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THE ETIOLOGY OF PERNICIOUS AND RELATED MACROCYTIC ANEMIAS*

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THE student of dietary deficiency disorders is usually concerned with the relationship of defects in the composition of the diet to such diseases. There is, however, evidence that nutritional disturbances may be complicated or actually induced by the presence of sufficient pathological changes in the alimentary tract to interfere with the digestion or assimilation of food adequate for the normal individual. As a result of observations carried out during the past eight years, it is our belief that Addisonian pernicious anemia and certain related macrocytic anemias present examples of such a process and afford an opportunity for the study of a somewhat specialized mechanism which is apparently responsible for the prevention of such anemias in the normal individual. The concept of these anemias as in many instances manifestations of "conditioned" deficiency disease has been developed through studies made in association at various times with Dr. Wilmot C. Townsend, Dr. Clark W. Heath, Dr. Maurice B. Strauss, Dr. Herman A. Lawson and Dr. C. P. Rhoads. Dr. Strauss has been especially concerned with the problems of the macrocytic anemia of pregnancy; and Dr. Rhoads has since made notable contributions to the understanding of the macrocytic anemias, especially of sprue. If the results of the observations, which are summarized below, seem lacking in detail, it is largely because studies carried out in man must be made as opportunity is afforded by the clinical material. On the other hand, in animal experiments there is

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always a possibility that the results may not be directly applicable to the human species.

When this work was begun in 1927, three pertinent facts had been established concerning pernicious anemia. The absence of free hydrochloric acid in the gastric secretion had been shown to be an almost constant finding. The megaloblastic hypertrophy of the bone marrow had been shown by Peabody[1] to be the result of arrested development of the red blood cells with consequent diminished blood production. Minot and Murphy[2] had shown that the administration of liver regularly and promptly caused pronounced improvement of the blood and of the clinical condition of the patients. This fact especially made it a logical conclusion that pernicious anemia was a disease due either to a metabolic defect or in some sense to dietary deficiency.

The etiological significance of the defective gastric secretion had been suggested in 1880 by Fenwick,[3] whose surmise in this respect can scarcely be bettered to-day. He believed that, as a result of the gastric atrophy which he observed post-mortem, defective digestion of the "albuminous material" of the food led to a condition in which "the various tissues were starved of their usual supply of nourishment." Faber[4] and Hurst[5] are especially responsible for the continued interest in the causative rôle of achlorhydria. Hurst believed that it allowed the development of an abnormal type of bacterial flora in the intestinal canal. To us it appeared that the "deficiency" hypothesis of Fenwick was more consistent than the "bacterial" hypothesis with the then recently discovered facts concerning the results of therapy with liver. Because of the possibility of easily observing effects upon blood formation, especially by means of the reticulocyte reaction already employed by Minot and his associates,[6] the problem was attacked directly. It was postulated that "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."

The technique of the observations consisted in the daily administration to suitable patients with Addisonian pernicious anemia of various preparations of normal human gastric juice and beef muscle alone or in combination. A preliminary incubation, entirely unnecessary for the production of the effects observed, rendered the material sufficiently liquid to pass through a small stomach tube. To provide a control inherent in each patient, so far as was possible a first period of ten to fourteen days of the administration of a substance without activity was followed by a second period of similar length during which an effective substance was given. In order to exclude other sources of hematopoietic material than those specifically administered, the patients were maintained on diets containing no meat, liver or kidneys and very little egg, poultry or fish. The incubated mixtures were given to the patients at least six hours after any food had been taken. The results of these observations have been published elsewhere in full[7, 8, 9, 10, 11] and will be only briefly summarized here.

The daily administration of 200 grams of beef muscle as such or after digestion with pepsin and hydrochloric acid was without significant effect. The daily administration of 300 cc of human gastric juice secreted by normal fasting subjects in response to the injection of histamine was likewise ineffective. When normal human gastric juice and beef muscle were given together, however, with or without preliminary incubation at pH 2.5 to 3.5 and subsequent adjustment to pH 5 to 7, reticulocyte responses, increases of the red blood cells and hemoglobin and clinical improvement promptly appeared and continued so long as the material was administered, quite as if moderate amounts of liver were being given. It was therefore evident that the increased blood formation depended upon the interaction of two factors, one in the beef muscle (extrinsic) and one in the normal human gastric juice (intrinsic). It was also clear that in the patient with pernicious anemia the gastric factor was lacking. Attempts were then made to learn something of the properties of these factors and the site and conditions of their interaction.

