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ACHRESTHIC ANAEMIA

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As a result of the intensive investigations in recent years into the mechanism of haemopoiesis, and particularly into the aetiology of Addisonian pernicious anaemia, the clinical and haematological definition of that anaemia has become much more precise. It is now considered to be a syndrome presenting essentially (a) a megalocytic anaemia; (b) achylia gastrica; (c) frequently involvement of the central nervous system or peripheral nerves; and (d) a characteristic response to specific treatment with the anti-(pernicious) anaemic factors present in liver or stomach, with a maintenance of the normal blood picture so long as adequate quantities of these factors are given. It has also been clearly demonstrated that pernicious anaemia develops when there is (1) a deficiency of the gastric enzyme (haemopoietin); (2) a deficiency of the substrate or extrinsic factor (food); (3) lack of interaction of these two factors; or (4) lack of absorption of the products of the interaction of (1) and (2). Certain other megalocytic anaemias closely resembling pernicious anaemia are also now well recognized,^{2 3 4 9 13 15 18 21} and it is clearly realized that a megalocytic anaemia of itself does not signify Addisonian pernicious anaemia.

Nevertheless, when all these have been considered, there still remains a group of megalocytic anaemias that cannot satisfactorily be fitted into any known classification, although they so closely resemble pernicious anaemia in many respects. As a rule, these cases have been considered to be anomalous examples of pernicious anaemia, either because they failed to respond to liver or other specific therapy, or because they showed unusual features such as free hydrochloric acid in the gastric juice (cf.¹⁴). Certain essential differences, however, in some of these patients have raised grave doubts as to the appositeness of considering them to be cases of pernicious anaemia, for they vary not only in symptomatology and response to treatment, but also in prognosis and aetiology.

A careful survey of such instances in the literature indicates that the majority of them must be disregarded, on account either of insufficient data (often blood counts entirely lacking) or because of what now appears to have been mistaken diagnosis. Further, it must be noted that many of these cases that were resistant to liver treatment appeared during the first few years after the introduction of this therapy, and the importance of care in its preparation and the use of a full and adequate dosage was not appreciated. It has, however, been realized more and more in recent years that oral treatment may be completely vitiated by gastro-intestinal disturbances and lack of absorption, so that in such cases the therapeutic test may be only of value as a diagnostic measure when

parenteral liver extracts are employed—a view that is supported by Vaughan⁹ and others. These extracts were not readily available until 1931, but since that time large quantities have been given, with a marked reduction in the number of cases reported as resistant to treatment. Occasional cases are, however, still described from time to time, and the reason seems to be twofold: the preparations are inactive or insufficiently prescribed (cf. Wilkinson^{11 12}); or the cases, although showing a megalocytosis, are not of the Addisonian pernicious anaemia type.

In a series of over 600 cases of pernicious anaemia collected and examined by one of us (J. F. W.) during the last few years in this clinic, a number of instances of megalocytic anaemia, closely resembling pernicious anaemia, were excluded on account of certain striking fundamental discrepancies. These patients have been, and are being, carefully studied, and there is no doubt now that seven of them closely resemble one another and represent a definite and distinct clinical entity. This type is very rare, showing about 1 per cent. of the frequency of pernicious anaemia, with which it is usually confused. As will be shown later, there is reason to believe that the anaemia may be due to an inability to *utilize*, or possibly *mobilize*, from the storage depots (such as liver, kidney, brain) in the body, the anti-anaemic principle responsible for the correct maturation of the megaloblasts, although such may be present in the body in adequate quantities. For this reason it is proposed to term this group the “achresthic anaemias” (from *χρησθαι*, to utilize). The condition is easily diagnosed, and differs essentially from pernicious anaemia and the so-called “haemolytic anaemias” (with which it is most likely to be confused) in aetiology, symptomatology, course, prognosis, and response to treatment.

Case I

A gardener's labourer, aged 34, was first admitted to the Manchester Royal Infirmary on July 15th, 1930. He complained of palpitation, dyspnoea, yellowness of the skin, weakness (which had been progressively increasing for the past seven months), and occasional numbness and tingling in both hands. There were no gastro-intestinal symptoms or soreness of the tongue. Some cough, with a moderate amount of sputum, had been present; weight steady; bowels regular; micturition normal; no haemorrhages. Previous medical history was good. No similar complaints in the family.

Examination revealed a fairly well nourished man of sallow brown complexion. Tongue was clean and moist, with some atrophy of the papillae; teeth very septic; left dacryocystitis. Liver not enlarged; spleen not palpable. The heart, lungs, central nervous system, and urine revealed no abnormalities.

