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Etiological considerations of pernicious anemia

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ETIOLOGICAL CONSIDERATIONS
OF PERNICIOUS ANEMIA

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INTRODUCTION

At the outset it must be understood that there is no attempt at originality in this paper; nor does it represent a complete review of the abundant literature on the subject of Pernicious Anemia. I have used the literature freely; it forms the foundation of the entire paper, and any conclusions reached are based upon it. In other words, it represents a bit of arm chair philosophy based upon the works and observations of others. For these reasons I shall make an honest attempt not to become dogmatic at any time, and I shall discuss only briefly and lightly those topics having a direct bearing upon the subject. Thus it is my purpose to present a paper which is brief and concise so that one may in a short space of time gain a few pertinent bits of knowledge on this much debated subject.

There is a tendency, in the rush and hurry of our medical school training, to develop the feeling that such diseases as diabetes and pernicious anemia, for which we have specific therapy, are closed chapters, and that most of the problems concerning them have been solved. Nothing could be farther from the truth. I shall attempt to show that the therapy of pernicious anemia is only substitutive, which is a far cry from
the ideal of preventative therapy. Naturally, the approach to preventative measures is possible only through complete understanding of the etiological factors involved.

In this paper I shall consider only the problem of the anemia characterized by macrocytosis, megalocytosis, and an achlorhydria. I shall attempt to show that it is possible for such an anemia to develop from several different fundamental pathological states, but that in the final analysis it is probably the result of some, as yet undiscovered, nutritional deficiency, acting in conjunction with a superimposed constitutional or hereditary factor. For as Meulengracht has aptly said:

"The causes leading to the development of a disease lie partly in the individual himself and partly in external factors."

The importance of any problem in the field of medicine lies in two general fields. These are: 1. The frequency with which the problem is met in general practice, and, 2. its relationship to other problems which may arise. While pernicious anemia is not a rarity, it is also not one of the common diseases. In general, however, in the United States and other temperate and northern areas, it occurs frequently enough so that the
smallest practitioner usually has at least one case under his care. It is a generally accepted fact that in order for him to recognize and adequately care for these cases, he should be well acquainted with the known basic features of the problem, rather than simply being a dogmatic dispenser of medicine.

Birkeland makes the observation that like carcinoma, the incidence of pernicious anemia seems to be increasing, but he feels that this is due to more adequate recognition of the disease and to the fact that more people now seek the physician's advice.

Sturgis quotes Evans' figures that, in general over the United States, there are three to four pernicious anemia patients per thousand patients admitted to hospitals. He also gives the figures that at Peter Bent Brigham Hospital there are 143 pernicious anemia patients to 105 with typhoid fever and 401 with lobar pneumonia. He also notes the geographical and racial features and states that the disease occurs frequently in the United States, Canada, England, Ireland, and countries of Northern Europe, while it is rare in the tropics, China, South America, and in negroes. He states that most frequently cases are seen between the ages of 40 and 65, but that when compared with the
population of the various ages, the highest percentage age is from 65 to 70, and that it is very rare among young children. He feels that the incidence is about the same in the two sexes, and that in ten per cent of cases there is definite proof of an hereditary tendency such as one or more additional cases in the immediate family.

The importance of the investigation of the etiology of pernicious anemia in relationship to other problems and fields can hardly be overemphasized. In these investigations much knowledge of value concerning the gastro-intestinal tract, the liver, the bone marrow, nutrition and other anemias has been obtained. West⁴ states:

"The observation of Minot and Murphy that adequate liver feeding induces and maintains remissions in pernicious anemia has led to far reaching results. In addition to establishing the first effective therapy in this and some allied diseases, it has initiated investigations that have resulted in a marked revision of ideas concerning gastric physiology and deficiency diseases and should further contribute materially to our knowledge of cellular physiology, particularly that of nerve tissue and bone marrow."
HISTORICAL REVIEW

The history of the development of ideas concerning pernicious anemia is in itself a long and interesting story. It is one made up of acute observation, ceaseless work and investigation, and battles between conflicting theories. In itself this history is replete with many lessons as stated by Dock:

"The history of pernicious anemia shows how greatly the experts vary in their interpretation of visible evidence, how easily men narrow their mental vision to the fashionable field, and how often their confident opinion is founded on pure fantasy."

Because the history is so long I shall summarize it only briefly, including only the important milestones of advancement which have led to our present concept of pernicious anemia.

It is probable that Combe of Edinburgh, in about 1822, first described the disease of pernicious anemia. He casually remarked that it is probably owing to some disorder of the digestive and assimilative organs that its characteristic symptom has its origin, and to the correction of this derangement we must look for a removal of the disease. It is interesting to note how close he was to our present day concept, yet it was
more than one hundred years later before Minot and Murphy announced their liver diet.

Addison, in 1849, gave the classical description of the disease, so that at present it is still named for him as Addisonian anemia. In 1855, he hazarded a guess that it was due to some form of fatty degeneration, but he never got any farther.5

In 1863, Habershon6 advanced a neurogenic theory which was based on good observation. He says:

"The first symptoms indicate gastric irritation and an interference with digestion; there was a deficiency in the quantity of nutrient absorbed and, hence, atrophy. After death, however, no trace of organic change could be found in the stomach — there was neither thickening nor cicatrix. It is to the nervous supply of the stomach that we must direct our attention; it was there that the fault originally commenced, and in that direction we must seek for the origin of the disease."

Fenwick7, in 1877, noted the relationship between atrophy of the gastric mucosa and idiopathic anemia and thought the disease was a direct result of an imperfect secretion of gastric juice. It remained, however, for Ewald and Martins to be the first to actually demonstrate the achylia5.

Guys Hospital in England, where Addison did his work, remained for some time the center of the English work on
pernicious anemia. In 1882, Pye-Smith, the leading clinician wrote quite extensively concerning the clinical features of the disease, but he made no proposals concerning etiology or treatment.

From this period up to 1928, little progress had been made as far as etiology was concerned, though Faber and Hurst proved the primacy of the achylia. Before this, the gastro-intestinal defect theory, as mentioned by some of the earliest men in connection with the disease, was lost to view in a controversy over the interpretation of the blood and marrow changes. Pepper, in 1875, thought it a "pseudoleukemia", while Cohnheim, in 1876, thought the hyperplasia of the bone marrow an evidence of return to an embryonal state, with retention of immature forms as the primary factor in the disease. Ehrlich, however, considered the megaloblastic reversion to be a result of the action of a poison, or a group of poisons, which caused blood destruction and interfered with blood formation. This theory that pernicious anemia is a hemolytic anemia was also maintained by Quincke in 1876, and Osler in 1877, who noted the pigmentation of the liver and spleen and the phagocytosis of red blood cells in the marrow.5

Hunter, in 1888, championed the theory that perni-
cious anemia was due to the action of a toxin derived from the gastro-intestinal tract, and occurred in individuals constitutionally predisposed. In 1909, he stated:

"In Addisonian anemia the septic factor is a most important antecedent and concomitant, but not the only factor. It precedes the disease, creating conditions of mucosa in mouth, stomach and intestines which permit the contraction of the specific (hemolytic) infection underlying the real characteristic features of the disease. These features include: (1) an intense hemolysis accompanied by pigment changes in the liver, kidney, and spleen; (2) glossitis with deep seated infection; (3) drain poisons from the septic glossitis."