The gastric factor has not been identified with any known constituent of the normal gastric secretion. It has been shown not to be hydrochloric acid, pepsin, rennin or lipase. It is present in the gastric secretions of certain patients with gastric achlorhydria who either have no anemia or have other types of

[1] F. W. Peabody, *Am. Jour. Path.*, 3: 179–202, 1927.
[2] G. R. Minot and W. P. Murphy, *Jour. Am. Med. Assn.*, 87: 470–476, 1926.
[3] S. Fenwick, "On Atrophy of the Stomach and on the Nervous Affections of the Digestive Organs," J. and A. Churchill, London, 1880.
[4] K. Faber, *Berlin. klin. Wchnschr.*, 1: 958–962, 1913.
[5] A. F. Hurst, *Lancet*, 1: 111–115, 1923.
[6] G. R. Minot, W. P. Murphy and R. P. Stetson, *Am. Jour. Med. Sci.*, 175: 581–599, 1928.
[7] W. B. Castle and E. A. Locke, *Jour. Clin. Invest.*, 6: 2–3, 1928.
[8] W. B. Castle, *Am. Jour. Med. Sci.*, 178: 748–764, 1929.
[9] W. B. Castle and W. C. Townsend, *Am. Jour. Med. Sci.*, 178: 764–777, 1929.
[10] W. B. Castle, W. C. Townsend and C. W. Heath, *Am. Jour. Med. Sci.*, 180: 305–335, 1930.
[11] W. B. Castle, C. W. Heath and M. B. Strauss, *Am. Jour. Med. Sci.*, 182: 741–764, 1931.

anemia than pernicious anemia. It may be absent from the gastric secretion in certain cases of pernicious anemia in the presence of normal amounts of hydrochloric acid and pepsin. The intrinsic factor is not present in normal human saliva or duodenal contents from which gastric juice has been excluded. It is readily destroyed by heat: boiling for five minutes, heating to 70° to 80°C. for half an hour, or to 40°C. for three days.

The food factor has also not been identified. It is present in beef muscle, eggs,[12, 13] autolyzed yeast, rice polishings and wheat germ.[14] Reimann has demonstrated it in liver;[15] and Fouts, Helmer and Zerfas[16] have found it in the liver fraction "G" of Cohn, Minot and their associates.[17] Hydrolysis of this liver extract with dilute sulphuric acid until its active principle for pernicious anemia has been destroyed, does not destroy the extrinsic factor. The substance in autolyzed yeast is capable of resisting autoclaving for five hours at 15 pounds pressure and is soluble in 80 per cent. alcohol. It is not present in leached casein, wheat gluten or in animal or yeast nucleic acid. Because of these properties we[18] suggested in 1932 that the extrinsic factor might be vitamin B_2, employing the term as synonymous with vitamin G. Since then others[19, 20, 21] have been unable to identify it with any portion of the vitamin B complex as defined by growth experiments in animals. Because whole yeast and aqueous extracts of yeast could not be shown to contain extrinsic factor, Wills[19] has suggested that the process of autolysis of yeast is responsible for the production of extrinsic factor.

The precise conditions necessary for the interaction of the food and gastric factors can scarcely be defined, since the site of their interaction is unknown. We have found that no effect takes place unless these substances are administered to the patient at approximately the same time. If a mixture incubated at pH 2.5 to 3.5 is not brought to pH 5 to 7 before administration, then also no effect is observed. These facts suggest, but do not prove, that at least one stage in the process of the formation of the end product active upon the bone marrow takes place in the gastrointestinal tract presumably at or near neutrality. We have attempted to discover the locus of this reaction by determining whether a thermostable product similar to the active principle of liver was formed *in vitro*. Appropriate incubations of beef muscle with normal human gastric juice and also subsequently with normal human duodenal contents at pH 7 do not lead to the production of a thermostable substance similar to that found in liver. Heating to 70° to 80°C. for half an hour or boiling for five minutes invariably destroys the activity of such preparations. Klein and Wilkinson's[22] claim to have synthesized the active principle of liver *in vitro* is not established by their experiments with beef muscle and hog stomach extracts, in which a temperature of only 60° to 70°C. for half an hour was found not to destroy the activity. In order to establish a thermal identity with the active principle of liver it is at least necessary to show that boiling is without destructive effect. It is, however, possible that Klein and Wilkinson have synthesized a precursor of the active principle of liver.