Wassermann and van den Bergh reactions were negative. Fractional gastric analysis showed hypochlorhydria; maximum free acid, 8 units. Similar results were obtained on many subsequent occasions. X-ray examination of the lungs showed these to be normal. The blood count was: red cells, 2,400,000 per c.mm.; white cells, 3,800 per c.mm.; haemoglobin, 52 per cent.; colour index, 1.08; polymorphonuclears, 71.5 per cent.; lymphocytes, 26 per cent.; large mononuclears, 1.5 per cent.; eosinophils, 1 per cent.; basophils, *nil*; nucleated red cells, *nil*; anisocytosis and poikilocytosis marked; platelets abundant. (He was originally considered to be an example of atypical pernicious anaemia, with free acid in the gastric juice.¹⁴) He was treated with desiccated hog's stomach (1 ounce daily), and moderate improvement was observed. An abridged list of the blood counts is shown in Table I.

The patient was discharged on August 19th, 1930, and remained in reasonable health for eleven months, with moderate red cell and haemoglobin values. On June 1st, 1931, the blood count had fallen considerably, although the patient said that he had taken treatment regularly. On July 6th he was readmitted to hospital. Desiccated stomach (1 ounce daily) was given for a month, with little change in the blood count, and a course (25 c.cm.) of parenteral injections of an active liver extract was equally inefficacious. On August 28th the patient had an attack of acute follicular tonsillitis. This rapidly subsided, and on September 7th a further course of ten daily injections of 5 c.cm. of intramuscular liver extract was begun. The desiccated stomach preparation was also continued simultaneously. These vigorous measures were accompanied by an almost immediate rise in the reticulocyte count, which was succeeded by an improvement in the patient's general condition, and he was transferred to our out-patient clinic at his own request. Treatment with desiccated stomach (1 ounce daily) was continued, but in spite of this his condition gradually declined.

FURTHER PROGRESS

On February 9th, 1932, he was again admitted to hospital with a recurrence of similar symptoms, associated with some diarrhoea. Examination revealed no new features; there was a marked yellow tinge of the facial skin. The red cells were reduced to 960,000 per c.mm. Daily doses of 5 c.cm. of intramuscular liver extract and 40 grams of desiccated stomach were without effect. On February 27th a blood transfusion of 600 c.cm. was given, with disappointing results. A few days later further treatment with parenteral liver extract was recommenced. This was followed by a sharp reticulocyte crisis (maximum 35 per cent.) and the blood and clinical condition greatly improved. On April 16th he was discharged on treatment with desiccated stomach (1 ounce daily). He remained in reasonable health until the end of February, 1933, when, after an attack of influenza, he once more began to relapse.

On April 13th he was readmitted with similar signs and symptoms as on previous occasions. The Price-Jones curve showed a mean red cell diameter of 7.85 microns, coefficient of variability 17.7 per cent., megalocytosis 28.2 per cent., and microcytosis 1.4 per cent. This time he remained in the hospital for three months. During this period he was treated with several intensive courses of parenteral liver extracts of known potency. Nevertheless (see Table I) the blood condition remained almost stationary. A small reticulocyte crisis, maximum 14 per cent., occurred on one occasion during the liver treatment, but otherwise reticulocytes remained low.

On July 12th the patient went home at his own request, and was treated with desiccated stomach as before. His condition remained more or less unchanged. On September 22nd he was readmitted on account of abdominal pain, vomiting, and diarrhoea. He had lost weight, and was very icteric. The red cell count was down to 800,000 per c.mm., and the haemoglobin to 21 per cent. Another course of intramuscular liver injections was prescribed. There was a transient rise of reticulocytes to 15 per cent., and the red cells rose to 1,452,000 per c.mm. To the desiccated stomach was now added marmite (20 grams daily). His condition remained stationary. A further prolonged course of parenteral liver treatment had no effect.

On December 31st he suddenly became much worse, and relapsed into a comatose condition. A blood transfusion of

570 c.cm. was given by the direct method, with encouraging results. During the month of January, 1934, he received a further six transfusions—a total of 3,690 c.cm. of blood. This drastic treatment raised his red cell count to 3,464,000 per c.mm., with a corresponding improvement in the clinical condition. On February 19th he returned home, and treatment with desiccated stomach and marmite was continued. Table I shows that the blood count slowly fell. On March 23rd another transfusion of 500 c.cm. was administered. He remained fairly well until May 14th, when he complained of some pain in the feet, but there was no detectable oedema. On May 28th he attended in a very collapsed state. He complained of intolerable pain in the ankles; there had been some expectoration of blood-stained mucus, and diarrhoea with flatulence had recurred. Petechial haemorrhages were discovered in the mucous membrane of the mouth. He was immediately readmitted, but died suddenly on May 30th, without response to treatment.