In 1924, Price-Jones announced his blood studies which have helped materially in diagnosis and guide to treatment. He measured and charted the variations in the size of the red blood cells. He noted that in pernicious anemia there is a high degree of anisocytosis which varies directly with the extent of the anemia.

Whipple and Robscheit-Robbins showed, in 1925, that in dogs made severely anemic by chronic blood loss, liver was the most important nutritional aid in promoting blood regeneration. Thus the stage was set for the epic work of Minot and Murphy. They noted that Biemer, in 1872, and Pepper, in 1875, appreciated diet-
ary factors, and that in 1863, Habershon noted that pernicious anemia patients improve with bracing air and a nutrient and stimulating diet. They give credit to Whipple, who in 1922, suggested that in pernicious anemia there maybe a scarcity of the material from which the stroma of the red blood cells are formed, or that a disease of the stroma forming cells of the marrow exists. Thus they concluded that liver and other foods rich in complete proteins may enhance the formation of red blood cells in this disease, especially by supplying material to build their stroma. In their first experiments they fed liver in large amounts, on a scientific basis, to pernicious and secondary anemia patients. In the former they noted obvious clinical improvement within two weeks, with an average rise in reticulocytes to 15.5% and an average increase in red blood cells from 1.47 million to 4.5 million. In the latter, however, there was only a very slow improvement.

In 1928, Means and Richardson\(^\text{13}\) confirmed the work of Minot and Murphy and made some very important speculations. They said:

"Many persons, in fact, most, live habitually on diets which contain an amount of the specific substance quite inadequate to relieve or maintain in normal blood balance a patient
with pernicious anemia, and yet they never develop that disease. One is forced to conclude, therefore, that the appearance of the disease is not due solely to an external shortage of a specific substance necessary to normal life. There must be in persons who develop pernicious anemia on what would be an adequate diet for the majority of mankind, either some internal obstacle to the acquisition of the specific substance or, because of some preexisting abnormality, an exaggerated requirement for that specific substance. In other words, for the production of the disease it seems likely that there needs must be something wrong with the individual, an hereditary or acquired defect, as well as, something wrong with his dietary."

It is probable that at the same time Castle was doing his work on the extrinsic and intrinsic factors, which brings us to the etiological factors present in pernicious anemia.
ERYTHROPOIESIS AND PIGMENT METABOLISM

Because the formation and destruction of red blood cells are problems which must be fairly well understood before one can discuss the etiological factors of pernicious anemia, it will be necessary to briefly review a few of the salient points of these processes. The problem of blood destruction and pigment metabolism is quite well established and accepted. However, the problem of erythropoiesis, particularly in pernicious anemia, is very controversial. One's conclusion at this point is determined to quite a great extent by whether he accepts the defective blood formation or the abnormal blood destruction theory of pernicious anemia.

Most of the controversy has revolved about the point as to whether or not the megaloblast, which is characteristic of the bone marrow in pernicious anemia, is the precursor of the normoblast, or whether it is a degenerative form indicative of a reversion to an embryonal type of blood formation. If one believes the megaloblast to be a degenerative form, he can accept the idea that the anti-anemic factor of the liver is necessary for the building of the stroma of the red blood cell. If one feels, however, that the megaloblast is evidence of an attempt to replace great numbers of red
blood cells which have been destroyed, then he can accept the view that the anti-anemic factor of the liver is necessary to prevent an hemolysis of red cells on a toxic basis.

This problem has received the attention of many hematologists all through the history of pernicious anemia. Kirschbaum\(^{14}\) champions the idea that the megaloblast is a degenerative form, and from his work reaches the conclusion that the megaloblast is not the precursor of the normoblast, and that in pernicious anemia the bone marrow reverts to the embryonal type. Diametrically opposed, however, is Jones\(^{15}\) who notes that after liver therapy the megaloblast completes its maturation as a normoblast and then as a reticulated and mature erythrocyte.

Other men, as Downey, Piney, and Naegli\(^{5}\) today feel that the megaloblast is distinct from the normoblast. However, Cohnheim and Peabody\(^{5}\) have always felt that the arrest of maturation was the outstanding functional defect.

Davidson\(^{16}\) presents both sides of the problem quite well. He feels that the reticulo-endothelial cell is the parent of all the formed elements of the blood. If the cell happens to be lining a blood space in lymphatic
tissue, it will produce lymphoblasts from which are developed the lymphocytic series of white cells. If, on the other hand, it is lining a blood space in the bone marrow, then depending on whether division is extravascular or intravascular, myeloblasts and megaloblasts are formed. From myeloblasts the myelocytes and leucocytes develop. Erythrocytes are formed from the megaloblasts. He calls to view Piney's belief that the megaloblast is a separate special cell formed only in fetal liver, except in a pathological state such as pernicious anemia. Piney feels that the megaloblast is of entodermal origin, while the cellular elements of the bone marrow as derived from the reticulo-endothelium are mesoblastic in origin. He believes that in pernicious anemia, remnants of entodermal tissue are left in the liver, and as a result of the absence of complete atrophy there is a concomitant functional weakness of bone marrow. This view of Piney's is not accepted but it may be that there is a constitutional weakness in both the bone marrow and liver.

Davidson goes on to point out that in the normal process of blood formation there is an amazingly constant production of formed elements. The number, size, shape, and hemoglobin content of the normal erythrocytes
show practically no variation. He feels that since the precursors of the mature circulatory cells are in the blood spaces of the bone marrow, and yet never, except in pathological condition, appear in the circulation, it must be assumed that the body produces some inhibitory mechanism which prevents them from escaping into the circulation. In addition, he says that there must be a positive stimulatory action which causes proliferation when needed by the body. This he attributes to the specific action of the anti-anemic principle of the liver. I believe that this is a good concept as all the well balanced physiology of the body is generally the result of two opposed forces kept in a fine balance.

