

## THE TREATMENT OF PERNICIOUS ANEMIA

RUSSELL L. HADEN, M.D.

Pernicious anemia is a true deficiency disease for which specific replacement therapy is available. In idiopathic pernicious anemia the deficiency once present continues throughout the life of the patient. The disease is never "cured." The deficiency responsible for the symptoms is satisfied, however, by complete and continued treatment. A symptomatic deficiency in the specific factor may occur temporarily, as in pregnancy where the need is for a time greater than the supply, or when absorption is interfered with as in sprue or other abnormality of the small intestine. Here the deficiency disappears with the relief of the underlying causative disease, although specific therapy is usually helpful.

The seriousness of idiopathic pernicious anemia is best emphasized by the fact that it was always fatal before the introduction of liver treatment by Minot and Murphy in 1926 and is still fatal without specific therapy. While anemia is always present and is usually the early symptom, neurologic involvement occurs almost always in time in untreated cases and usually in patients not completely treated. Subacute combined sclerosis of the spinal cord may lead to a crippling and permanent disability. A disease which is always fatal if untreated and often leads to serious permanent disability if insufficiently treated merits serious attention.

The first consideration is a correct diagnosis. If it is definitely determined that the patient has idiopathic pernicious anemia, treatment is necessary throughout life. All too often a patient is given liver extract for an anemia which has not been properly studied, and a definite diagnosis of pernicious anemia made. The patient improves but does not continue treatment because he does not understand that this is required permanently. Later a spinal cord lesion develops due to discontinuing the treatment; or it may not be realized by the physician that treatment must completely satisfy the deficiency to prevent progress in the neurologic involvement characteristic of the disease. If the anemia is not pernicious anemia, liver extract is seldom needed.

Pernicious anemia is a disease of older people. In 406 cases studied at the Cleveland Clinic only 5 were less than 30 years of age. In a total number of 558 I have observed the disease begin under 20 years of age in only one individual. The disease was first observed over 60 years of age in 41.7 per cent. One patient was 88 years old when first diagnosed. Fifty-two per cent were in the 40 to 60 group.

Three characteristic aspects or phases are observed in pernicious anemia: (1) gastro-intestinal, (2) hematologic, and (3) neurologic. The specific factor concerned is formed in the stomach by interaction of a ferment or other substance (intrinsic factor) secreted by the gastric glands on some element of ingested food (extrinsic factor). The substance formed by the interaction of intrinsic and extrinsic factors is absorbed from the gastro-intestinal tract. It is necessary for (1) normal gastro-intestinal function, (2) the normal growth and development of red blood cells, and (3) the normal nutrition of the nervous system. There should be an excess of the specific factor which is stored in the liver after absorption from the small intestine. This represents an overflow after the current needs of the body are satisfied and is stored to supply added demands.

No patient with idiopathic pernicious anemia has free hydrochloric acid in the stomach. The achlorhydria seems to precede the anemia and other symptoms of the disease by many years. It probably is congenital in most cases. The mucous membrane of the stomach is atrophic on gastroscopic examination. The papillae of the tongue are atrophic also. A coated tongue in active, untreated pernicious anemia is rarely seen. The surface is almost always clean, giving the tongue a "bald" appearance. The patient often complains of a sore tongue. This was a primary complaint in over 10 per cent of our series. Partly as a result of the absence of hydrochloric acid and probably partly as a result of a lack of nutritional factors, diarrhea is common. Many other gastro-intestinal symptoms are complained of, such as "indigestion", anorexia, nausea, vomiting, excessive gas formation, and jaundice. As a result of the gastro-intestinal disturbances most patients lose weight. With specific therapy the glossitis disappears, the papillae become normal and the tongue may become coated. Other gastro-intestinal symptoms usually clear up. The achlorhydria is permanent.

The blood findings are characteristic. The typical patient has a marked anemia with large red cells filled with hemoglobin (macrocytic and hyperchromic anemia). The mean volume of the erythrocyte is increased, so the volume index is high. Since there is no disturbance in hemoglobin formation, the stroma is filled with hemoglobin. The cells are larger than normal, so the mean cell hemoglobin content is increased and the color index is high. In 558 patients studied for red cell changes all have shown a macrocytosis if untreated. Often the volume index is high when the color index is normal or less than 1. The cell-size is by far the best diagnostic indicator of pernicious anemia and is the most important criterion of complete therapy.

The achlorhydria and the macrocytosis of the red cells are the two constant findings in untreated pernicious anemia. An anemic patient with large red cells (increased volume index) and achlorhydria almost without exception is suffering from pernicious anemia.