POST-MORTEM OBSERVATIONS

At the necropsy, carried out by Dr. H. L. Sheehan, the bone marrow (femur) was found to be bright red throughout, and much in excess of normal amount, extending along the whole length of the bone. The cortex of the femur was much thinned. There was very slight fatty degeneration of the myocardium. The aortic valve had only two cusps. The lungs were anaemic, but otherwise normal. In the stomach the mucosa was atrophic, without folds. The liver (1,720 grams) was a buff brown colour, and contained much free iron. The spleen (120 grams) was small, with pulp of normal appearance, and also contained much free iron. The other organs presented no particularly noteworthy appearances.

On microscopical examination the bone marrow was very cellular throughout, though the fat spaces were not obliterated. The predominant cells were megaloblasts (as seen in pernicious anaemia); other cells of red and white series were also present; megakaryocytes were seen frequently. There was some atrophy in the centre of the lobules of the liver; much haemosiderin present. The Malpighian bodies of the spleen were well marked; the pulp contained many erythrocytes; some excess of fibrous tissue and haemosiderin in large amounts were observed. The kidneys also showed haemosiderin, though in small masses. The mucosa of the stomach was normal, apart from post-mortem autolysis. The lymph glands were rather oedematous, follicles being somewhat disorganized; no haemosiderin was noticed.

HAEMOPOIETIC ACTIVITY OF THE LIVER

A suitable extract for parenteral (intramuscular) injection was prepared from the liver by the usual method employed by Wilkinson and Klein¹⁷ for making these anti-anaemic liver fractions. When this was administered to a suitably controlled patient with typical Addisonian pernicious anaemia an excellent haemopoietic response was obtained, indicating that the liver was rich in the anti-pernicious-anaemia liver principle.

Case II

A fitter, aged 27, was admitted on October 27th, 1933, with a two months' history of increasing weakness, severe epistaxes, and sudden dimness of vision occurring occasionally but without complete blindness. Nine months previously there had been a severe haemorrhage after a tooth extraction: no other haemorrhages; no rashes. Weight: had lost 14 lb. Appetite, poor; bowels, constipated; micturition, normal. In 1929 he had had pneumonia: no other serious illness.

On examination the patient appeared pale and ill. There were a few petechial spots on skin and conjunctivae; no icterus. Pulse rate 84, regular, poor volume; temperature, irregular pyrexia (99° F.). Teeth good; throat and tonsils normal; small ulcer above left upper canine. Tongue furred and moist; no glossitis. The spleen was not palpable; liver not enlarged. Lymphatic glands were not abnormal. Heart not enlarged, sounds fair, haemic murmur. Lungs: no unusual feature. Left retina: recent haemorrhage at upper margin of disk. Right retina: evidence of older haemorrhages around disk margins. Eye reflexes normal. Central nervous system normal. The Wassermann and van den Bergh reactions were negative. X-ray examination of femora revealed no abnormality. Fractional gastric analysis showed hypochlor-

TABLE I

Date	Red Cells, Millions	Hb per cent.	Colour Index	White Cells	Reticulocytes per cent.	Nucleated Red Cells per 400 White Cells	Treatment*
1930							
July 19	2.42	52	1.08	7,200	—	0	
July 27	3.73	67	0.90	7,600	—	0	S.
Oct. 6	3.45	46	0.66	4,400	—	—	S.
1931							
Jan. 5	3.36	76	1.15	4,000	—	—	S.
March 23	2.94	58	1.00	8,400	—	0	S.
June 1	1.91	51	1.33	5,300	—	0	S.
July 6	1.39	42	1.50	5,500	1.9	2	S.
July 27	1.29	41	1.58	8,800	1.7	6	S.
Aug. 28	1.89	46	1.20	18,000	9.2	1	L. S.
Sept. 9	1.95	47	1.18	9,000	13.3	0	L. S.
Sept. 21	2.62	62	1.15	7,900	9.9	0	L. S.
Dec. 7	2.74	62	1.13	5,600	—	1	S.
1932							
Jan. 28	1.43	32	1.15	16,200	—	4	S.
Feb. 13	1.00	22	1.16	5,000	1.2	2	L. S.
Feb. 29	0.87	18	1.02	3,900	0.6	3	T. L. S.
March 11	1.47	32	1.10	7,500	32.0	3	T. L. S.
March 23	2.87	54	0.95	7,200	1.1	—	S.
May 18	3.59	68	0.94	6,300	—	0	S.
Oct. 25	4.58	74	0.84	6,800	—	0	S.
1933							
Jan. 9	2.73	68	1.26	6,400	—	0	S.
March 13	2.09	50	1.19	7,100	—	—	S.
April 15	1.15	30	1.30	5,600	1.5	—	L. S.
May 1	0.84	24	1.40	—	0.9	—	L.
June 6	1.28	34	1.23	6,800	4.1	—	S.
Aug. 9	1.92	39	1.01	8,800	—	—	S.
Sept. 23	0.80	21	1.30	7,000	—	—	L.
Sept. 30	1.27	24	1.20	—	15.7	—	L.
Oct. 13	1.64	30	1.50	4,800	0.8	—	M. S.
Dec. 4	1.25	28	1.17	6,100	4.4	4	S. L. M.
Dec. 31	0.88	21	1.19	—	0.9	—	S. L. M.
1934							
Jan. 4	1.63	38	1.15	—	0.6	—	7 trans- fusions given
Jan. 17	2.51	50	1.00	—	1.3	—	
Jan. 30	2.91	56	0.56	4,400	0.2	1	
Feb. 19	3.09	66	1.66	5,000	—	—	S.
March 21	3.14	62	1.00	6,000	—	—	T.
April 23	2.66	56	1.04	9,200	—	0	S.
May 14	2.11	47	1.12	7,400	0.8	0	S.
May 28	1.32	39	1.50	4,800	0.1	—	