Minot and Castle\textsuperscript{17} conclude that the megaloblast is a degenerative form rather than a step in normal erythropoiesis from their observation that the percentage of reticulocytes in the peripheral blood are an index to the activity of the bone marrow, and feel, therefore, that it is probable that in pernicious anemia the bone marrow is degenerative rather than hyperplastic.

As easily can be seen the exact status of the megaloblast is not known. It is here that the conquest of pernicious anemia has much to offer in solving the problems of erythropoiesis. I feel that the weight of the
evidence tends toward Whipple's idea, that in pernicious anemia something is absent which is necessary for stroma building of the red cell. What this substance is and why it should be absent are the main problems of pernicious anemia.

Davidson\textsuperscript{16} feels that the normal life of an erythrocyte is about thirty days, and that there is a continuous production of new cells and removal of old cells. The old cells are phagocytized by the reticulo-endothelial cells. He feels that the manufacture of bilirubin is done by the endothelial cells, while the liver cells may store it, keeping it at a constant plasma level.

This concept of pigment metabolism is quite generally accepted and needs to be mentioned here, as an increase in bilirubin is one of the features of pernicious anemia. Hunter\textsuperscript{9} was one of the first to notice this and to prove it by showing the increased amount of iron in the liver and spleen in cases of pernicious anemia.

Cornell\textsuperscript{18} states that the disturbed bile pigment metabolism in pernicious anemia is evidenced by a hyperbilirubinemia, increased output of urobilinogen and urobilin by the liver, and increased urobilin output of the kidney. He also calls attention to the deposits of iron pigment in spleen, kidney, and liver. He feels that the
degree of the hyperbilirubinemia is in proportion to the degree of the anemia. He also states that the increase in pigment may be explained by the phagocytosis in the marrow of the precursors of the red cells. This however, is found at autopsy in most all subjects. The disturbed pigment metabolism has been used as a support of the toxic hemolytic theory of pernicious anemia, but it seems more likely that it is simply due to the formation of more hemoglobin than the marrow can use since it is deficient in stroma building material.

These phases of blood formation and destruction will be discussed more fully as they fall into different etiological theories.
ETIOLOGICAL CONSIDERATIONS

It was truly inevitable that a theory that the causation of pernicious anemia was on a septic hemolytic basis should develop. The hyperplastic bone marrow was interpreted as an attempt to furnish red cells to the circulating blood stream. This coupled with the findings of an increased pigment metabolism, naturally led to the idea that hemolysis was the basis for this. The findings of an achlorhydria with a glossitis led to the septic theory as the basis of the hemolysis. This cause was championed by Hunter in the early part of the twentieth century. His words bear repetition:

"In Addisonian anemia the septic factor is a most important and concomitant, but not the only, factor. It precedes the disease, creating conditions of mucosa in mouth, stomach, and intestines which permit the contraction of the specific (hemolytic) infection underlying the real characteristic feature of the disease. These features include: (1) an intense hemolysis accompanied by pigment changes in the liver, kidney and spleen; (2) glossitis with deep seated infection; (3) drain poisons from the septic glossitis."

Muir, Askanazy, Growitz and others also interpreted the marrow changes as a response to rapid hemolysis, while Peabody pointed out that the bilirubinemia, hemoglobinemia and hematninemia were only explicable by
assuming a hemolytic process.

Hurst and Bell\textsuperscript{19}, after Collier in 1921 had proved conclusively that subacute combined degeneration of the cord and achlorhydria are different manifestations of the same disease, felt that the cord degeneration and anemia were due to oral sepsis, achlorhydria and consequent intestinal infection with intoxication. They felt that the digestive symptoms could be due to the achlorhydria or to nervous changes. In the following year, Hurst\textsuperscript{20} proposed that in pernicious anemia there was both a neuro-toxin and a hemolytic toxin as a result of bacterial action due to the achlorhydria. He believed that an important part in the treatment was to overcome intestinal infection by thoroughly dealing with oral sepsis, removing infected teeth and tonsils, and the administration of hydrochloric acid. He even went so far as to prepare autogenous vaccines from the streptococci of the throat.

After the advent of vitamins, it was logical that someone should look to them as an etiological factor. Koessler, Maurer, and Laughlin\textsuperscript{21} felt that vitamin A deficiency may cause atrophy of the gastric mucosa, leading to an achylia which allows an invasion by many micro-organisms which form soluble poisons, which they
term hemolytic, myelotoxic and neurotoxic.

After the work of Minot and Murphy, it became necessary to incorporate the specificity of the liver substance in the theories of hemolytic action. Harris advanced the idea that the specific liver substance is an endocrine (antihemolysin) which controls the hemolytic action of the reticulo-endothelial system. He feels that the pathological changes in the liver and gall bladder found in pernicious anemia suggest a chronic hepatitis which may inhibit the action of, or destroy, the liver cells that secrete antihemolysin.

Davidson points out that the anisocytosis and poikilocytosis in pernicious anemia are evidence of hurried and abnormal attempts at blood regeneration. He upholds the idea that the blood and nervous changes are due to a toxin following gastro-intestinal sepsis which is a result of achlorhydria. He feels that in these patients there is a constitutional weakness in the stomach, liver, bone marrow and nervous system, and then explains the development of the syndrome by an ingenious combination of the theories of Cohnheim, Hunter, Minot and Murphy:

"The gastro-intestinal toxin first affects the erythrocytes in the portal circulation - when the cells are normal and mature
it has no effect, but when abnormal or immature it weakens them for phagocytosis. This toxin is carried to the liver, which for a long time destroys the toxin. Eventually, by middle life, the liver is worn out in this respect and the toxin escapes to the systemic system. Then the central nervous system, liver, and kidney may be involved so that the hormone (anti-pernicious anemia substance) level of the blood is lowered. Then with lack of the specific substance, the marrow reverts to the embryonic type."

Barker and Hummel point out that the action of the liver substance is far from clear. They feel that excessive bacterial activity in the intestine may cause pernicious anemia by:

"1. By prevention of formation of hematopoetic factor or destroying it.
2. Elaboration of toxic products which are not neutralized."

They have assumed from their work that the action of liver principle is the detoxification of the hemolytic and neurotoxic toxins.

It is easy to see that in most of these ideas, the assumption that abnormal blood destruction is the fundamental point. As pointed out before, the matter of whether there is abnormal blood destruction or abnormal blood formation has not been settled. Most of the work on blood destruction just mentioned, however, seems to
me to be largely the result of reasoning without experimental basis.