The bone marrow reflects the effects of a deficient supply of the erythrocyte-maturing factor. The first change is slowing of the rate of release of red cells. The cells released are larger than normal since maturation is not complete. This increase in the size of the cell is the first and most sensitive indicator of a deficient supply of the specific factor responsible for pernicious anemia. The immature erythrocytes remain longer and crowd the marrow so the marrow becomes red due to filling with cells which normally would be delivered into the circulation. As the deficiency progresses such cells as do reach the blood stream are of many sizes and shapes and some are nucleated. Many cells die in the marrow. The end product of hemoglobin destruction is bilirubin. The increased amount of the bile pigment may exceed the capacity of the liver to excrete it, so definite clinical jaundice may develop. It was once thought that the finding of megaloblasts in the blood film was the best diagnostic criterion of pernicious anemia. The appearance of microcytes, poikilocytes, nucleated red cells and basophilia is a late development in pernicious anemia. The one constant and characteristic early sign is the macrocytosis, and the hematologic diagnosis of pernicious anemia should be based on this finding. The reticulocyte count is low in pernicious anemia. When specific liver therapy is given, the reticulocyte count rapidly rises to a peak since the immature, unfinished red cells are now completed and delivered into the circulation. The height of the reticulocyte curve rises with the degree of hyperplasia and immaturity of the marrow. The redder the marrow the more severe the disease and the higher the reticulocyte count on treatment since there are larger numbers of immature cells to be released.

The leucocyte count is seldom above normal in pernicious anemia. The leucocytes in the circulation are often larger than normal and usually well lobulated. The hyperplasia of the erythroblastic tissues in the marrow seemingly interferes with the normal growth of granulocytes by crowding out the leucoblastic tissues. The granulocytes remain longer than normal in the marrow so when released show hypersegmentation of the nucleus indicating they are older than the average granular or white cell. The platelets are often decreased, probably for the same reason.

To summarize the blood findings in pernicious anemia: The first change is an increase in volume (macrocytosis) of the red cells and an anemia due to slowing of rate of release of the red cells into the blood

stream. As the disease progresses the anemia becomes more marked, the macrocytosis persists, and more immature cells—poikilocytes, megaloblasts, and normoblasts—appear. The reticulocyte count is low. The bone marrow is hyperplastic and red. The leucocyte count is below normal and the white cells in the circulation tend to show increased lobulation. With adequate specific therapy the reticulocyte count rises sharply showing that the erythrocytes are being matured in the marrow. With complete treatment the blood returns to normal and remains so. The one constant abnormality when the disease is active is the macrocytosis of the red cells. It is the earliest variation from normal to appear and the last to disappear and is the best indicator of pernicious anemia from the blood standpoint. It is by far the best criterion of the completeness of treatment. All untreated patients in our series of 578 patients with pernicious anemia have had a macrocytic anemia, and often only the macrocytosis. All correctly and completely treated patients show no macrocytosis.

The neurologic lesions are both peripheral and central. There is probably always some degree of neuritis, usually some degeneration of the tracts of the spinal cord, and at times cerebral symptoms due to involvement of the brain. It seems proved that the neurologic lesions are due to a deficiency in the nutrition of the nervous system. It is likely that the same nutritional factor necessary for the maturation of the red cells is required for the nervous system also. It is possible that other substances are involved, but it is known that the deficiency responsible for the neurologic lesions is satisfied by the use of liver and liver substitutes regardless of whether it is dependent on the same factor or some related or independent factor.

The neurologic involvement is manifested by paresthesia of the hands and feet, in-co-ordination or spasticity. The most common finding on examination is a loss of vibratory sense in the lower extremities. Abnormalities in the reflexes and position sense are often present. In 325 patients on whom the vibration sense was tested this was found abnormal (lost or diminished) in 245 or 72.3 per cent. Nearly half (45.8 per cent) of the entire group of 406 patients complained on admission of numbness and tingling in the extremities. Over 10 per cent already had a spinal cord lesion making walking difficult due to in-co-ordination or spasticity. A true psychosis was observed in only one patient.

In treating pernicious anemia the object is to satisfy completely and permanently the deficiency responsible for the disease. Whole liver by mouth, oral stomach extracts, and oral and parenteral liver extracts are available forms of specific treatment. While it is an excellent idea for patients to eat liver as a part of the diet, it is difficult to treat satis-

factorily pernicious anemia by eating liver. Stomach extracts can be given by mouth only. Liver extract given intramuscularly is thirty times as active as the same amount taken by mouth. By far the best method of treatment is the intramuscular or subcutaneous use of a potent liver extract. Some extracts can be given intravenously, but the intravenous method has no advantages over subcutaneous or intramuscular administration. It is probable that a patient is more apt to become sensitive to the extract if given intravenously. There are many different liver extracts on the market varying greatly in strength. The strongest extract contains at least 15 units per cc., a unit being the amount of specific principle theoretically required to supply the amount of specific factor needed for a day. There is no exact method for assaying liver extracts. Many extracts labeled 15 units may contain many more. The same manufacturer may offer numerous extracts varying only in potency, which is confusing. I see no point in treating most patients suffering from pernicious anemia with other than a concentrated extract (15 units per cc.).

Since extracts of different manufacturers may vary, it is wise to select one good extract and use this with all patients. Where the neurologic involvement is serious, some clinicians have thought that a less concentrated extract might contain some substance which is not present in the concentrated extract and which is an aid in relieving the disease of the nervous system. This view is debatable.

