death, may perhaps be avoided by a drachm or a drachm and a half made up into a lemonade and sipped with each meal. Perhaps liver should be given also, even in the pre-anaemic stage. Hydrochloric acid should be given permanently. Liver feeding is, however, the main treatment.

Minot and Murphy's special diet is one which is rich in proteins and food iron, especially in the liver. In addition to this they recommend fresh fruits and vegetables, while reducing carbohydrates and fats. Fats were reduced because unsaturated fatty acids are haemolytic. (Authorities, however, do not agree that there is an excess of unsaturated fatty acids in the blood in pernicious anaemia.) Following the use of this diet some very remarkable events have been noted. In a few days after its commencement reticulocytes are poured into the blood stream. Their number goes up from 1 per cent. to 10 or 15 per cent., and remains so for a few days, and then gradually falls, so that the number reaches 1 per cent. again in about three weeks. We saw that reticulocytes are immature red cells. This phenomenon is called "the reticulocyte bump." It appears to be a constant result of liver feeding. It does not occur in the natural remissions of the disease, or after any other known method of treatment. Liver therapy appears, therefore, to exert some very definite and specific action on the blood-forming functions of the marrow.

PERNICIOUS ANAEMIA, WITH FREE HYDROCHLORIC ACID IN GASTRIC CONTENTS: DUODENAL ULCER: PERFORATION: OPERATION: RECOVERY.

BY

STANLEY DAVIDSON, B.A.CAMB., M.D., CH.B.,
F.R.C.P.ED.,

ASSISTANT PHYSICIAN, ROYAL INFIRMARY, EDINBURGH; RESEARCH
WORKER, MEDICAL RESEARCH COUNCIL, BACTERIOLOGICAL
DEPARTMENT, UNIVERSITY OF EDINBURGH.

THE complete absence of hydrochloric acid in the gastric contents of cases of pernicious anaemia is a finding which has been so constantly reported in every country in the world that it is now recognized to be a cardinal sign of the disease. The achlorhydria, moreover, is functional, and is not the result of pre-existing gastritis, and has been found to be present in every case examined previous to the onset of symptoms. It is uninfluenced by the phases of remission or relapse or by any method of treatment. The constitutional or hereditary factor in the disease is shown not only by the facts stated above, but also from our knowledge that blood relations of cases of pernicious anaemia are often achlorhydric even when young children. The absence of hydrochloric acid automatically stops gastric digestion, as free acid is necessary for the activation of pepsin. Gastric digestion, however, is of relatively small importance, because the digestive juices of the pancreas and small intestine are ample for the purpose of breaking down the sugars, fats, and proteins of foodstuffs to the simple molecular form in which they are absorbed. On the other hand, achlorhydria is held by many workers to be of great importance in pernicious anaemia because of the resulting altered biochemical reaction of the gastrointestinal contents. Whereas the stomach and upper levels of the small intestine are, in normal individuals, practically or actually free from pathogenic bacteria, in pernicious anaemia sepsis from above and ascension of organisms from below render the gastro-duodenal flora similar to that found in the lower ileum or colon. While I am satisfied that no specific causal agent for pernicious anaemia exists, and particularly that haemolytic organisms are of no etiological importance, I feel that if the absorption of toxins, bacterial or metabolic, does not take place in these circumstances it is impossible to conceive that it ever does. Lastly, the recent work of Castle,⁵ if confirmed, is worthy of consideration. He found that if beefsteak, previously digested in a normal person's stomach, is given in suitable amounts to a case of pernicious anaemia, a typical reticulocyte response could be obtained, although beefsteak itself, the gastric juices alone, or beefsteak artificially

digested, failed to do so. This would point to pernicious anaemia patients' stomachs being deficient in some property which enabled them to utilize or manufacture the specific blood hormone from animal protein.

For the above reasons it is right that achlorhydria should be held to be a cardinal sign in pernicious anaemia, and I have consistently taught that the finding of free hydrochloric acid definitely excludes the diagnosis of pernicious anaemia. This teaching was based on bacteriological and biochemical investigation of 50 cases of pernicious anaemia before, during, and after treatment. The following case, therefore, appears to me to warrant publication.

