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Achlorhydria and Anæmia.

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THE treatment of pernicious anæmia by liver is one of those instances not infrequent in medicine in which a method is worked out by scientific reasoning and it is afterwards realized that the discovery was little more than a happy accident and that some other explanation must be sought for the success obtained. Minot and Murphy based this treatment of pernicious anæmia on experiments by Whipple, which had shown the value of substances rich in hæmoglobin constituents, such as heart muscle, liver and kidney, in the treatment of hæmorrhagic anæmia in animals. The preparation of liver extracts which are curative in pernicious anæmia and relatively ineffective in other forms of anæmia suggests that liver acts rather by supplying a specific substance which corrects the disordered blood formation in pernicious anæmia and ensures the orderly maturation of the red cells. Castle has recently devised experiments which go far to provide a satisfactory explanation of the treatment and link it with previous knowledge.

It is well known that achlorhydria is a constant symptom of pernicious anæmia, and it appears from Castle's work that this is the essential etiological factor in the disease. In brief, his experiments are as follows. If beefsteak is given to a patient with pernicious anæmia no improvement follows. If artificial gastric juice is given to patients with pernicious anæmia no improvement follows. But if beefsteak is

allowed to digest for an hour in the stomach of a normal man and the mixture is then syphoned off and given to the patient with pernicious anæmia, improvement occurs in the same way as with liver therapy, reticulocytes are poured out and the blood returns to normal. Clearly something has been formed in the digestion of the beef protein in the healthy stomach which the patient with pernicious anæmia and achlorhydria is unable to form and which is necessary for blood formation. It is probable that this unknown substance is stored in the liver and kidneys and is obtained in a concentrated form in the extracts of these organs. The etiological significance of achlorhydria is confirmed by the relative frequency of pernicious anæmia in patients who have had the stomach completely removed and have survived the operation for any length of time. Of great interest also is a patient who was under the care of Dr. Hurst at Guy's Hospital, perhaps the only instance of complete recovery from pernicious anæmia :—

This man developed gastritis with achlorhydria as the result of a gastro-intestinal infection. Pernicious anæmia set in some time afterwards, the diagnosis being confirmed by a Price-Jones curve which showed the characteristic increase in diameter of the red cells. He was treated for some time with transfusions, removal of septic foci, hydrochloric acid and arsenic, with moderate success. Later he made a very great improvement and a fractional test meal showed the reappearance of hydrochloric acid in the stomach in normal concentration. He has now been for some years without any treatment and has remained in perfect health.

Pernicious anæmia, then, may be considered to be due to defective assimilation of food in the absence of normal gastric juice and it may be compared with other deficiency diseases, especially sprue and pellagra. In sprue there occur glossitis, a megalocytic anæmia and frequently achlorhydria. In pellagra, glossitis, anæmia and in advanced cases achlorhydria and sub-acute combined degeneration of the spinal cord. In the present paper I wish to describe two other types

of anæmia which are associated with achlorhydria, which are not uncommon, and which present such clear-cut clinical features that they deserve to be better known than they are at present. Knud Faber, in an analysis of 207 cases of achylia gastrica, found 22 cases of pernicious anæmia, and 22 cases of non-pernicious anæmia with a hæmoglobin less than 65 per cent. In my experience simple achlorhydric anæmia is much more common than pernicious anæmia. The disease is not recognized and the patients are not admitted to hospital.

I have already commented on the occurrence of pernicious anæmia after gastrectomy and reference must now be made to the frequency of severe secondary anæmia after gastro-enterostomy. The hæmoglobin value in patients who have been submitted to this operation is nearly always below normal, and in many cases the anæmia is severe. The following case is a typical example of achlorhydric anæmia resulting from gastro-enterostomy. In this woman the anæmia was so severe that she suffered anginal pain on exertion from the anoxæmia of the heart muscle. This is a well-known symptom of pernicious anæmia but it does not commonly occur in simple anæmia.