Nye\textsuperscript{24} began some interesting bacteriological work in an effort to prove the septic hemolytic theory. He did his first work with B. Welchii infection. Hunter, van der Reis and Seyderholm had noted a relationship of B. Welchii infection of the gastro-intestinal tract to pernicious anemia, and Herters and Simonds had noted the prevalence of B. Welchii in the stools of pernicious anemia patients. Nye found the ratio of spores to vegetative forms to be 1:20 in pernicious anemia and 1:5,000,000 in normal individuals. In both, however, the number of vegetative forms was about the same. He then showed that in an alkaline media there is a tendency for B. Welchii to form spores, and that there is the same increase in spores in cases of simple achylia as there is in cases of pernicious anemia. He was able to conclude that the spore increase in pernicious anemia is secondary to the gastric achylia rather than that pernicious anemia is caused by a chronic intestinal infection with B. Welchii. Nye, Zerfas, and Cornwall\textsuperscript{25} then repeated much the same work with yeast-like fungi. They concluded that these fungi are no more common in pernicious anemia than in gastric achylia and other
anemias, and that the fungi are unimportant as an etiologic factor not only in pernicious anemia but also in sprue.

Cornell points out that although the phagocytosis of red cells in the marrow of pernicious anemia patients is an evidence of abnormal blood destruction this also occurs in pneumonia, typhoid fever, and tuberculosis, and that it alone cannot account for the oligocytopenia of pernicious anemia. He also calls to attention the fact that combined system degeneration also occurs in lead poisoning, arsenic poisoning, ergot poisoning, pellagra, diabetes, leukemia, diptheria, carcinoma, senility and pregnancy, so that one must think of other factors before ascribing this condition in pernicious anemia to a bacterial toxin.

Castle feels that the bacterial toxic theory is untenable because he has shown that the flora of the gastro-intestinal tract remains the same in pernicious anemia both during relapses and remissions. This, of course, is circumvented by the theory that the liver principle is a detoxifying agent.

Although there is much logical evidence in favor of the bacterial toxic hemolytic theory, there is no experimental evidence in its support, and there is some
experimental evidence against it, so that I feel the abnormal blood formation theory is the more tenable.

Although the theory that abnormal blood destruction was the fundamental lesion of pernicious anemia held sway for a great number of years, the counter theory that it was due to an abnormal blood formation was not without its supporters. Cohnheim and Ehrlich in 1876, the early history of pernicious anemia, felt that the syndrome was due to defective blood formation based on megaloblastic degeneration of the bone marrow. They had no way, however, to explain the megaloblastic degeneration.

In later years, particularly since the work of Minot and Murphy, the theory of defective blood formation has had the strongest support. Peabody was one of the first to advance his ideas which were made from observations on patients on liver therapy, who were allowed to go into relapse. He feels that the essential lesion of the bone marrow in relapse is an hyperplasia of the myeloid cells in which the megaloblasts play the chief part. He notes that in relapse the megaloblasts proliferate very rapidly while in remission they tend to disappear. He then makes a statement which points toward the possibility that pernicious
anemia is not a specific disease entity.

"Although the megaloblastic hyperplasia seems to be the essential feature of the pathology of the bone marrow it cannot be stated that the lesion is necessarily specific for this disease."

He then goes on to point out that when treatment is instituted the megaloblastic hyperplasia begins to decrease before the red count rises, which would tend to disprove the theory of abnormal blood destruction. He then states:

"The megaloblastic hyperplasia of pernicious anemia produces a bone marrow with diminished functional capacity and it leads to the belief that this type of anemia is the result of the pathologic lesion of the bone marrow."

Middleton made the observation that copper, as used in the treatment of secondary anemia at that time, was not the active agent in relieving the defective blood formation in pernicious anemia.

Whipple who has always been a prominent figure in the study of blood dyscrasias makes the statement:

"Pernicious anemia is a deficiency disease in which there is a deficiency of stroma building material or a disturbance of the stroma building mechanism. The toxic theory has little to support it and has been responsible for much confusion. Studies of pigment
metabolism, pathologic condition of the marrow and the reaction of the disease to any liver extract all favor the view that pernicious anemia is due to a lack of something rather than to an obscure poison."

Some of the more recent work along this line has been an attempt to accurately place the megaloblast in erythropoiesis. Israels notes that the administration of liver factor enables erythropoiesis to return to normal, the megaloblasts and other primitive forms disappearing from the marrow and being replaced by normoblasts. From the fact that megaloblasts are also found in pregnancy anemia, bothriocephalus latus inestation and sprue, he makes the conclusion that megaloblasts appear in the marrow when there is interference with the proper activity of what is known as the liver anti-pernicous anemia principle - as in pernicious anemia, dietary deficiencies, or poor absorption from the gastro-intestinal tract as in sprue. He also feels that since the megaloblast plays no part in normal erythropoiesis as from blood loss and since proerythroblasts are common to both groups the divergence of the normoblast and megaloblast series occurs when development proceeds beyond the proerythroblast stage, as: (See diagram on next page)
He feels that liver factor is necessary to make the proerythroblast develop toward the normocyte series. He explains anisocytosis and poikilocytosis by the fact that the irregular megalocytes lose their nuclei and become hemoglobinated.

Davidson31 feels that macrocytosis is not specific evidence for pernicious anemia but rather depends upon the bone marrow. He makes the statement that all megalocytic anemias are macrocytic, but all macrocytic anemias are not megalocytic. It is his opinion that a macrocytic anemia developing from a megaloblastic bone marrow is consequent upon a deficiency of a specific factor essential for the continuation of normal blood formation.

Thus it appears that at the present time there is a tendency to consider pernicious anemia as a syndrome
based upon a deficiency which may be brought about by various pathological lesions. This will be brought out in more detail when the gastro-intestinal factors are discussed.

As noted in the historical review, the relationship of the gastro-intestinal tract and the bone marrow in pernicious anemia was an early observation. However, it is only recently that much in the way of conclusive work has been done which indicates just what the relationship may be.

The presence of achlorhydria and atrophy of the gastric mucosa have been observations of long standing. Levine and Ladd\textsuperscript{32} in studying 150 cases of pernicious anemia made the observation that in all but three cases there was an absolute anacidity, and that in two of the three cases the diagnosis was questionable. They feel that anacidity is the most constant finding of the disease.

Hurst\textsuperscript{20} has made the observation that the achlorhydria precedes the development of the anemia, and that this usually gives rise to a long history of digestive trouble which has also proceeded the anemia. He also brings up the point, however, that the achloyhydria is a constitutional thing with an hereditary tendency,
being present in 4% of normal young men. He feels that in certain cases, pernicious anemia may follow a secondary achlorhydria. These men, however, have reached no conclusions as to the causal relationships of the achlorhydria.

Harris\textsuperscript{22} who supported the toxic hemolytic theory felt that the relationship between achlorhydria and pernicious anemia might be:

1. Concomittant - Due to the same infection which involves the liver and gall bladder.

2. Contributory - Loss of antiseptic efficiency of gastric juice which allows the entrance of pathogenic organisms into the duodenum, biliary passages, and liver with a resulting hepatitis.