The patient, a factory labourer aged 34, gave a history of having had influenza in 1918. In 1919 he suffered from pain in the stomach, which was diagnosed by his doctor as chronic indigestion. The pain was dull in character and constantly present. It was not relieved by or related to food. He had no vomiting. He was constipated. The attacks lasted some weeks and continued on and off for over two years, when he was admitted to the Royal Infirmary, Edinburgh. After five weeks' stay in hospital his symptoms were relieved and he remained well for eighteen months.

In 1925 the pain returned and was much more severe; it was only relieved by morphine. He was admitted to Ward 31, Royal Infirmary, Edinburgh. The test meal examination showed that his free acid=50; total acid=66. His spleen was enlarged, and he had a somewhat "doughy" abdomen. His condition was diagnosed as abdominal tuberculosis. He was discharged, much improved, and remained well until September 13th, 1926, when the abdominal pain returned and he had to stop work.

On November 13th, 1926, he was again admitted to Ward 31. The pain was very sharp and was situated in the left epigastrium. It extended over the lower four left ribs. It was not related to, or aggravated by, food. Although mostly in front, it sometimes shot through to the back, but never downwards. Sometimes it was very acute. There was no pain on micturition and no frequency, nor was it aggravated by deep respiration or straining at stool. There was no vomiting, sweating, or diarrhoea, but the patient had periods of constipation.

Asked as to previous illnesses, he stated that he had had measles and influenza. His general surroundings were good, but his work, which was moderately hard, was done in a bad atmosphere. He was a moderate smoker and nearly a total abstainer from alcohol.

Family History.—Mother and father both alive and well; two brothers, aged respectively 35 and 19, were alive and well; one brother and one sister died in infancy. There was no similar disease and no tuberculosis in the family.

State on Examination.—He was 5 feet 4 inches in height, and weighed 8 st.; he was of average intelligence, and was poorly developed and thin; temperature 97° F. He stated that his appetite had been poor for years. He often had a feeling of weight after food, but consistently denied that food aggravated or alleviated the pain. There were no eructations, acidity, or heartburn. His teeth had all been extracted six weeks previously.

Inspection of the abdomen showed it to be rather scaphoid; there was no local prominence or retraction. On palpation, no tenderness or rigidity of muscle was elicited. There was a suggestion of a doughy feeling; no splashing. The liver was not enlarged. The spleen was enlarged and palpable two inches below the costal margin in the mid-axillary line; it was not tender and there was no friction on auscultation.

A test meal given on November 18th showed free acid=23, total acidity=50.

X-Ray Report.—"J-shaped stomach of good tone and peristalsis. Duodenal cap persistently deformed and tender. At end of six hours the head of the meal had reached the hepatic flexure. The stomach was again filled and the deformity was again seen. At the end of twenty-four hours the whole of the colon was outlined, which is evidence of marked spasticity. Conclusion: The x-ray examination is very suggestive of duodenal ulcer."

Haemopoietic System.—A blood count on November 16th, 1926, showed: red blood cells 2,640,000 per c.mm., white cells 11,000 per c.mm., haemoglobin 76 per cent., colour index 1.04.

A detailed report on the nervous, urinary, circulatory, and respiratory systems is given in the case history, but as nothing abnormal was found it is unnecessary to repeat the information.

On November 21st, 1926, the patient suddenly got an acute pain in the right epigastrium, accompanied by profuse sweating and board-like rigidity of the abdominal muscles. The condition was diagnosed as a perforated duodenal ulcer, and the patient was transferred to the surgical side for operation. The following day, at 1 a.m., Mr. Illingworth operated. He found greenish fluid exuding from a perforation in the anterior wall of the duodenum. The stomach, gall-bladder, liver, and appendix were perfectly normal. The spleen was enlarged. A posterior gastro-enterostomy was performed and the patient made a perfect recovery.

On July 23rd, 1928, the patient was admitted to Ward 32 complaining of weakness and loss of weight and pain in the back and right epigastric region, which was not aggravated or relieved by food. On examination, I confirmed the past findings and history, as stated above. The patient was thin and emaciated, and weighed only 6 st. 13 lb. His skin was yellowish, suggesting slight jaundice. It in no way resembled the lemon-yellow tinge so typical of pernicious anaemia. He was obviously anaemic and suffered from breathlessness on exertion and had soft systolic murmurs over the mitral and pulmonary valves. Apart from palpation of the spleen two inches below the costal margin, there

was nothing to be made out in any system except as stated below.

