem digestion solution of the gastric mucosa did not even take place unless acid were added, and the gastric contents would not digest egg albumin. These observations of Fenwick are most important in the light of present knowledge of the relation of the stomach to pernicious anemia. This atrophic condition of the gastric mucosa in pernicious anemia can now be verified in life by gastroscopy.

William Hunter long emphasized the relation of the digestive tract to pernicious anemia. He considered the gastric atrophy as resulting from a gastritis due to swallowing bacteria, and the characteristic glossitis to be produced by a specific micro-organism. He believed that a toxin of bacterial origin in the intestinal tract was absorbed into the portal blood and destroyed red cells.

The earlier students of pernicious anemia did not recognize central nervous
system involvement. In 1887, Lichtheim described 3 patients with severe anemia and involvement of the central nervous system. Lichtenstein in 1884 had previously described cases of pernicious anemia with findings suggesting tabes dorsalis. We now think these patients had pernicious anemia with subacute combined sclerosis. In 1892, Minnich described 2 patients with pernicious anemia who had serious cord involvement and studied the cord at autopsy. He found changes especially in the posterior columns of the spinal cord. In this country Dana in 1891, in a discussion of degenerative diseases of the spinal cord, described a case with extreme anemia and diarrhea which was evidently pernicious anemia with cord involvement. In the same year Putnam described 8 patients with combined sclerosis which we recognize as having pernicious anemia from the characteristic anemia and other symptoms. It is interesting that few of the early observers did blood counts on their patients, so the anemia was evidently quite extreme to be recognized only by pallor or weakness. These observers continually emphasized that the nerve involvement is due to poor nutrition resulting from the anemia. After 1890, following such early reports numerous articles appeared describing cord lesions. In 1902, McCrae reported 50 patients with pernicious anemia from the Johns Hopkins Hospital and found neurologic manifestations in 20 of these. In 1900, Frank Billings took as his subject for the Shattuck Lecture in Boston, "The Changes in the Spinal Cord and Medulla in Pernicious Anemia." He emphasized the now well established relation of diffuse cord degeneration and pernicious anemia. He thought the anemia and cord changes resulted from a simple toxin which was probably of intestinal origin. His article is illustrated with many sections of spinal cord obtained at autopsy.

Russell, Batten, and Collier in 1900 in discussing subacute combined degeneration of spinal cord described this condition as occurring in patients with severe anemia which was evidently pernicious anemia. They thought there was no etiologic relation of the anemia to cord changes. In the earlier articles there is necessarily much confusion since the criteria for the diagnosis were not clear. Many diagnoses were missed and often cases of severe anemia due to other causes were called pernicious anemia.

The central nervous system is affected in 80–85 per cent of cases of true pernicious anemia. The most common evidence of cord involvement is a diminution of vibratory sense. The cord lesion may be the only significant manifestation of the disease; it may be more serious than the anemia. There is no parallel between the degree of anemia and involvement of central nervous system. Subacute combined sclerosis may arise from other causes. The cord lesions usually respond, at least partially, to liver therapy. Sometimes the damage to the central nervous system is beyond repair, so neurologic symptoms and signs may persist when the anemia is entirely relieved.

The proof of the relation of the stomach to the origin of pernicious anemia is a most important discovery. It is easy to see how the stomach was early incriminated since the anemia had been conceived of as a wasting disease due to impaired nutrition. This was well expressed by Austin Flint in 1860, as already quoted. Immerman's classification of pernicious anemia as a disease of nutrition, and Fenwick's
work, begun in 1871, on gastric atrophy as a cause of anemia, have already been mentioned. Henry and Osler\textsuperscript{35} in 1886 described a case of pernicious anemia as due to gastric atrophy. Numerous other clinicians made similar reports. Pepper,\textsuperscript{31} in his very complete article, however, lays no emphasis on changes in the stomach. Then, as gastric analyses were more widely employed, came the discovery that patients with pernicious anemia had an achlorhydria, and finally the conclusion of all clinicians that achlorhydria is invariably in the idiopathic form of the disease. Achlorhydria usually, if not always, precedes the development of the anemia by many years, and persists even in complete remissions. Free hydrochloric acid is not only absent in idiopathic pernicious anemia but the amount of gastric secretion is greatly decreased. Askey\textsuperscript{36} has recently reviewed 47 cases of pernicious anemia reported as showing free hydrochloric acid on gastric analysis. He emphasized that none can be considered true Addisonian pernicious anemia by present day criteria.