Cornell\textsuperscript{18} noted the invariable association of achlorhydria in cases of pernicious anemia and felt that it forms in these cases, a necessary link in an etiological chain, to which by the addition of further unknown links, pernicious anemia is made to appear.

As can be readily seen, little had been accomplished this far by investigation of the achlorhydria. It remained for Castle\textsuperscript{26} with his ingenious experimental procedure to lead the way toward unraveling some of the complex problems. He noted the invariable achlorhydria of
pernicious anemia even after the subcutaneous injection of histamine. He also made the observation that cases of carcinoma of the stomach or a gastrectomy which lead to an achlorhydria may subsequently develop pernicious anemia. He then made his famous hypothesis:

"The significant defect in the patient with pernicious anemia is an inability to carry out some essential step in the process of gastric digestion, thus causing a lack of whatever substance is successfully derived by the stomach of the normal individual from his food."

He then fed beef muscle to normal individuals and removed the stomach contents in one half an hour. This material was then incubated after being made acid in reaction and then fed to patients suffering with pernicious anemia. These patients improved as well as though treated with liver, but when fed only ground beef alone there was no improvement. Therefore his first conclusions were:

1. Pernicious anemia is a deficiency disease.
2. In the normal stomach during the digestion of beef muscle there is some substance capable of promptly and markedly relieving pernicious anemia patients.

After further work, Castle felt that the inadequate gastric digestion was that of protein which allowed
the development of a virtual deficiency in the presence of a diet adequate for normal man. This he attributed to a defective quality of gastric secretion. In more extensive work with Townsend and Heath, Castle incubated beef muscle with normal saliva and with normal human duodenal contents so obtained as to be free from gastric secretion. This he found to be without effect in cases of pernicious anemia. Duodenal contents, however, which contain gastric secretion when incubated with beef muscle he found to be effective. He also found that beef muscle incubated with hydrochloric acid and pure pepsin are without effect. When the mixture of beef muscle and normal human gastric juice were heated to 70 - 80°C for one half hour, the effectiveness was lost. From this work he felt that an active constituent of normal human gastric juice is secreted by the mucosa of the stomach and is not detectable in other parts of the gastro-intestinal tract. This substance he called intrinsic factor. He called the substance found in beef muscle the extrinsic factor, and he felt that the two react and produce a material which when administered to pernicious anemia patients has a marked hematopoietic effect. It was also his conclusion that it is a lack of intrinsic factor which is the essential defect in
pernicious anemia.

Castle and Minot\textsuperscript{36} have noted that although achlorhydria occurs without symptoms in otherwise normal individuals and with increasing frequency with age it is very commonly associated with hypochromic anemia and deficiency states accompanied by gastro-intestinal symptoms. This may be a lead toward the cause of a lack of intrinsic factor. They also point out that some cases of pernicious anemia do not respond to liver extract orally which indicates that the inability to absorb the anti-pernicious anemia substance is a factor in some cases. This is further evidence that pernicious anemia may be a syndrome due to a variety of fundamental causes.

In an exhaustive study of Bothriocephalus anemia, Birkeland\textsuperscript{2} feels that it is practically indistinguishable from true pernicious anemia. He has observed that many persons may carry the parasite without manifestations of anemia, yet there is a geographic distribution to the amount of worm patients developing anemia which corresponds closely to that of pernicious anemia. It is his belief that there is a constitutional factor in the ones affected which is responsible for the anemia. Thus it may be that the fundamental etiology of all pernicious anemia is a constitutional thing while other factors are
precipitating. Birkeland feels that the effect of the worm may be:

1. Render the intestinal contents toxic.
2. Injure the intestinal wall allowing normal toxins to enter.
3. As an irritant they may disturb the endocrines of the gastro-intestinal tract.
4. Their toxins may enter the blood stream and act on the blood forming organs.

This work also substantiates the viewpoint that the etiology of pernicious anemia is multiple. Investigation is taking many cases out of the idiopathic field.

Brown36 has made the observation that all cases of pernicious anemia show a chronic inflammatory reaction of the gut, and an early disappearance of the acidophilic cells. He supports the idea of the polypathogenesis of pernicious anemia and presents the following outline of possible etiological factors:

I. Extrinsic
   A. Deficient diet
   B. Inadequate mastication of food

II. Intrinsic
   A. Interference with digestion or absorption
in addition to the failure to secrete hydrochloric acid, patients with pernicious anemia secrete very little fluid into their stomachs either while fasting, or after the subcutaneous injection of histamine hydrochloride. This brings up the point that not only are the acidophilic cells of the stomach involved but also probably all the other secretory cells of the gastric mucosa. In further work along this tack, Goldhammer found that a normal subject secretes about 150 cc. of gastric juice per hour with histamine stimulation, while a case of pernicious anemia in relapse secretes only about 20 cc. per hour. In pernicious anemia cases in induced remissions the amount was about 45 cc. per hour. This would tend to show that liver therapy does have some effect on the gastric juice. It had been the idea of most pathologists that the gastric lesion was permanent in spite of treatment. Goldhammer also found that there is a direct relation between age and amount of secretion, but no relation between the amount of secretion and level of red blood cells in treated cases. This substantiates and gives reason for the age incidence of pernicious anemia. He made the conclusion that pernicious anemia is but one type of a group of macrocytic anemias and one must rule out the various other forms due to a removal of intrinsic
factor or its source, as by surgery, carcinoma of the stomach, et cetera.

It was Castle's first idea that the loss of the intrinsic factor was complete in a case of pernicious anemia yet this could not explain spontaneous remissions or the response of some cases to autolyzed yeast as will be mentioned later. In the light of new work, he was able to reach the conclusion that the deficiency of the gastric factor is apparently the dominant mechanism in pernicious anemia, but it is probable that the defect is relative rather than absolute.

The next logical line of investigation was of course to find the cells responsible for the setting up of the syndrome of pernicious anemia. Meulengracht found that the chronic gastritis with atrophy of the glands is mainly connected with the hydrochloric acid and pepsin producing part of the stomach, while the pyloric gland organ (area of intrinsic factor) was moderately intact. Thus he believes that the following points may be the explanation of this apparent contradiction:

1. The glands of the fundus may act as a starter or pacemaker for the pyloric gland system either through the production of hydrochloric acid, pepsin or by hormonal action.
2. Changes in the small intestine due to achlorhydria may render conditions unfavorable for the interaction of intrinsic and extrinsic factors.