Alimentary System.—"Barium outlined a small high stomach from which the food was leaving rapidly through the gastro-enterostomy opening, which appeared well formed and over which there was no tenderness. No barium was leaving by the pylorus, but no filling defect of distal portion of the stomach could be made out which might suggest new growth. *Six hours:* Residual flakes of barium round stroma. Stomach was refilled and previous examination confirmed. No evidence of a gastric lesion was found." (Report from Radiological Department.)

Haemopoietic System.—No enlargement of glands anywhere. A blood count taken on July 25th showed: red blood cells 1,320,000 per c.mm., white cells 7,000 per c.mm., haemoglobin 32 per cent., colour index 1.2. This was confirmed on July 26th and on August 4th, except that on the latter date his white blood cells numbered 10,000 per c.mm. The blood picture showed marked megalocytosis and anisocytosis, and was absolutely typical of pernicious anaemia except for the absence of leucopenia. The white blood cells varied from 7,000 to 10,000 per c.mm. on different occasions, 80 per cent. of which were polymorphonuclear leucocytes. Except when there has been concomitant disease of the kidneys, I have never found a white count so high as this in any case of pernicious anaemia. The fragility test was normal. The van den Bergh test showed direct reaction—weak delayed reaction; indirect reaction—positive reaction. This was indicative of haemolytic (non-obstructive) jaundice. The Wassermann reaction was negative.

Test Meals.—Three test meals were given at different times. The first two showed no free hydrochloric acid. This was not surprising since the fluid tested was a greenish bile-stained mixture of gastric and duodenal contents. The third test, made just previous to discharge from hospital, consisted mainly of stomach contents which turned red litmus blue, Congo red blue, and gave a positive Gunzberg reaction. Titration showed: free acidity=25; total acidity=51.

Treatment.

The patient was placed on light diet and given alkalis and liver by the mouth. Following this treatment the gastric pain disappeared and the patient put on weight rapidly. He gained $1\frac{1}{2}$ st. in six weeks. The symptoms and signs of anaemia quickly disappeared, and his blood count rose from 1,350,000 red cells per c.mm. and haemoglobin 28 per cent. on August 4th, to 3,690,000 red cells per c.mm. and haemoglobin 60 per cent. on August 27th. The white blood corpuscles remained at 8,000 per c.mm. A typical reticulocyte rise occurred, and the response to treatment was exactly what one is accustomed to get in a case of pernicious anaemia, but not in secondary anaemias. The enlarged spleen remained unchanged.

The patient was discharged from hospital looking and feeling very well.

Summary.

It is interesting to obtain a long history of epigastric pain which the patient consistently denies is affected by the taking of food, and yet find he is suffering from duodenal ulcer. The presence of marked megalocytosis and anisocytosis, a colour index over unity, and a van den Bergh reaction characteristic of haemolytic jaundice, are all classical signs of pernicious anaemia. On the other hand, the presence of free hydrochloric acid in the stomach and the absence of leucopenia contraindicate the diagnosis. Moreover, there is considerable evidence to show that pernicious anaemia patients conform to a constitutional type or build. Thus Addison noted that the disease occurred chiefly in persons of a somewhat large and bulky frame. More recently Draper,¹ by his laborious method of anthropological measurements of 45 cases, confirmed this observation, and showed that the pernicious anaemia group tended in their measurements very decidedly to approach the acromegaly. My own clinical experience agrees with these views. My first visual impression of the patient described in this paper was of a small, badly developed, emaciated, haggard man, who was probably suffering from a simple or malignant ulcer of the stomach. Without many blood examinations I would have been loath to diagnose the case as pernicious anaemia.

Hurst² and Hartman³ have reported pernicious anaemia occurring after gastrectomy in a very few cases. Conybeare⁴ has reported a case following gastro-enterostomy.