Having selected a potent concentrated extract the method of administration must be decided upon. Many different ways have been advised. The whole subject is much colored by personal opinion. I believe strongly that the most satisfactory method is intensive therapy at the beginning of treatment. Certainly in some cases less intensive treatment might be equally as good. There is no way to gauge from the standpoint of the patient the amount of specific factor needed by any individual. The material is not expensive and the results of inadequate treatment are so serious it seems sensible to administer the liver extract in amounts which would cover the needs of all patients. After the initial period of intensive therapy the injections need not be given so often.

The method found uniformly satisfactory is the following schedule:

- First two weeks daily injections of 1 cc. of a potent extract containing 15 units per cc.
- Next three-month period twice weekly injections of 1 cc. of the same extract.
- Next three-month period weekly injections of 1 cc. of the same extract.
- Remainder of the patient's life monthly injections of 1 cc. of the same extract.

This plan of treatment has been followed for the past fifteen years. With it the blood is always returned to normal and maintained if the diagnosis is correct. The neurologic lesions never advance and usually improve often to a striking degree; the gastro-intestinal symptoms are relieved entirely although the achlorhydria is uninfluenced.

With adequate treatment the patient in four or five days notices an improvement in the appetite and develops a sense of well being. The weight soon begins to increase; a sore tongue disappears and gastro-intestinal symptoms clear up. This clinical improvement is paralleled by a steady rise in the red cells and hemoglobin and an outpouring of young cells (reticulocytes). Soon the reticulocyte count falls to normal (less than 1 per cent) but the change in the blood continues until the red cell count and hemoglobin are normal and the red cell size is normal as shown by a volume index of 1 or less. The papillae of the tongue return entirely to normal.

By far the best indicator of the adequacy of treatment is the erythrocyte size. If the volume index does not return to normal and remain normal, the treatment is not complete. A patient should always have a careful blood study at three or six-month intervals to measure the results of treatment. If the red cell count remains five million or over, one can also be sure that treatment is adequate. It is best, however, to do a volume index or other test to determine cell size as even a slight increase in size is a warning that more treatment is needed.

The neurologic signs and symptoms are the hardest to influence and improve much more slowly than the anemia. If progress is not satisfactory, injections should continue to be given at weekly intervals indefinitely. The lack of improvement neurologically may be due to permanent damage to the nerve tract which cannot be altered. So often this damage takes place while the patient is receiving treatment but inadequate treatment. It is remarkable how striking the improvement in a neurologic lesion can be when properly treated. A patient may be completely crippled due to an extensive cord lesion and still regain use of the legs and walk satisfactorily. Seldom is the vibratory sense completely regained—some parasthesia is apt to persist. A neurologic lesion should never develop or progress in an adequately treated patient.

The treatment of any deficiency disease is influenced by certain intercurrent diseases, especially infections. More extract should be given if such occur.

One troublesome complication of liver therapy is the development of allergic reactions, principally hives, following the injection of liver extract. Most extracts are made from hog liver. Others are made from beef, horse, and sheep products. If difficulty is experienced, different ex-

tracts should be tried. So far I have not seen a patient who could not take some potent extract. Mild reactions may be controlled by giving small doses of adrenalin with the liver extract.

Iron is seldom required unless needed for some reason such as blood loss, apart from the pernicious anemia.

It is doubtful if added vitamins influence the neurologic lesions if liver therapy is given properly and intensively and an adequate diet is eaten. Hydrochloric acid is seldom needed.

### SUMMARY

1. Pernicious anemia is a disease characterized by (a) macrocytic anemia with (b) achlorhydria, an atrophy of the papillae of the tongue and other gastro-intestinal symptoms, and (c) frequent neurologic signs and symptoms manifested by numbness and tingling of the extremities, lost vibratory sense, and disturbances in gait due to combined sclerosis of the spinal cord.

2. In a series of 406 consecutive patients with pernicious anemia (a) free hydrochloric acid was found in the gastric contents in only 1 patient, (b) all untreated patients had a macrocytic anemia, (c) the tongue was clean or atrophic in most patients, (d) nearly half complained of parasthesia or difficulty in walking, and (e) in three-fourths the vibratory sense was absent.

3. All symptoms and signs except the achlorhydria are due to a lack of some specific substance normally formed by the interaction of a ferment secreted by the stomach on some constituent of the ingested food and stored in the liver.

4. The deficiency in idiopathic pernicious anemia is permanent, so treatment is required throughout the life of the patient. The object of treatment is to satisfy completely the need for the lacking substance.

5. A satisfactory method of giving liver extract has been outlined.

6. Iron, hydrochloric acid, and other medication is seldom needed. A complete diet should be insisted upon.

7. With adequate therapy (a) the blood returns to normal and remains so, (b) the tongue becomes normal and other gastro-intestinal symptoms such as indigestion and diarrhea disappear, (c) the neurologic symptoms improve or even clear completely, and (d) the achlorhydria is permanent.

8. In pernicious anemia (a) the seriousness of the disease must be appreciated, (b) the disease must be correctly diagnosed, and (c) treatment must be complete and permanent.