While these points have not been proven they are surely logical and worthy of attention. Although all areas of the intestine have some degree of anti-pernicious anemia activity Meulengracht\textsuperscript{41} thinks that beyond the "pyloric organ" is due to the presence of the completed substance of the liver factor, or to an intermediary product. He found that prolonged washing of the ileum removes its hemopoietic activity which would show that the principle is formed elsewhere and is absorbed by the intestinal wall.

Ungley\textsuperscript{42} has confirmed Meulengracht's observation that the pepsin and anti-anemic factor are dissociated anatomically and physiologically in the stomach, and he was unable to find any pathology in the area of the pylorus in pernicious anemia. He concludes that the gastric lesion is not the result of an inflammatory gastritis, but is more of an atrophic process of unknown cause which may be the end result of some endocrine or nutritional deficiency, or may even be of congenital origin.

Schindler and Serly\textsuperscript{43}, however, by the use of the
gastroscope have observed superficial gastritis, superficial plus atrophic gastritis, and patchy or diffuse atrophy of the gastric mucosa in cases of pernicious anemia. It is probable, however, that one should accept the microscopic observations instead of those of the gastroscope.

Barker and Hummel have found many cases of intestinal anastomoses performed surgically for the relief of stricture or obstruction which show macrocytic anemia. All were benefited by liver therapy, yet 47% of them showed free hydrochloric acid in the stomach differentiating them from true pernicious anemia. It is interesting to note that some of these were made well by taking down the anastomoses. They feel that the cause of the anemia in these cases may be deficient absorption of the hematopoietic principle. Although these observations strengthen the relationship of the gastro-intestinal tract to the blood forming organs they give little help to the understanding of the etiology of true Addisonian anemia.

Brunschwig has presented an entirely new idea of disturbed gastro-intestinal physiology, and feels that the achlorhydria may be associated with the formation of some substance which, acting on the gastric mucosa,
leads to the inhibition of the secretion and liberation of hydrochloric acid. He injected gastric juice intravenously in dogs with gastric pouches and found that the gastric juice of 89% of pernicious anemia patients caused a transitory marked depression of secretion and achlorhydria. A similar depression occurred due to the gastric juice of only 18% of normal people. While these results appear to be fairly conclusive, I do not believe that the experiments were adequately controlled and there has been no confirmation of the results. Furthermore, there is little application to the clinical case possible.

Some brilliant work on the source of the intrinsic factor has been done by Jacobsen. He notes that argentaffine cells occur in the cardia and pylorus but are practically absent from the corpus of the stomach. He has shown that these cells contain granules which contain a carbohydrate and a purine known as pterine. There is a striking parallelism in the distribution of the argentaffine cells and the localization of the principle active against pernicious anemia in the mucosa of the gastro-intestinal tract. He has also clearly shown that cases of pernicious anemia show almost a complete lack of argentaffine cells. It is his belief that the argentaffine cell plays an important part in normal erythro-
poiesis and he has further shown that the pterines are
erythropoietic in experiments on rats. The argentaffine
cells may carry the active principle or may contain a
substance by means of which the cells can synthesize
the active principle.

By quite extensive work, Dexter\textsuperscript{46} confirmed the
location of the source of the intrinsic factor. He
found that washing removes the hematopoietic activity of
the lower half of the intestine while it has no effect
on the stomach. Mincing before washing did remove the
effect of the duodenum but had no effect on the stomach.
Thus he believes that the hematopoietic activity of the
intestine is due only to passive adsorption of gastric
juice.

Much of the recent work concerning pernicious anemia
has been investigation directed toward determining the
nature of Castle’s extrinsic and intrinsic factors and
the reaction that occurs between the two. Castle\textsuperscript{47}
postulated such a reaction when he said:

"Normal human gastric juice does not
contain on oral administration, an anti-
pernicious anemia principle effective with-
out contact with food (extrinsic) factor."

and
"There is an interaction between beef muscle and human gastric juice which produces from these two completely or relatively inactive constituents some substance capable of causing the appearance of a remission in cases of pernicious anemia." 33

Meulengracht41 has much the same viewpoint as Castle and believes the normal process controlling the development of erythrocytes to be:

1. Extrinsic factor is supplied by food.

2. Intrinsic factor is produced by pyloric glands, i.e., glands located in the pylorus, in the duodenum, and to a lesser extent in the cardiac region of the stomach.

3. These two factors interact in the small intestine forming the ultimate principle.

4. The principle is absorbed - especially via the ileum.

5. The principle is carried to the liver and other organs where it is stored for further use.

In a recent work, Isaacs48 indicates the relationship of constitutional factors to the intrinsic factor which is quite well accepted. With his collaborators, it is his belief that pernicious anemia develops in patients who are born with stomachs which fail to secrete first, hydrochloric acid, then enzymes, and finally the intrinsic factor. They feel that the name, pernicious
anemia, should be reserved for the megaloblastic anemia arising from loss of intrinsic factor in association with a constitutional defect in gastric secretion.

Goldhammer pointed out that Castle's theory that the intrinsic factor is absent in cases of pernicious anemia does not explain, 1. Spontaneous remissions, 2. Variability of blood counts in relapse, and 3. Why pernicious anemia patients can produce any red blood cells during a relapse. He proved that small amounts of intrinsic factor are present in cases of pernicious anemia during relapse, by incubation of their gastric contents with beef muscle which proved effective in producing a mild reticulocytosis. Thus he suggests that the intrinsic factor is deficient in quantity rather than quality and that the rate of hematopoiesis is dependent upon the quantity of intrinsic factor produced.

Since the extrinsic factor is apparently present in many foods (Ungley states it has been found in brewer's yeast, rice polishings, eggs, milk, liver and tomatoes) a relationship to the Vitamins has been considered. Wintrobe made the following studies on yeast:

1. Whether oral yeast regularly causes a hematopoietic effect in pernicious anemia patients;
2. Whether yeast is made more potent by preliminary mixing with gastric juice;

3. Whether the antianemic effect of yeast is dependent on the persistence of the intrinsic factor in the patient;


From his results, he was able to conclude that autolyzed yeast was effective in one-third the cases of pernicious anemia treated and that incubation with normal gastric juice did increase its potency. He could find no relationship between the yeast factor and any of the known vitamins.

Heinle and Miller, investigating yeast, kept in mind the fact that in all cases of pernicious anemia there is a small amount of intrinsic factor present and they felt that the little results they obtained by feeding yeast were due simply to the great excess of extrinsic factor given.

In investigating the intrinsic factor, little has been determined except its physical characteristics. Ungley states that it is readily destroyed by heating to 70 - 80°c. for one half hour and that it is not identifiable as hydrochloric acid, pepsin, pepsinogen, renin, or lipase. Strauss and Castle feel that the
extrinsic factor is definitely associated with the vitamin B complex.