What is the relation of achlorhydria to the causation of pernicious anemia? We are indebted to Castle\textsuperscript{37,38} for the proof that achylia gastrica is a necessary link in the development of the nutritional deficiency producing the disease. He showed that a patient fails to secrete in the stomach some unknown substance, probably a ferment, which acts on the food to produce a substance or substances necessary for the maturation of the red cells in the bone marrow and for the normal metabolism of nervous tissue. The proof is simple. Ground beef partially digested in the stomach of a normal man with normal gastric secretion when fed to a patient with active pernicious anemia initiates a remission, and causes active blood formation as shown by a rise in reticulocytes and increase in red cells and hemoglobin. Similar preparations exposed to digestion in the stomach of a person with pernicious anemia cause no reticulocytosis or erythrocytosis in other patients suffering from pernicious anemia to whom the material is fed. Such observations proved that a substance supplied by gastric mucosa is a necessary link in the protection against pernicious anemia. It was also shown that the achlorhydria by itself is not a factor but the ferment is never absent if free hydrochloric acid is present. On the other hand the specific ferment may be present if free hydrochloric acid be absent. Castle's work furnished the final proof that pernicious anemia is a deficiency dependent primarily on a gastric defect. Many workers, such as Austin Flint, were right in considering the absence of normal gastric digestion as a cause of anemia though they never thought of such specific action as that demonstrated by Castle. Pernicious anemia may follow total gastrectomy. Meulengracht\textsuperscript{39} thinks Brunner's glands in the duodenum supply the specific ferment also. If true, this explains normal blood formation after some cases of gastrectomy.

Castle's work disproved other theories of pernicious anemia. Gastrointestinal toxemia, infection, and other possible causes are no longer mentioned. The disease becomes a negative one due to the lack of something; and not a hemolytic one, due to the action of some positive toxic agent.\textsuperscript{*}

The discovery of a specific treatment for pernicious anemia is the most dramatic episode in the long history of this serious disease. Many different methods of

\textsuperscript{*} However, a hemolytic component, causation obscure, is usually present. \textit{Eds.}
treatment had been used prior to 1926—iron, hydrochloric acid, arsenic, transfusion, splenectomy, removal of infection, special diets, and drainage of the intestinal tract. At times any method of treatment seemed to produce a remission. Sometimes the effect of transfusion was lifesaving by initiating a remission. No treatment, however, could be depended on to stay permanently the course of the anemia. It was almost always progressive, and usually ended in death from anemia unless some intercurrent fatal disease developed.

In 1920, Whipple and his associates had begun a systematic study of the effect of different methods of treatment, especially food and drugs, on experimental hemorrhagic anemia in the dog. They found that the most valuable agent in ameliorating the anemia was whole liver. Other foods, such as red meat, had a similar effect to a varying degree but the effect was not so striking as with liver. While Whipple was working with hemorrhagic anemia he emphasized in 1925 that "even in complex anemia such as pernicious anemia, anemia with nephritis, and cancer cachexia food factors deserve serious consideration in the clinical management of the blood conditions." Whipple did not apply his discoveries to clinical medicine, however. It remained for Minot and Murphy to find in a routine trial of liver in various types of anemias, that the response in pernicious anemia was strikingly different from that in other types of anemia. They were helped by the knowledge that the level of reticulocytes is an ideal method of gaging response to treatment. Minot and Murphy's discovery was first announced in 1926 and was rapidly verified by clinicians everywhere.