TABLE II

Date	Red Cells, Millions	Hb per cent.	Colour Index	White Cells	Reticulocytes per cent.	Nucleated Red Cells per 400 White Cells	Treatment*
1933							
Oct. 25	1.45	32	1.13	1,800	10.0	0	M.
Nov. 16	1.44	32	1.14	3,200	11.2	0	L.
Dec. 7	1.94	41	1.09	2,500	13.0	0	S.
Dec. 21	1.70	32	0.97	3,000	4.8	0	
1934							
Jan. 4	3.52	64	0.90	4,600	3.8	0	3 trans- fusions given
Jan. 18	4.19	82	0.98	3,000	—	0	
March 12	2.58	65	1.25	5,200	—	1	S.
May 15	2.66	59	1.10	6,200	9.1	0	S.
July 2	2.93	68	1.13	5,200	6.4	0	S.
Aug. 27	3.03	72	1.23	5,900	7.2	0	S.
Sept. 11	3.22	70	1.07	5,600	4.4	1	S.
Oct. 8	2.77	60	1.07	3,200	6.5	0	S.
Nov. 5	2.78	62	1.11	6,800	4.7	1	S.
Dec. 3	2.42	63	1.25	4,900	4.3	0	S. M.

Note.—Tables I-VII are abridged from the originals on account of space; blood counts were actually done on these patients several times, weekly or monthly, according to their condition.

* Fe = Ferri ammon. cit.

L. = Parenteral liver extracts.

M. = Marmite.

S. = Desiccated stomach.

T. = Blood transfusion.

TABLE III

Date	Red Cells, Millions	Hb per cent.	Colour Index	White Cells	Reticulocytes per cent.	Nucleated Red Cells per 400 White Cells	Treatment*
1933							
Nov. 27	1.37	40	1.40	2,000	2.5	—	
Dec. 22	1.71	52	1.50	4,200	1.3	—	S.
1934							
Jan. 23	1.62	40	1.25	3,100	2.2	0	L.
Jan. 30	1.81	45	1.25	3,400	12.2	2	L.
Feb. 13	1.24	44	1.19	2,800	1.4	4	T.
Feb. 19	2.32	46	1.00	2,500	0.7	0	T.
Feb. 26	2.57	66	1.30	3,200	0.3	0	
March 29	2.28	48	1.04	2,900	0.6	1	
April 5	3.02	55	0.89	4,000	0.6	0	T. S.
April 27	3.18	58	0.92	4,400	1.2	1	S.
June 1	2.70	55	1.01	3,800	4.2	16	S. L.
Aug. 24	1.46	35	1.16	2,800	12.8	14	L.
Sept. 6	2.76	56	0.98	1,800	2.0	0	T.
Sept. 12	2.68	54	0.98	2,600	0.5	0	T.
Sept. 27	2.40	43	0.90	3,400	—	0	S.
Oct. 25	1.52	42	1.40	2,800	—	8	S.
Nov. 1	2.68	53	0.99	3,600	5.2	3	T.
Nov. 15	2.48	54	1.08	3,200	4.2	1	S. M.
Nov. 29	1.62	43	1.30	6,400	4.1	6	S. M.