While investigating the extrinsic and intrinsic factors, Greenspan\textsuperscript{53} reached the conclusion that there is no reaction between the extrinsic and intrinsic factor to form a third factor. He feels that the so-called extrinsic factor simply adsorbs pepsin which allows the intrinsic factor to act. His experiments show that pepsin is antagonistic to intrinsic factor. This seems quite illogical to me for if such were the case, pernicious anemia could be caused by a dietary deficiency or by giving an excess of pepsin, and such is not the case.

After the work of Minot and Murphy, it seemed only logical to assume that there is a specific antianemic factor present in the liver. Much work has been done in an attempt to isolate this substance and demonstrate not only its physio-chemical properties but to also discover its mode of action. Cohn\textsuperscript{16} has done much of this work and has demonstrated that the active substance from liver is water soluble but ether and alcohol insoluble, and that it represents about 1\% of the total liver. He has also shown that it contains nitrogen but is non-protein in nature. There has been little more accomplished concerning the chemistry of this substance and
at the present time it can neither be isolated in pure form nor synthesized.

The relationship of the antianemic factor to perni-
cious anemia has been adequately proven and is well put forth by Minot who states:

"The diagnosis of Addisonian pernicious anemia and related macrocytic anemias as occur, for example, with pregnancy, sprue, and celiac disease, is aided by the fact that failure of liver therapy implies an incorrect diagnosis, inadequate treatment or the existence of a complication sufficiently serious in itself to be disastrous for the patient."

Means and Richardson from their experience feel that raw liver, cooked liver, or active fractions of liver in adequate amounts precipitate in practically all cases of pernicious anemia a rapid remission and restoration to an essentially normal status of blood balance and state that:

"The conclusion is inescapable that in liver there occurs a substance quite as specific in its effects as are any of the known vitamins or autacoids, the lack of which in sufficient quantity or form is responsible for most of the manifestations and derangements found in the syndrome called pernicious anemia."

An observation of great significance was made by Ordway and Gorham shortly after the advent of liver
therapy. They noted that liver exerts a specific influence on the development of faulty red blood cells but that it has no effect on the underlying process and hence, cannot be called a cure. This implies naturally, that as insulin in diabetes, liver in pernicious anemia is substitution therapy and must be maintained for the duration of life.

By using in vitro action with stomach and beef, Wilkinson prepared an active protein free product which resembled the liver principle, which is a chemical confirmation of Castle's work. He could not obtain this material when using stomach from a pernicious anemia patient.

The fact that pernicious anemia is also accompanied by a glossitis and by subacute combined degeneration of the cord has made the acceptance of a single specific liver factor seem a bit rash at times. West feels that although it is not yet possible to say whether a lack of a single substance is responsible for both spinal cord and blood involvement, it seems quite probable. Castle and Minot feel that the response of the disease to liver therapy shows it to be a deficiency disease, and that since the neural lesions cease progress with liver therapy they are also probably due to the
same deficiency. In contrast to Hunter's ideas, they feel that the glossitis is not infectious in nature but is also on a deficiency basis. For proof they point to the fact that the glossitis is relieved by only a few days therapy with liver extract.

The idea that pernicious anemia is a deficiency disease is now well accepted, but the method of action of the liver substance is quite controversial. Barker and Hummel have recently revived the toxin theory in a new manner. They suggest that liver principle may be necessary to promote proper detoxification of some chemical compound or compounds which if unneutralized, might give rise to a variety of harmful changes throughout the body. And, they assume that the beneficial action of liver therapy may be due to the ability of the liver principle to detoxify the excess of toxins absorbed from stagnating intestinal contents in subjects with strictures or anastamoses of the small intestine. When applied to Addisonian pernicious anemia it would be assumed that there is a failure of the body to synthesize the detoxifying principle in sufficient amounts to neutralize the toxic substance absorbed from the intestinal tract, when stagnation is not necessarily a factor. In view of the points brought out in the discussion of
erythropoiesis and abnormal blood formation, it is my opinion that this viewpoint need not be seriously considered.

Davidson\textsuperscript{31} points out that a macrocytic anemia may develop in patients with disease of the liver when there is failure of storage or of final synthesis of the antianemic factor in that organ. In cases not responding to parenteral liver therapy he does not believe that a defect in storage can be responsible for the anemia, but feels it possible that the liver may play some role in final elaboration of the antianemic product. Although this is a very recent viewpoint, I believe that one should accept the product of the reaction of Castle's extrinsic and intrinsic factor to be the same as the liver principle until it is proven otherwise, as both have very much the same actions in pernicious anemia.

In a very recent bit of work, Wilkinson\textsuperscript{57} investigated the possibility of the excretion of the antiperanemia principle in urine, hoping that it might be a means of establishing an early diagnosis. He did find an extract in normal urine and in the urine of pernicious anemia patients maintained in remission which was not present in the urine of pernicious anemia patients in relapse. This extract had the ability to
produce a reticulocytosis in a case of pernicious anemia but was present in such high dilutions that there could be little practical application. He does speculate, however, that a low renal threshold for this factor could ultimately cause a deficiency sufficient to cause a megaloblastic anemia, which may help to explain some types of anemias in association with certain renal conditions.

The results of the action of the antianemic principle on the bone marrow are quite well established but the mechanism bringing about these results is quite obscure. Means and Richardson\(^\text{13}\) state:

"The changes that take place subsequent to liver therapy are: first, a brief leukocyte rise, then a marked but also brief reticulocyte rise, and finally a steady climb in the red cell count and hemoglobin to normal levels. There is a tendency for the hemoglobin to lag behind the red count. The speed and intensity of the reaction is related to the dose of the anti-pernicious anemia substance and to the blood level at the beginning of treatment. The reticulocyte peak occurs between the fourth and tenth days, varying between 8% and 56% with an average of 20%. The red blood cell increase average 700,000 per week."

In his work which laid the foundation for the discovery of Minot and Murphy, Whipple\(^\text{11}\) stated that liver feeding is the most potent factor for the continued
production of hemoglobin and red cells in anemia. He explained the action of liver by assuming that the body stores in the liver parent substances which are used in the construction of hemoglobin and red cells. His later viewpoint that the liver principle is necessary for the stroma building of the red cell seems to be borne out by the fact that the red cell count rises more rapidly than the hemoglobin when liver therapy is instituted.

Peabody, from his pathological studies, reached much the same conclusion. He felt that the function of liver used in therapy of pernicious anemia is to provide some factor which affects cell metabolism and promotes the development and differentiation of mature red blood cells. West is of the same opinion and feels that the active liver material causes the megaloblasts to mature and reach the peripheral circulation, first as reticulocytes, and later as normal adult blood cells.