We have approached the problem of the site of interaction of the food and gastric factors by attempting to ascertain whether the parenteral injection of suitable mixtures of each after appropriate incubation leads to increased blood production in pernicious anemia. The results so far obtained have been so variable as not to enable us to answer this question. The chief obstacle is that the parenteral administration of materials containing protein or protein derivatives, though causing reticulocyte responses, is not necessarily associated with consistent increases of red blood cells or clinical improvement. For this reason certain evidence in the literature that the parenteral administration of gastric juice,[23] of preparations of hog stomach[24] and of digests of beef muscle and hog stomach[22] leads to specific effects comparable to those observed with oral administration must be accepted with caution. Fouts, Helmer and Zerfas[16] have shown that the reticulocytogenic substance in concentrated gastric juice[23] is not present until the material has been subjected to incubation. Wilkinson has shown that very large amounts of normal human gastric juice administered by mouth are ineffective in pernicious anemia. Experiments with orally administered substances do not support the idea that intrinsic factor is effective without inter-

[12] K. Singer, *Wien. klin. Wchnschr.*, 45: 1063, 1064, 1932.

[13] D. K. Miller and C. P. Rhoads, *New Eng. Jour. Med.*, 211: 921–924, 1934.

[14] W. B. Castle, *Ann. Int. Med.*, 7: 1–5, 1933.

[15] F. Reimann, *Med. Klin.*, 27: 880–881, 1931.

[16] P. J. Fouts, O. M. Helmer and L. G. Zerfas, *Am. Jour. Med. Sci.*, 187: 36–50, 1934.

[17] E. J. Cohn, G. R. Minot, G. A. Alles and W. T. Salter, *Jour. Biol. Chem.*, 77: 325–358, 1928.

[18] M. B. Strauss and W. B. Castle, *New Eng. Jour. Med.*, 207: 55–59, 1932.

[19] L. Wills, *Lancet*, 1: 1283–1286, 1933.

[20] H. C. A. Lassen and H. K. Lassen, *Am. Jour. Med. Sci.*, 188: 461–472, 1934.

[21] F. Diehl and J. Kühnau, *Deutsch. Arch. f. klin. Med.*, 176: 149–153, 1933.

[22] L. Klein and J. F. Wilkinson, *Biochem. Jour.*, 28: 1684–1692, 1934.

[23] R. S. Morris, L. Schiff, J. H. Foulger, M. L. Rich and J. E. Sherman, *Jour. Am. Med. Assn.*, 100: 171–173, 1933.

[24] W. Ederle, H. Kriech and M. Gänsslen, *Klin. Wchnschr.*, 10: 313, 1931.

action with extrinsic factor, although they do not exclude the possibility that this reaction may take place parenterally.

As a result of these observations, it is believed that a physiological mechanism exists in the normal individual which is usually absent in the patient with Addisonian pernicious anemia in relapse. Both the food and the stomach are involved in this process, which will obviously be initiated in the normal individual whenever extrinsic factor is taken in the food. It is logical to conclude that the integrity of this mechanism prevents the development of pernicious anemia in the normal individual; and that its absence leads to a deficiency of the active principle of liver and so to pernicious anemia. It is, however, evident that a deficiency of the active principle finally effective in the body might be brought about by at least three different types of derangement of this mechanism in the gastrointestinal tract.[11] A lack of intrinsic factor in the stomach, a lack of extrinsic factor in the food or a failure of the absorption or the destruction of these substances or their end product in the intestinal tract would have the same result. It is, moreover, possible for the participation of each of these derangements to be variable in different patients and at different times in the same individual. Furthermore, an interruption or inhibition within the body of any link in the chain of chemical events leading to the production of the end product active in the bone marrow would also have a similar effect. For the last supposition there is no detailed evidence at present except the variations in the effect of the parenteral administration of a given amount of the same liver extract in different patients with pernicious anemia; and the fact that arteriosclerosis and infections appear to be common in patients responding poorly to parenterally administered liver extract. The evidence that disease of the liver may specifically produce an interruption in the metabolism of the active principle of liver has not been convincingly established. The arguments in favor of such a supposition neglect the fact that the animal kidney is as effective a source of the active principle of liver as is that organ itself. Although much has been learned concerning the nature of the active substance in liver, especially through the work of Cohn[25] and West[26] and their respective associates, its precise nature remains unknown.