TABLE IV

Date	Red Cells, Millions	Hb per cent.	Colour Index	White Cells	Reticulocytes per cent.	Nucleated Red Cells per 400 White Cells	Treatment*
1934							
March 31	2.48	55	1.10	6,800	7.0	2	
April 14	2.04	48	1.20	7,600	6.2	—	S.
April 23	2.07	48	1.14	9,400	5.5	4	L.
May 7	2.03	46	1.14	8,900	2.6	2	M.
May 14	2.10	48	1.14	7,800	5.3	6	M. S.
May 17	2.64	60	1.14	10,400	4.7	—	T. S.
June 4	1.74	42	1.20	9,900	1.1	3	S.
June 9	2.59	60	1.16	11,800	3.8	2	T. S.
June 23	3.48	70	1.02	12,900	—	—	T. S.
Aug. 16	2.27	37	0.84	6,400	6.8	—	S.
Aug. 30	1.96	36	0.90	18,500	—	10	S.
Sept. 4	2.99	52	0.90	7,400	2.0	6	T. S.
Oct. 25	2.67	54	1.00	8,900	5.8	14	S.
Nov. 22	2.35	54	1.15	5,800	4.1	12	S.
Dec. 6	2.16	52	1.18	6,600	3.9	4	S. M.

TABLE V

Date	Red Cells, Millions	Hb per cent.	Colour Index	White Cells	Reticulocytes per cent.	Nucleated Red Cells per 400 White Cells	Treatment*
1933							
Nov. 21	3.08	68	1.10	—	—	—	
1934							
May 1	2.82	63	1.21	4,000	—	—	
May 31	3.10	67	1.08	3,400	2.2	0	S.
July 26	4.39	73	0.87	5,800	3.6	0	S.
Sept. 20	3.52	73	1.04	3,400	4.5	0	S.
Nov. 15	3.73	80	1.08	2,600	3.0	0	S. M.
Dec. 6	3.41	74	1.09	4,400	2.8	0	S. M.

TABLE VI

Date	Red Cells, Millions	Hb per cent.	Colour Index	White Cells	Reticulocytes per cent.	Nucleated Red Cells per 400 White Cells	Treatment*
1934							
Aug. 8	1.36	26	0.93	5,200	3.6	4	Fe
Aug. 18	1.28	26	1.00	5,000	6.5	2	Fe
Aug. 25	1.23	28	1.15	3,000	5.6	0	L.
Sept. 20	3.27	66	1.00	3,600	0.6	0	2 trans- fusions given
Oct. 19	2.48	58	1.16	8,800	0.3	0	S.
Nov. 16	1.49	38	1.27	3,700	—	1	S.
Nov. 20	2.11	47	1.12	6,000	—	—	T. M.

TABLE VII

Date	Red Cells, Millions	Hb per cent.	Colour Index	White Cells	Reticulocytes per cent.	Nucleated Red Cells per 400 White Cells	Treatment*
1934							
July 7	1.78	48	1.40	1,400	—	0	
July 14	2.08	56	1.40	3,000	2.5	—	
Aug. 4	2.06	55	1.30	2,600	1.6	0	L. S.
Nov. 17	1.52	60	1.60	2,800	3.7	0	S.

hydria (maximum free acid, 7 units; histamine, 18 units); fragility of red cells was within normal limits. The Price-Jones curve gave a mean diameter of 7.78 microns, coefficient of variability 9 per cent., megalocytosis 12.6 per cent., microcytosis *nil*. The blood count was: red cells, 1,450,000 per c.mm.; haemoglobin, 32 per cent.; colour index, 1.1; white cells, 1,800 per c.mm.—polymorphonuclears, 25 per cent.; lymphocytes, 71.5 per cent.; large mononuclears, 3.5 per cent.; no eosinophils, basophils, or nucleated red cells. Anisocytosis and poikilocytosis were marked; platelets, scanty; reticulocytes, 10 per cent.

During a short observational period his condition remained stationary, as shown in Table II. There was another right retinal haemorrhage on November 10th. Treatment with marmite (20 grams daily) and a course of intramuscular liver injections brought about no improvement. Desiccated stomach powder caused abdominal pain, and was discontinued. On December 29th a blood transfusion of 500 c.cm. was given, with excellent results. Two further transfusions of 650 c.cm. each raised the red cell count to 4,190,000 per c.mm. and the haemoglobin to 82 per cent. He was discharged, and told to report regularly.

As will be seen from Table II the blood condition slowly deteriorated. Further epistaxes occurred. Treatment with desiccated stomach was recommenced, at first in doses of 1/2 ounce per day, and then of 1 ounce. There was no untoward reaction, and some slight improvement in the blood condition. Marmite (40 grams daily) has been taken without producing any significant change. At the present time his clinical condition is fair, and his weight has increased slightly.

Case III

A night watchman, aged 62, was first seen on November 27th, 1933. There was a four months' history of dyspnoea on exertion, undue fatigue, increasing pallor, swelling of the feet and ankles, and indigestion—discomfort and substernal pain immediately after taking food, relieved by belching or alkalis. No vomiting had occurred. Appetite, good; bowels, regular; micturition, normal. No haemorrhages apart from slight epistaxis. Weight, steady. Some winter cough and infrequent "sweats" during rest. Nothing of note in previous medical or family histories.