After his shrewd experimental work, Castle pointed out the close relationship in the normal individual between the stomach, liver and bone marrow. He very forcefully brought the belief that the integrity of the stomach is unnecessary to proper body metabolism into question.

It is only natural that the belief in the stroma
building mechanism of the liver principle should be brought into question, particularly by the adherents of the toxic blood destruction theory. Harris believes that the liver substance is probably an endocrine (antihemolysin) which controls the hemolytic action of the reticulo-endothelial system. As stated before, such a theory is quite unlikely in view of the points already discussed concerning blood formation and destruction.

Davidson brings out the point that occasional hyperchromic macrocytic anemias do not respond to liver therapy by any route. This, he feels, may be due to a failure of the bone marrow to utilize the specific antianemic factor, as in the so-called achreastic anemias. The failure of the bone marrow to respond to anti-pernicious anemia therapy may also be due to exhaustion of the bone marrow as in aplastic anemia. Thus another point is established which may be important in the causation of some cases of so-called primary anemias.

With a clear relationship established between the gastro-intestinal tract and the bone marrow in hemopoiesis, it is natural that there has been much speculation that pernicious anemia may be due to dietary deficiencies. This has been particularly true in recent
years which have seen the exploitation of the vitamins. As mentioned previously, Fenwick in 1880, postulated that the gastric atrophy causes defective digestion of the "albuminous material" of the food leading to a condition in which "the various tissues were starved of their nourishment." Recent work, however, has attempted to place the gastric atrophy on a deficiency basis.

Castle has noticed that many pernicious anemia patients give histories of prolonged and peculiar dietary habits, many having a distaste for meat; and also that under conditions in which the diet is kept sparing in meat, milk, eggs and other sources of vitamins, spontaneous remissions seem to have largely disappeared.

Wills and Evans have demonstrated that tropical macrocytic anemia is on a dietary deficiency basis and that it closely resembles pernicious anemia in its blood and bone marrow picture.

It has been well stated by Means and Richardson that pernicious anemia is in some sense a deficiency disease rather than an infectious, toxic or neoplastic one, but that the effect of active liver fraction is not due to any of the known vitamins.

It is the belief of Isaac that in extremely rare instances a macrocytic anemia may arise when there
is a temporary loss of the intrinsic factor, due to prolonged dietary deficiency with chronic gastritis. He feels that this will account for rare cases, which with treatment get a permanent cure with return of hydrochloric acid and intrinsic factor.

Davidson\textsuperscript{31} believes that cases which respond to autolyzed yeast may be cases of macrocytic anemia which develop from a lack of extrinsic factor, which is a dietary substance. These cases, however, have normal gastric acidity and never develop lesions of the central nervous system.

In a rather extensive study of tropical macrocytic anemia which he calls exogenous pernicious anemia, Alsted\textsuperscript{59} suggests that a deficiency of the extrinsic factor causes achylia, and that this in turn results in impaired absorption of the already scantily available extrinsic factor and of the eventually formed antianemic principle. He speculates that "exogenous pernicious anemia" occurs more frequently than believed but that its presence is obscured because liver and stomach preparations are equally effective for the exogenous and endogenous forms.

To establish a reason for loss of the intrinsic factor, Miller and Rhoades\textsuperscript{60} set up the following
hypothesis:

"It is probable that the inflammatory lesions of mucous membranes precede the anemia and achlorhydria and is due to a lack of intake of, or an inability to utilize, some constituent of yeast. Yeast and normal gastric juice in pernicious anemia are helpful. The mucous membrane lesions alter the gastric mucosa so that it is unable to secrete a ferment capable of converting the essential principle of yeast extract into a substance required to effect hematopoiesis."

To prove this hypothesis they fed swine a diet which caused black tongue in dogs. In swine this caused a disease much like pernicious anemia in man. So much so, that they drew the inference that pernicious anemia in man is due to a lack of intake, or utilization of, some poorly defined dietary constituent. These swine were made well with liver extract but the achlorhydria was not changed.

It does appear that there is some relationship of pernicious anemia to food factors, but from the work given, it is apparent that what the nature of this relationship may be is very obscure.
CONCLUSION

I have attempted to make a brief review of the more important literature pertinent to the problem of the etiology of pernicious anemia. It seems to me that the following conclusions are justifiable:

1. The problem of the etiology of pernicious anemia is not solved at this time.

2. It is probable that pernicious anemia is a group of anemias, showing similar blood and bone marrow changes, which may be caused by a number of varying lesions. The group of diseases known as pernicious anemia are decreasing in amount and it is probable that before long there will be no idiopathic or pernicious anemia.

3. The typical Addisonian anemia is probably the result of some, as yet undiscovered, nutritional deficiency, acting in conjunction with a superimposed constitutional or hereditary factor.

To make these conclusions more clear, a summary of the relationships of the stomach, diet, liver, and bone marrow will be given. In the normal individual these factors all unite to produce a substance essential for erythropoiesis.

All but the most deficient diets contain an abundance of extrinsic factor which reacts in some manner with the intrinsic factor elaborated by the gastric mucosa (possibly by the argentaffine cells). The result
of this reaction is a water soluble, non-protein which is known as liver principle or antianemic principle. This substance is absorbed by the gastro-intestinal tract and stored principally in the liver and kidneys. This substance is elaborated into the blood stream as stroma building material is required by the bone marrow for the production of normal erythrocytes.

Thus a macrocytic and megaloblastic anemia may occur:

1. When the bone marrow is unable to utilize the liver principle as in achrethnic and aplastic anemia.

2. When there is liver disease so that the antianemic principle cannot be released into the blood stream as needed by the bone marrow.

3. When there is gastro-intestinal pathology, including surgical gastrectomy, which interferes with the absorption of the antianemic principle or prevents the reaction of the extrinsic and intrinsic factors to form the antianemic principle.

4. When there is a deficiency of the extrinsic factor.

5. When there is a deficiency of the intrinsic factor.

From the study of the literature it appears that number five is the only condition consistently associated with persistent achlorhydria, macrocytosis and megalocytosis.
and is the only macrocytic anemia remaining which may be labelled as primary or pernicious.

It is quite evident that when there is a deficiency of the intrinsic factor without pathological lesions, the achlorhydria is probably the causative factor. From the evidence at hand, it is my belief that an achlorhydria may be on an hereditary and dietary deficiency basis. It will lead to a loss of intrinsic factor, probably through a secondary enzyme, with subsequent development of pernicious anemia in those individuals who have a constitutional and hereditary tendency to develop that disease.

The dietary deficiency which may be responsible for the achlorhydria may be some, as yet unknown, factor of the vitamin B complex.
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