A woman aged 42 complained of gripping pain around the chest which came on during exertion. She had had a gastric ulcer excised twelve years previously and gastro-enterostomy was performed for recurrence of symptoms a year later. She had never been really fit since this and had suffered from frequent attacks of vomiting. For the last two or three years she had been very anæmic and had to go to bed for long periods on account of the distress produced by exertion. There was obvious pallor of the face and the visible mucous membranes. Her finger nails were depressed and spoon-shaped. The tongue was very smooth and showed no papillæ, and she complained that it often became ulcerated round the edges. The pulse was accelerated and of a water-hammer character, but the heart was normal except for a soft blowing murmur at the mitral area. The spleen was not palpable and there were no changes in the central nervous system. A fractional test meal showed complete achlorhydria. There was no evidence of active peptic ulcer: the occult blood test on the fæces was negative, and X-ray examination

showed that the food left the stomach through the stoma. The blood count was : red blood cells, 2,370,000; white blood cells, 3,100; hæmoglobin, 24 per cent.; colour index 0.5; Hijmans van den Bergh's reaction was negative. She was treated with dilute hydrochloric acid and large doses of iron and ammonium citrate, and at the end of two months her hæmoglobin had risen to 80 per cent. and the anginal pain on exertion had disappeared. As she is still subject to attacks of vomiting, it is proposed to undo the gastro-enterostomy after convalescence, and in this way to relieve both the digestive disturbance and the anæmia.

Achlorhydria may be congenital, it may be produced by operation, or it may result from gastritis. It becomes increasingly common with advancing years. On this account simple achlorhydric anæmia is a disease of middle and later life. Women are affected more often than men and the first symptoms may arise during pregnancy or lactation. The disease is extremely chronic and shows no tendency to spontaneous recovery. Medical advice is usually sought for symptoms referable to the anæmia—pallor, undue fatigue, palpitations, œdema—and many of the patients have been living lives of invalidism for years. Death may occur.

The pallor is often striking. It has not the lemon yellow tinge of pernicious anæmia and the van den Bergh reaction is negative. The nails are often spoon-shaped (koilonychia). This seems to be a direct result of the anæmia as the nails regain the normal convex shape when this is repaired. The tongue is smooth and devoid of papillæ and in every way resembles the tongue of pernicious anæmia. Many patients have had all their teeth extracted without improvement in the glossitis or the anæmia. I have also seen patients improve on treatment with diet and iron, although infected teeth were still present. Not all cases have a glossitis, and I do not think oral sepsis is a causative factor in the anæmia or the glossitis, though it is advisable to remove infected teeth. Achlorhydria or extreme hypochlorhydria is present in all cases, and careful inquiry usually elicits a history of dyspepsia or

attacks of diarrhœa. There may be paræsthesia of the hands and feet. The spleen is sometimes enlarged, but not to an extreme degree. The blood shows a secondary anæmia with a low colour index, hæmoglobin being disproportionately reduced and the average diameter of the red cells being diminished. White cells and platelets are normal. In one of my patients, who died after a transfusion, there was red marrow throughout the femur, and other observers have obtained erythroblastic marrow on puncture of the sternum. It is clear from these findings that there is no aplasia of the bone marrow. But the bone marrow reaction is not as marked as in pernicious anæmia, and in three recent cases, in which I punctured the upper third of the tibia, I obtained only fatty marrow.

At present we are working on the hypothesis that iron is not properly absorbed in the absence of gastric juice. Iron is a specific remedy for the disease. It is prescribed as iron and ammonium citrate in a simple mixture with glycerine and peppermint water. The dose is increased to 30 or 40 grs. thrice daily after meals. When I adhered to the ordinary pharmacopœial doses I had many failures, but all respond to the higher dosage. I have never seen any intolerance to iron and ammonium citrate, and I would not hesitate to use larger amounts if necessary. There are many elegant preparations of iron on the market which contain far too little of the element and are very expensive. I should also advise against injecting iron as I do not think full doses can safely be given in this way. There is abundant experimental and clinical evidence of the superiority of soluble preparations of iron such as iron and ammonium citrate given in large amounts by mouth. Arsenic is not indicated and transfusions should only be used in emergency. Liver extract has no effect, but substances rich in iron such as whole liver, kidneys and green vegetables should be included

in the diet. Dilute hydrochloric acid should also be given, a half to one and a half drachms being diluted in a tumblerful of water and sipped during the meal; it can be flavoured with sugar and fruit juice if preferred. Treatment must be continued indefinitely or relapse occurs. The following case illustrates the usual response to treatment :—