Liver and liver extracts affect the stroma of erythrocytes only. This verified Whipple's idea expressed in 1922 that there is a scarcity of stroma-building material in pernicious anemia. With adequate liver therapy the blood of a patient about to die rapidly responds and returns completely to normal. The glossitis and other gastrointestinal symptoms disappear entirely. The neurologic symptoms become improved or do not progress; at times they disappear entirely. There is nothing more dramatic in medicine than the effect of liver therapy on a patient with pernicious anemia. Only the use of sulfa drugs and other antibiotics such as penicillin afford such brilliant results.

It was soon found that a liver extract acted just as well as whole liver. Extracts have been improved until now these are almost perfect in their action. A monthly injection of a potent extract will keep the blood normal and prevent the development of a neurologic lesion. An extract of normal gastric mucosa has a similar action as one would expect from Castle's discovery.

Many attempts have been made to isolate from liver and liver extract a single specific substance responsible for the beneficial effect. While highly concentrated preparations have been made no single substance has been isolated. In the meantime, a single chemical substance has been found which gives a specific blood response in pernicious anemia and related macrocytic anemias. Folic acid, a substance found in liver, yeast, spinach, and grasses, has proved to be necessary for the growth of certain bacteria and to relieve the anemia developing in certain vitamin deficient diets. This substance was found to be effective in macrocytic anemias due to a deficiency such as sprue, and other related conditions.
Folic acid is a single chemical compound (pteroylglutamic acid) which causes a specific response also in pernicious anemia. It matures the megaloblasts of the bone marrow so that the blood returns to normal. It probably has little effect on the cord lesion. The latest reports indicate a cord lesion may even develop while the anemia is disappearing and the blood count is normal.

With folic acid the reticulocyte response is not so pronounced as with a potent liver extract but the full effect is excellent and the blood will return to normal. No secondary reticulocytosis occurs in a patient treated with folic acid when liver extract is added. The question is still unsettled whether liver extract and folic acid give a better result than liver extract alone. Folic acid alone should never be used in the treatment of pernicious anemia since it is not the antineuritic factor. It fails to prevent the development or progression of neurologic symptoms indicative of subacute combined sclerosis.

The anemia of pernicious anemia is due to the lack of a specific red cell maturing factor necessary for the normal development of the erythrocyte. This may well be folic acid since the response of the anemia with adequate amounts of folic acid is complete. The relation of liver extract to folic acid is now being investigated. Liver extract contains small amounts of folic acid but not enough to explain its antianemic action. Liver extract has a widespread effect on the individual needing it, possibly through its action on cellular metabolism, as shown by the feeling of well-being exhibited by a person with pernicious anemia after the treatment for a few days with liver extract. The rapid clinical improvement is not due to a relief of the anemia. It has been suggested that liver extract restores normal pteroylglutamic acid metabolism possibly by freeing it from its conjugate form in which it normally occurs in foodstuffs. According to this concept folic acid is related to the blood lesion only. Further research may well show that other specific substances necessary for normal metabolism of nerve tissue are activated by liver extract. Liver extract thus acts as an activator of cellular metabolism rather than as furnishing specific substances preventing or relieving pernicious anemia. This work suggests that a complex type of cellular enzyme disturbance exists in pernicious anemia. The action of liver principle in restoring normal pteroylglutamic metabolism probably constitutes only one of its therapeutic effects.

**Summary**

I have tried to review and clarify steps leading to our present knowledge of pernicious anemia as a clinical and etiologic entity. The early history is most illuminating. The development of the present concept of this complicated disease is a triumph of medical research. Many great names both in clinical and research fields are associated with the advance in knowledge of pernicious anemia. Further research will almost certainly clarify problems still unsolved.

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PERNICIOUS ANEMIA FROM ADDISON TO FOLIC ACID


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