Deficiency of the gastric factor is apparently the dominant mechanism in Addisonian pernicious anemia in relapse. It is probable, however, that the gastric defect is relative rather than absolute. We[11] have demonstrated the recrudescence of gastric factor in one patient after treatment with liver extract. Such was also apparently the case in the patients observed by Barnett.[27] This observation probably explains the response of occasional patients with pernicious anemia to the oral administration of extrinsic factor, especially of autolyzed yeast in large amounts. Ungley and James[28] have recently shown that in such patients autolyzed yeast preparations are not effective when administered parenterally.

Sprue with macrocytic anemia, on the other hand, has been successfully treated by Elders,[29] Ashford[30] and others in some instances with diets rich in animal protein, and recently autolyzed yeast[31] has been found to be effective in some patients. Wills[32] has observed excellent results in the treatment of the macrocytic anemia of pregnancy in India with autolyzed yeast; and Vaughan and Hunter[33] have demonstrated reticulocyte responses and improvement of the blood values in the macrocytic anemia of idiopathic steatorrhea following the administration of autolyzed yeast. The fact that hydrochloric acid is often present in the gastric contents of such patients suggests that intrinsic factor was also present in sufficient amounts to interact with these sources of extrinsic factor. Although in certain cases of sprue intrinsic factor has been shown to be lacking,[31] the prevalence of defective diets in both sprue and the macrocytic anemia of pregnancy in India suggests that extrinsic factor defect is etiologically important.

In any of these types of macrocytic anemia defects of absorption apparently may be present and contribute to a deficiency of the active end product. In certain cases of pernicious anemia[11] and especially in advanced cases of sprue[31, 34] very large doses of liver extract are not effective when given by mouth. The fact that usual doses of parenterally administered liver extract are sometimes found to be normally effective suggests, but does not necessarily prove, that the orally administered material is not being adequately absorbed, because it is also known that the responses of different patients with pernicious anemia to the parenteral administration of the same amount of active principle vary considerably. Until it is known what are exactly comparable doses of a single

[25] E. J. Cohn, T. L. McMeekin and G. R. Minot, *Tr. Assn. Am. Phys.*, 45: 343–349, 1930.

[26] H. D. Dakin and R. West, *Jour. Biol. Chem.*, 109: 489–522, 1935.

[27] C. W. Barnett, *Am. Jour. Med. Sci.*, 182: 170–177, 1931.

[28] C. C. Ungley and G. V. James, *Quart. Jour. Med.*, 27: 523–548, 1934.

[29] C. Elders, *Lancet*, 1: 75–77, 1925.

[30] B. K. Ashford, *Ann. Clin. Med.*, 4: 13–20, 1925.

[31] W. B. Castle and C. P. Rhoads, *Lancet*, 1: 1198–1199, 1932.

[32] L. Wills, *Brit. Med. Jour.*, 1: 1059–1064, 1931.

[33] J. M. Vaughan and D. Hunter, *Lancet*, 1: 829–834, 1932.

[34] C. P. Rhoads and D. K. Miller, *Jour. Am. Med. Assn.*, 103: 387–391, 1934.

source of liver extract which can be given both orally and parenterally, it is impossible to come to a final conclusion. The clinical association of pernicious anemia with intestinal short circuits and stenoses and the morphological changes sometimes observed in the intestinal wall make the supposition of intestinal impermeability very likely. In the usual case of pernicious anemia the effectiveness of parenterally administered material appears to be at least sixty times as great as when given by the oral route. Whether this is entirely a physiological difference or whether it represents pathological changes in intestinal absorption is at present unknown.