A man aged 65 was admitted to Guy's Hospital with the complaint of general weakness and gnawing pain in the abdomen. He was extremely pale and ill and a provisional diagnosis of carcinoma of the stomach was made. He had been ill for about eighteen months. The pains were localized vaguely in the epigastric region and were not related to meals. He had not vomited. He had been in India over forty years before and had been treated there for enlargement of the liver. At 30 years of age he had had a hæmatemesis. For the last ten years he had been short of breath on exertion. His pulse was irregular and an electro-cardiogram showed that this was due to a slow fibrillation. There were some infected teeth but the tongue was normal and general physical examination was otherwise negative. X-ray examination showed no lesion of the stomach or duodenum and the test for occult blood in the fæces was negative. A fractional test meal showed extreme hypochlorhydria, free acid being present only in the last samples. The blood count was : Red blood cells, 2,800,000 ; white blood cells, 5,100 ; hæmoglobin, 32 per cent. ; colour index, 0·57 ; the differential white count was normal ; van den Bergh's reaction was negative. He was treated for two months with hydrochloric acid and iron and ammonium citrate. At the end of that time his general condition had improved out of all recognition and the hæmoglobin had risen to 85 per cent.

Simple achlorhydric anæmia should only be diagnosed after careful exclusion of organic disease or hæmorrhage. The cardinal symptoms are a chlorotic type of anæmia, glossitis, koilonychia, occasional splenomegaly, and achlorhydria or extreme hypochlorhydria. In pernicious anæmia the blood picture is quite different. In aplastic anæmia the gastric secretion may be normal, there is a high colour index, white cells and platelets are much diminished, and there is a tendency to hæmorrhage and necrotic ulceration. Enlargement of the spleen may suggest splenic anæmia, but achlorhydria and the absence of signs of cirrhosis of the liver would render trial of treatment by iron advisable. Malignant disease of the

stomach or intestin so often presents itself in the guise of an obscure anæmia that it must always be carefully considered. The fæces should be examined for occult blood, and if the test is negative malignant disease can be ruled out. Great difficulty is sometimes experienced with women in whom achlorhydria and anæmia are associated with excessive menstrual loss. In these cases I recommend examination by the gynæcologist, and if he finds no local lesion I assume that the bleeding is the result of anæmia and loss of tone in the uterus. If it persists, treatment by radium may be advisable. The diagnosis from chlorosis is of little practical importance as both diseases are cured by iron; chlorosis occurs only in females at puberty or in adolescence, and the gastric secretion is normal or hyper-acid.

The second form of simple anæmia with achlorhydria is known as the Plummer-Vinson syndrome, or dysphagia and anæmia. The occurence of paræsthesia of the pharynx in women about the menopause has long been recognized but its association with anæmia is of more recent discovery. A few cases occur in men, and the disease has also been described in children, but the great majority of the cases are women between the ages of 40 and 50. There is a history of dysphagia, often going back for many years. Sometimes the onset is sudden and referred to a special occasion, such as a choking attack or tonsillectomy or extraction of teeth. In other patients the difficulty develops slowly and insidiously. In the majority dysphagia precedes the anæmia for years, but pallor may be the first symptom. The diet is progressively restricted, meat and vegetables usually being given up entirely and the food confined to tea and slops of carbohydrate food. Meal times are interminably protracted, and every mouthful is chewed for several minutes before swallowing is attempted. In one of my patients the neck between the lower jaw and the larynx swelled visibly

at meal times owing to the accumulation of unswallowed food.