In the case reported here the blood condition was present previous to operation, and, so far as I am aware, the coexistence of duodenal ulcer and pernicious anaemia in a patient has never previously been reported.

I have to thank Professor Edwin Bramwell for the early notes of this case during the patient's stay in his ward, and Dr. Alexander Goodall for his assistance and his permission to publish the case.

REFERENCES.

- ¹ Draper, G.: *Human Constitution*. Saunders Company, Philadelphia, 1924.
- ² Hurst, A. F.: *Medical Essays and Addresses*. London, 1924, p. 81.
- ³ Hartman, J. T.: *Amer. Journ. Med. Sci.*, 1921, 162, 201.
- ⁴ Conybeare, J. J.: *Guy's Hospital Reports*, 1922, 62, 166.
- ⁵ Castle, W. B., and Locke, E. A.: *Journ. Clin. Investigation*, 1928, vi, 2.

CHRONIC NEPHRITIS IN CHILDHOOD.*

BY

J. C. SPENCE, M.D.,

Honorary Assistant Physician and Chemical Pathologist,
Royal Victoria Infirmary, Newcastle-upon-Tyne.

From the standpoint of morbid anatomy there are no forms of chronic nephritis which are peculiar to childhood, and conversely, even an arterio-sclerotic granular kidney may occasionally be found in children. There are, however, certain clinical features about the disease in children which deserve attention. So in this discussion it will be profitable both to describe our experiences of the various forms of the disease in children and also to consider if there be anything peculiar or characteristic about them in childhood which will throw light on some of the obscure problems of the subject. It is in this light that the study of disease in childhood may be looked upon as an important branch of comparative medicine; and as such should concern us no less than the study of actual "children's diseases," of which, *sensu stricto*, there are very few examples.

For the convenience of description and discussion a classification of the various forms of chronic nephritis must be attempted. It is usual to deplore the fact that the various clinical types of the disease are difficult to correlate with the classifications given to us by the morbid anatomists, but I think that we can agree that there are at least three groups of the condition which occur in childhood, and that in the main they are widely different and best considered as separate diseases. These are: (a) chronic interstitial nephritis; (b) chronic parenchymatous nephritis, including nephrosis; and (c) chronic ascending pyelonephritis.

It is probable that each of these three groups can be further differentiated into types which in themselves are distinct diseases, but for the present they will serve our purpose, being clinical entities which we are accustomed to recognize and content to diagnose.

I have purposely included chronic ascending pyelonephritis for discussion. Truly it is not a primary disease of the kidney, but the same may perhaps be said of nephrosis, and it has this clinical importance, that it may impair the renal function in the same way as chronic interstitial nephritis, and so is likely to be mistaken for it. Moreover, it deserves some comment, for occasionally the ascending infection is due to an obstruction of the urinary tract which can be treated successfully; this is more than can be said for most other forms of chronic nephritis.

My classification does not include two conditions which are sometimes spoken of as forms of chronic nephritis—namely, chronic haemorrhagic nephritis, and a syndrome to which Heubner gave the name "paedo-nephritis." The first of these is characterized by attacks of haematuria without oedema, which usually follow throat infections. I am inclined to look upon them as examples of recurrent attacks of slight acute glomerular nephritis. It is true that some of these cases do ultimately develop chronic interstitial nephritis with hypertension, but I know of at least two cases which have suffered from these attacks for more than ten years, and so far there has been no impairment of general health or of the renal function. "Paedo-nephritis" is a term which could now be discarded. Heubner coined it thirty years ago to describe doubtful forms of chronic nephritis in children who showed no other signs than albuminuria and anaemia. It is probably no distinct entity, but includes conditions such as latent chronic nephritis, toxic albuminuria, and orthostatic albuminuria.

CHRONIC INTERSTITIAL NEPHRITIS.

It is this form of chronic nephritis in childhood which will yield some of the most interesting points for discussion. At one time it was considered a great clinical rarity, and in 1896 Leonard Guthrie, while writing a wonderful description of its signs and symptoms, was able to collect from the literature only seven cases under the age of 14. By 1903 Sawyer was able to collect twenty-four cases. But

* Read in opening a discussion in the Section of Diseases of Children of the Annual Meeting of the British Medical Association, Cardiff, 1928.