On examination the patient was well built, and rather stout and pale. There was slight icterus of the conjunctivae. Pulse 90, collapsing character; temperature normal. Tongue: smooth, moist, and clean. Throat and tonsils appeared healthy. The teeth were artificial. The abdomen was obese, but not ascitic. Liver: smooth and tender, and enlarged to two inches below the costal margin. The spleen was not palpable. The heart was somewhat enlarged; there was a generalized precordial systolic murmur; blood pressure, 118/62 mm. Lungs were emphysematous; there were a few scattered rhonchi. Central nervous system: *nil* abnormal. Urine: acid; no albumin, sugar, or casts. The blood count (December 11th, 1933) was: red cells, 1,688,000 per c.mm.; haemoglobin, 51 per cent.; colour index, 1.53; white cells, 4,000 per c.mm.—polymorphonuclears, 24 per cent.; lymphocytes, 70 per cent.; large mononuclears, 6 per cent.; eosinophils, basophils, and nucleated red cells were absent. Anisocytosis and poikilocytosis were marked; platelets, scanty; reticulocytes, 1.1 per cent.; no polychromasia or punctate basophilia.

Treatment with desiccated stomach did not bring about any great improvement, and on January 15th, 1934, he was admitted to the Infirmary for further investigation. Fractional gastric analysis showed hyperchlorhydria (maximum free acid, 78 units). Wassermann reaction was negative. Van den Bergh test: delayed direct response. Fragility of red cells was within normal limits. The Price-Jones curve revealed a mean red cell diameter of 7.88 microns, coefficient of variability 13.5 per cent., megalocytes 24.8 per cent., and microcytosis *nil*. X-ray examination of the lungs gave no evidence of tuberculosis.

FURTHER TREATMENT

A course of 24 c.cm. of intramuscular liver extract was administered over eight days. As indicated in Table III there was a slight rise of red cells, accompanied by a small reticulocyte crisis (maximum 12.2 per cent.). This response was very poor. Two transfusions were therefore given of

600 and 750 c.cm. respectively at an interval of eight days. Table III shows the initial improvement, followed by a further relapse. Another transfusion of 500 c.cm. on April 4th was attended by satisfactory results. The patient was then allowed to go home, on treatment with desiccated stomach (1 ounce daily). His condition was again maintained for some weeks, but then began to decline. On June 1st a dose of concentrated intramuscular liver extract (3 c.cm.) was prescribed. Shortly after this the patient failed to attend for two months, during which time he had no treatment. When he reappeared the blood count had fallen greatly. During the next week 18 c.cm. of active liver extract were injected intramuscularly, but the blood count continued to fall, and on August 31st he was readmitted to hospital. Two transfusions of 800 c.cm. and 700 c.cm. respectively led to improvement of his condition. He was discharged on September 13th, and ordered desiccated stomach (1 ounce daily).

Again the blood count fell steadily from a red cell count of 2,680,000 on discharge to 1,520,000 per c.mm. after six weeks. Another transfusion (750 c.cm.), on October 31st, raised the blood level to its previous height. Once more, in spite of treatment with desiccated stomach and marmite, the blood count followed the same downward course. At present his condition is far from satisfactory, and it is impossible to say how long this process of transfusion and slow deterioration will be kept up.

Case IV

A gardener, aged 46, was admitted to hospital on March 29th, 1934. He stated that five months previously he had had an attack of lumbago, since when he had not properly recovered his health. For the last two months he had complained of excessive fatigue, dyspnoea and palpitation on exertion, and dizziness. Appetite good; no indigestion; bowels regular; some flatulence. Micturition, normal. Weight, steady. Some winter cough. No soreness of the tongue. Pallor had become noticeable. Swelling of the ankles had occurred. Previous medical and family histories contained nothing of note.

On examination he was a well-nourished man, pale, with slight icterus. Pulse rate 88, rather compressible. Temperature normal. Teeth, artificial. Tongue: moist, furred, no glossitis. Throat and tonsils appeared normal. Spleen was not palpable; liver not enlarged. Heart showed no unusual features: blood pressure 120/80 mm. Hg. Lungs and central nervous system presented no noteworthy features. Lymph glands were not enlarged. Urine, normal. Wassermann and Van den Bergh reactions were negative. Fractional gastric analysis revealed the presence of free acid (maximum 18 units). Fragility of red cells was within normal limits. The Price-Jones curve gave a mean red cell diameter of 7.79 microns, coefficient of variability 12.1 per cent., megalocytosis 15.2 per cent., and microcytosis *nil*. The blood count (April 6th) was: red cells, 2,020,000 per c.mm.; haemoglobin, 50 per cent.; colour index, 1.25; white cells, 7,600 per c.mm.—polymorphonuclears, 66 per cent.; lymphocytes, 26 per cent.; large mononuclears, 1 per cent.; eosinophils, 1 per cent.; basophils, absent; myelocytes, 1 per cent.; Türk cells, 5 per cent. There were two nucleated red cells per 400 white blood cells; anisocytosis and poikilocytosis were marked; punctate basophilia was present; platelets were fairly abundant; reticulocytes, 1.7 per cent.