It can also be demonstrated that the same participation of factors for the production of macrocytic anemia may not exist in a given patient at all times.[14] The fact that before the introduction of liver therapy it was often possible in the early stages of the disease to produce temporary remissions in patients with pernicious anemia by the use of high caloric diets rich in meat suggests that some intrinsic factor was still present. This is apparently much more frequently the case in early cases of sprue. The recrudescence of intrinsic factor has been demonstrated in a patient with pernicious anemia who originally secreted free hydrochloric acid without intrinsic factor in the gastric juice.[11] In the pernicious anemia of pregnancy, at least in some instances, the administration of extrinsic factor before delivery may produce no effect upon blood formation. After delivery, however, this material may induce clinical improvement and a reticulocyte response, which may then be augmented when normal gastric juice is added.[35] The disappearance of the intrinsic factor of the gastric juice during pregnancy is occasionally paralleled by the disappearance of the hydrochloric acid, which likewise may return after the birth of the child.

Objection may be raised to the hypothesis which we have developed on the basis that *total* extirpation of the stomach in man is not necessarily followed by the development of pernicious anemia even after several years. There are several reasons which render this criticism not necessarily valid. In the first place, the store of active principle in the liver, kidneys and other organs may be sufficient to prevent the anemia for some time. The parenteral injection at appropriate intervals of material derived from an amount of animal liver equivalent to the weight of that organ in man will suffice to maintain a patient with pernicious anemia in health for at least a year. Moreover, with surgical ablation of the stomach intestinal permeability is not necessarily affected, as is probable in the spontaneously developing disease. Since the liver, kidney and brain of normal animals have been shown to contain the active principle, it is possible that animal tissues more commonly consumed than these also contain smaller amounts of the same substance which might be readily absorbed from the normal intestine. Another explanation is provided by the studies of Meulengracht,[36] who has recently produced evidence that the active principle of hog stomach, the therapeutic value of which was first demonstrated by Sturgis and Isaacs,[37] is present largely in the pyloric region, where glands of a type closely resembling those of the duodenum of both man and the hog are found. Meulengracht has also shown that at least the upper portion of the hog's duodenum, like the pyloric region of the stomach, can be successfully used in the treatment of pernicious anemia. This observation suggests that surgical ablation of the entire stomach would still leave a source of intrinsic factor in the duodenum.

In 1921 McCarrison[38] published the results of experiments on deficiency disease in animals, which in the light of our observations appear to be even more significant than at the time of their publication. Whatever the difficulty of ascertaining the exact nature of the dietary defects or the influence of secondary infection in these experiments, it is clear that McCarrison was able to produce profound and wide-spread pathological changes in the alimentary tract. He noted degenerative changes in the secretory cells of the stomach and intestines and inferred that dietary deficiency causing alteration of the alimentary tract might result in secondary defects of nutrition. It is our belief that, when fully developed, Addisonian pernicious anemia is a deficiency disease conditioned, not so much by defective diet as by defects in the gastrointestinal tract. McCarrison's experiments, however, suggest a possible explanation for the original changes in the alimentary tract.

Recent observations by Miller and Rhoads[39] also tend to indicate the importance of McCarrison's observations, at least in respect to types of macrocytic anemia occurring in regions where defective nutrition is common. By the use of diets presumably defective in vitamin B_2 (G) or some closely related substance, these authors have been able to produce in swine a chronic condition analogous to black tongue in the dog studied by Goldberger and his associates. Their animals developed in many instances stomatitis,

[35] M. B. Strauss and W. B. Castle, *Am. Jour. Med. Sci.*, 185: 539–551, 1933.

[36] E. Meulengracht, *Acta med. Scandinav.*, 85: 79–88, 1935; *Proc. Roy. Soc. Med.*, 28: 841–870, 1935.

[37] C. C. Sturgis and R. Isaacs, *Jour. Am. Med. Assn.*, 93: 747–749, 1929.

[38] R. McCarrison, "Studies in Deficiency Disease," Henry Frowde and Hodder and Stoughton, London, 1921.