The anæmia is sometimes not very obvious, but in other patients there is extreme pallor. The lips are pale and fissured at the corners, the tongue is smooth and pale, its papillæ atrophic. Most of the patients seen are edentulous, the teeth having been removed as a possible source of the stomatitis and dysphagia. The pillars of the fauces are pale and glossy and the mucous membrane of the pharynx is atrophic. "On direct examination with the œsophagoscope the same thin pale appearance of the mucosa is seen, flecked with white sticky patches of mucus. Sometimes the lumen of the gullet may appear greatly reduced by a thin membranous web, or tense bands of raised, thinned mucosa may pass in various directions. Occasionally there may be complete absence of the sphincter-like appearance found in the deep part of the normal hypopharynx. In other cases a tonic contraction at the commencement of the gullet is found, making difficult the passing of the tube" (Jones and Owen). Histological examination has revealed degeneration of Auerbach's plexus and the dysphagia seems to be due to a disorder of the neuro-muscular mechanism similar to that which occurs in cardiospasm. In some patients cardiospasm also is present. The anæmia is of the secondary type, the average red cell count being about 4,000,000, hæmoglobin 50 per cent. The white cells and platelets are unaffected. In about one quarter of the cases the spleen is enlarged. The fractional test meal reveals a complete achlorhydria in the great majority of the cases. Dyspeptic symptoms such as diarrhœa probably depend on this. Paræsthesia of the hands and feet also occurs. The mental state is often very abnormal and a large percentage of the patients leave hospital before treatment can be completed on account of their groundless fears. One is reminded of

the paranoid symptoms of pernicious anæmia.

The disease seems to continue indefinitely unless appropriately treated. Two very serious complications may follow—malignant disease and pernicious anæmia. Carcinoma of the hypopharynx is not uncommon in middle-aged women. There is evidence that some of these cases are preceded by the Plummer-Vinson syndrome, the chronic inflammation encouraging the development of malignant disease. On this account simple dysphagia and anæmia should never be diagnosed without careful examination of the hypopharynx. Dysphagia is not one of the symptoms of pernicious anæmia, but Mason Jones and Owen recently described a woman who had dysphagia and pernicious anæmia. The changes in the pharynx were identical with those of the Plummer-Vinson syndrome. She had had dysphagia for some years before pernicious anæmia developed, and it seemed likely that this was a late complication.

The mode of origin of the symptoms is not certain. There is little to support Hurst's suggestion that they are due to streptococcal infection. No improvement follows removal of teeth, tonsils, or other septic foci, and though streptococci can be isolated from the mouth—as they can be in healthy subjects—they are not agglutinated by the blood serum of the patient. More probably it is a dietetic or deficiency disease. Some cases begin as a hysterical dysphagia, and as a result of the restriction of diet, stomatitis, pharyngitis, anæmia and impairment of gastric secretion subsequently follow. In other cases achlorhydria leads to defective food absorption, as a consequence of which anæmia, stomatitis and pharyngitis with dysphagia occur. In either event a vicious circle is established, the restricted diet leading to pharyngitis and dysphagia, and the dysphagia encouraging further restriction of diet. Treatment is fortunately simple and effective.

The œsophagoscope or a large bougie is passed through the upper aperture of the œsophagus, and after one or two passages the patient swallows freely. A full diet containing beef, liver, kidneys and green vegetables can then be taken and iron and hydrochloric acid are also prescribed. The anæmia is rapidly repaired, stomatitis becomes quiescent and splenomegaly disappears. Occasionally symptoms recur. The bougie is then passed again and if necessary the operation is repeated at intervals of a few months.

There are still many gaps in our knowledge of the rôle of achlorhydria in the production of anæmia. It is difficult to understand why all patients with achlorhydria are not anæmic and why some develop pernicious and others simple anæmia. Efforts to treat pernicious anæmia by giving an artificial gastric juice have hitherto been unsuccessful and it seems that there is some other factor besides hydrochloric acid and pepsin. Much work also remains to be done in linking these anæmias associated with achlorhydria with the anæmias of dietetic deficiency, and in ascertaining the importance of both these factors in the anæmia of pregnancy. Nevertheless, the recognition of achlorhydria as an etiological factor in anæmia and the discovery of successful treatments for those forms of anæmia associated with it are very considerable advances of knowledge.

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