Treatment with desiccated stomach was begun, but, as Table IV indicates, the red cell count fell. A course of 16 c.cm. of intramuscular liver extract was commenced on April 18th. The red cell count rose a little, but there was no reticulocyte response. A further similar course was also without effect. Marmite (20 grams daily) was prescribed, and later desiccated stomach (1 ounce per day), but the patient's condition remained stationary. Blood transfusions were therefore given: the first (550 c.cm.), on May 16th, was followed by a slight rigor and a transient but marked polynucleosis; subsequent transfusions (700 c.cm. on June 8th and 700 c.cm. on June 22nd) were not attended by any reaction. Desiccated stomach was ordered between the transfusions. The patient's condition was much improved, and he was allowed to go home on treatment with 1 ounce daily of desiccated stomach powder. Between this date and

the end of August the blood condition slowly deteriorated. The patient was troubled with some boils at this time, but their presence did not produce any significant change in the blood counts. On August 30th a further transfusion of 800 c.cm. was given with much benefit as before. Table IV shows that since then the same process has been repeated—a gradual fall in the blood counts, and the general condition of the patient becoming less satisfactory, in spite of treatment with desiccated stomach and marmite.

Case V

A translator, aged 62, first attended the hospital out-patient department in November, 1933. He complained of generalized itching of twelve months' duration, a "tight feeling" over the forehead, slight dyspnoea and palpitation on exertion, and a feeling of lassitude. Appetite, good; weight, steady; bowels, normal; micturition, normal; no indigestion, sore tongue, paraesthesiae, or haemorrhages. Fourteen years previously he had had "gastritis." An x-ray examination of the alimentary tract was negative, and he recovered on treatment with alkalis and a milk diet. The patient was treated for the itching, and given iron and ammonium citrate. He attended intermittently until May, 1934, when he was referred to our clinic. His condition was much the same, except that the dyspnoea and palpitation were more marked.

On examination he was a nervous, well-nourished man of yellowish complexion. Tongue, furred and moist; no glossitis. Teeth, artificial; throat and tonsils, apparently normal. Pulse: rate 76, regular, and full. Temperature normal. The abdomen was full, but there was no ascites: spleen not palpable; liver not enlarged. There were no enlarged lymph glands. The heart was not abnormal; blood pressure, 150/80 mm. Hg. No unusual features were observed in respiratory or central nervous systems. Urine, normal. Wassermann reaction, negative. Van den Bergh test showed a weak positive indirect reaction. Fractional gastric analysis revealed a climbing type of curve, with maximum free acid 68.5 units. The Price-Jones curve gave a mean red cell diameter of 8.05 microns, coefficient of variability 10.3 per cent., megalocytosis 24 per cent., and microcytosis *nil*. The blood count (May 1st) was: red cells, 2,820,000 per c.mm.; haemoglobin, 68 per cent.; colour index, 1.21; white cells, 4,000 per c.mm.—polymorphonuclears, 61 per cent.; lymphocytes, 31 per cent.; large mononuclears, 6 per cent.; eosinophils, 2 per cent.; basophils, absent. Nucleated red cells were absent; anisocytosis and poikilocytosis were present; platelets, scanty.

Treatment with desiccated stomach (1/2 ounce daily) was begun, and he improved for a time (see Table V). At present the blood count is fluctuating somewhat, with a downward tendency. The dose of desiccated stomach has been increased to 1 ounce per day, and marmite (20 grams) has been added, but without obvious result.

Case VI

A married woman, aged 66, was admitted to hospital on August 7th, 1934, complaining of loss of energy, fatigue, and loss of weight. This condition had been slowly getting worse for many months, but particularly during the past three months. There had been dyspnoea on exertion, palpitations, and occasional vomiting when fatigued. The appetite was poor; no true indigestion; no flatulence. The bowels were regular. The menopause had occurred normally at 55 years of age. Occasional paraesthesiae in the fingers and toes had been noticed. No haemorrhages or rashes. There was nothing of note in the previous medical or family histories.