[39] D. K. Miller and C. P. Rhoads, *Jour. Clin. Invest.*, 14: 153–172, 1935.

gastric anacidity and macrocytic anemia responding to the administration of extracts of liver known to be effective in pernicious anemia. Of greatest immediate importance, however, is their observation that the intrinsic factor disappeared from the gastric juice of certain affected animals and that their livers were shown no longer to contain the thermostable principle effective in pernicious anemia. Here, then, is evidence that by a type of dietary deficiency the essential gastric defect of pernicious anemia has been produced. Although it is probable that defective diets are not the sole cause of such changes in Addisonian pernicious anemia, defective diets are very common in related types of macrocytic anemia such as occur in sprue and in pregnancy in certain parts of India. The facts disclosed by Miller and Rhoads must nevertheless be taken into account in any consideration of the possible original causes of the changes of the gastric secretion in Addisonian pernicious anemia. Even in this disease, aversion to meat was described by Fenwick[3] in 1880 and other peculiarities of the diet are often noted. Lindgren[40] has recently found that gastric anacidity in the general population is unusually common in Sweden in regions in which diets low in meat, vegetables and fruit and high in starchy foods are prevalent. It is hoped that students of nutritional deficiency may recognize that for an adequate explanation of the manifestations of deficiency disease in man the effects of dietary deficiency upon the gastrointestinal tract are worthy of further study.

SCIENTIFIC EVENTS

COURSES IN GAME MANAGEMENT AT THE STATE UNIVERSITIES

COURSES in game management, to be set up in the several state universities, will have the active support of the Bureau of Biological Survey, which is prepared to supply instructors and to cooperate with the universities and with state game commissions in financing the new development.

J. N. Darling, chief of the bureau, in announcing this new policy, stated that one of the leading American manufacturers of arms and ammunition has agreed to contribute $30,000 a year for the purpose. The Biological Survey will be able to supply $42,000. The game commissions and universities also will share in the expense.

Research work in wild-life subjects as well as in teaching the application of methods of modern game management will be included in the courses. Many universities now have important schools of forestry and it is anticipated that the new educational service in game management will follow similar lines.

Several schools and state game commissions are ready to proceed with the inauguration of courses in game management. The Biological Survey has men competent to direct the work. The courses will be designed to fit students with practical and scientific knowledge in game management and to turn out graduates equipped to do work in the restoration of valuable forms of wild life.

Mr. Darling points out that for years colleges and universities have been training foresters and park-planning engineers and developing specialists in the use and preservation of many of our natural resources, but nowhere are there facilities to prepare young men for the equally important task of administering the supply of wild birds, animals and fishes. As a result of this neglect there are few men who have the scientific and technical qualifications necessary to enable them to deal with the steady decrease in our wild life. by applying the known principles of game restoration.

Under this new policy the Biological Survey will supply institutions with technically trained instructors who will make available to students, farmers, landowners and sportsmen the results of experimental work conducted by the wild-life agencies of state and federal governments and by conservation organizations. These units under the direction of the Bureau of Biological Survey will do away with this duplication of effort.

THE LEVERHULME FELLOWSHIPS AND AWARDS FOR RESEARCH

AWARDS of Leverhulme Research Fellowships in 1935 and grants to research workers are announced by the Advisory Committee and are given below. The Advisory Committee have recommended and the trustees have approved 20 nominations to fellowships and seven grants in aid of research, tenable for varying periods up to two years.

The names of the fellows and the subjects of the researches in the sciences are as follows:

W. N. BAILEY, M.A., D.Sc., senior lecturer in mathematics, University of Manchester.—"The Study of Functions of Hypergeometric Type."

D. B. BLACKLOCK, M.D., D.P.H., professor of tropical Medicine, University of Liverpool.—"A Study of the Present Practise of Hygiene (including Rural Hygiene) in Certain Eastern Countries."

MRS. M. G. BLACKLOCK, B.Sc., M.B., B.Ch., curator of the museum, Liverpool School of Tropical Medicine.—"A Comparative Study of the Organizations for the Improvement of Health of Women and Children in Eastern Countries."

[40] S. Lindgren, *Acta med. Scandinav.*, Suppl. 48: 1–235, 1932.