On examination the patient was a pale, slightly icteric woman of small stature; she had clearly lost weight. There was marked pallor of the mucous membranes; there was no atrophy, fissuring, or soreness of the tongue. Teeth, artificial; throat and tonsils, no apparent abnormality; pulse, 84, regular and of fair volume; temperature normal. The abdomen was fairly "full." Liver: smooth and palpable, 1½ inches below the costal margin. Spleen: smooth and tender, also deeply palpable about an inch below the costal margin. There were no enlarged lymph glands. Heart was not enlarged. Blood pressure, 130/80 mm. Hg. No abnormalities were revealed in other systems. Wassermann reaction was negative. Van den Bergh reaction—positive indirect. Fractional gastric analysis showed hypochlorhydria (maximum 12.5 units); there was a free secretion of acid after histamine

injection (maximum, 51 units). X-ray examination of the alimentary tract disclosed nothing of note. The blood count (August 8th) was: red cells, 1,360,000 per c.mm.; haemoglobin, 26 per cent.; colour index, 0.93; white cells, 5,200 per c.mm.—polymorphonuclears, 77.5 per cent.; lymphocytes, 16.5 per cent.; large mononuclears, 2.5 per cent.; eosinophils, 2.5 per cent.; basophils, 1 per cent. There were 4 nucleated red cells per 400 white cells; marked polychromasia; anisocytosis and poikilocytosis; fairly abundant platelets; reticulocytes, 3.6 per cent.

In spite of the rather low colour index it was felt that the clinical condition of the patient and the blood picture as a whole suggested an anomalous anaemia of type similar to the preceding cases, and the results of the gastric analysis and x-ray examination confirmed this. Iron was prescribed in suitable doses, and then 16 c.cm. of a concentrated parenteral liver extract. On August 25th the red cells were 1,230,000 per c.mm.; haemoglobin, 28 per cent.; colour index, 1.15. A Price-Jones curve at this time revealed a mean red cell diameter of 7.87 microns, coefficient of variability 10.6 per cent., megalocytosis 18 per cent., and microcytosis *nil*. There was no response to the first doses of liver: a further course of 16 c.cm. produced no change in the blood count or the reticulocytes (see Table VI). Two transfusions of 700 c.cm. and 600 c.cm. respectively raised the red cells to 3,270,000 per c.mm., with much improvement in the clinical condition. The patient was discharged to our out-patient clinic on September 22nd, the treatment consisting essentially of iron therapy. One month later the blood count had fallen somewhat; treatment with desiccated stomach (1 ounce daily) was therefore recommended. At her next attendance the count had fallen to 1,490,000 red cells per c.mm., and, although the patient said she felt fairly well, she was readmitted a few days later for another transfusion (600 c.cm.). The treatment at present is marmite (20 grams daily), desiccated stomach (1 ounce daily), and parenteral liver extract. A further relapse has just necessitated readmission.

Case VII

A female rubber trimmer, aged 20, attended the out-patient clinic on July 7th, 1934, on account of undue fatigue and swelling of the feet after work. There were no other complaints. The appetite was good, the bowels regular, menstruation normal, and weight steady. No haemorrhages, rashes, or excessive bruising. Previous medical history comprised only an attack of laryngitis. Family history: her elder sister died from an illness characterized by great pallor and excessive haemorrhages.

On examination the patient appeared very well nourished, and had an excellent complexion and colour. The conjunctivae were somewhat pale. Tongue: moist and clean, no glossitis. Teeth, some carious; throat and tonsils, normal. Pulse rate 84, good volume. No pyrexia. There was some puffiness around the ankles—not true oedema. The abdomen showed no abnormality; spleen not palpable, liver not enlarged. There were no enlarged lymph glands. Heart: normal size and sounds. No unusual features in other systems. The blood count was: red cells, 1,780,000 per c.mm.; haemoglobin, 48 per cent.; colour index, 1.4; white cells, 1,400 per c.mm.—polymorphonuclears, 58 per cent.; lymphocytes, 38 per cent.; large mononuclears, 3.5 per cent.; eosinophils, 0.5 per cent.; basophils, *nil*. No nucleated red cells; polychromasia, absent; anisocytosis and poikilocytosis, marked; platelets, scanty; reticulocytes, 2.5 per cent. The Price-Jones curve gave a mean red cell diameter of 8.43 microns, coefficient of variability 9 per cent., megalocytosis 46.7 per cent., and microcytosis *nil*. The fractional gastric analysis proved acid secretion to be within normal limits (maximum free acid 33 units). The patient refused to become an in-patient in the hospital, and was treated by her doctor at home. Five doses of 4 c.cm. of intramuscular liver extract were prescribed, and desiccated stomach (1/2 ounce per day) was taken. There was no change in the blood count following these measures, though the patient said she felt improved. She continued to take desiccated stomach, but at her next visit the blood count (see Table VII) was much as before. This patient attends very irregularly, as, at present, she persists in continuing with her work.

(To be completed in next week's issue, where a full list of references will be given.)