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PERNICIOUS ANAEMIA OF PREGNANCY AND THE PUERPERIUM

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Addisonian pernicious anaemia is an uncommon disease, but pernicious anaemia of pregnancy is much rarer still. Thus of 521 cases of macrocytic anaemia examined by us during the past seven years only 31 were associated with pregnancy and of these only four have been seen since the introduction of folic acid. It is therefore not surprising that no report on the therapeutic value of folic acid on this type of megaloblastic anaemia has appeared in British medical literature, and that records of only four cases have been published in America—three cases by Spies (1946) and one by Moore *et al.* (1945). In all four cases folic acid was given by the parenteral route, and a satisfactory response was obtained in each instance. We now submit records of three cases of pernicious anaemia of pregnancy and one case of Addisonian pernicious anaemia that relapsed as a result of pregnancy, all of which responded to folic acid. The haemoglobinometer used in this investigation was a Haldane instrument standardized by the National Physical Laboratory.

Case 1

A married woman aged 30 was admitted to our wards on Nov. 13, 1947, on account of severe anaemia. Her first confinement was in December, 1944, and the second in July, 1946. Because of anaemia she was treated in 1946 with iron before parturition and with anahaemin for three months subsequently and gradually made a good recovery. No details are available in regard to the type or the severity of the anaemia. In 1947 she again became pregnant and was confined in a neighbouring hospital on Nov. 2. Twins were delivered, and she lost a considerable amount of blood. No information about the state of her blood previous to this confinement was available other than the fact that her haemoglobin was 48% one month before delivery. During this month she was given 6 gr. (0.4 g.) of ferrous sulphate thrice daily and 2 ml. of anahaemin twice weekly. Consequent on the loss of blood at parturition the haemoglobin level fell to 40%.

After admission to our wards questioning revealed that her social and dietetic history was satisfactory and that there was no family history of anaemia or of diarrhoea. The patient had never been abroad and had never suffered from dyspepsia, dysphagia, or diarrhoea. Physical examination revealed no abnormality of the tongue, finger-nails, or skin. There was no subjective or objective evidence of involvement of the nervous system, and no source of blood loss was discovered. There

was no jaundice or fever. The liver, spleen, and lymph nodes were not enlarged, and no pathological features were found in any system other than the haemopoietic system. A test meal revealed free hydrochloric acid in all specimens, and the urine contained an excess of urobilinogen. Her blood count on Nov. 14 was: red cells, 1,570,000 per c.mm.; haemoglobin, 30%; colour index, 0.96; reticulocytes, 1.4%; white cells, 12,400 per c.mm. A megaloblastic bone marrow indistinguishable from that of Addisonian pernicious anaemia was found. Folic acid was given in a dosage of 20 mg. daily by mouth for 12 days, and thereafter 10 mg. daily. This resulted in a reticulo-

FIG. 1.—Chart of Case 1. ---- indicates counts done before we saw the patient.

cyte peak of 31% on the fifth day and an increase of red cells and haemoglobin of 2,400,000 and 58% respectively in 55 days. (Fig. 1.)

Case 2

This patient, a married woman aged 23, was admitted to the Simpson Memorial Maternity Pavilion of the Royal Infirmary, Edinburgh, on Jan. 29, 1948, with a diagnosis of pre-eclamptic toxæmia because of oedema, albuminuria, and hypertension. On Feb. 7 she was delivered of a healthy full-time female child. There was no history of previous pregnancy or of miscarriages. A haemoglobin level of 60% was found the day before the baby was born.

The patient said she had always been pale, but the only serious illness she had had was diphtheria at the age of six, which was followed by a right-sided hemiplegia. There was no family history of anaemia or diarrhoea. She was pale and slightly built, had never suffered from dysphagia, dyspepsia, or diarrhoea, and had never been abroad. Her dietetic history was satisfactory. There was no enlargement of the liver, spleen, or lymph nodes. The tongue was slightly atrophic, with several

sore patches, and the finger-nails showed some ridging. There was no jaundice, and no source of blood loss was discovered. The urine contained albumin and a marked excess of urobilinogen. A test meal showed histamine-fast achlorhydria. The blood pressure was normal, and no disease was found in the cardiovascular or respiratory system. Apart from the residual signs of the hemiplegia mentioned above no abnormality of the nervous system was found.

A blood count carried out by us on Feb. 20 was as follows: red cells, 2,300,000 per c.mm.; haemoglobin, 44%; colour index, 0.9; white cells, 4,000; reticulocytes, 1.2%. The bone marrow was megaloblastic and indistinguishable from that of untreated Addisonian pernicious anaemia, despite the fact that 2 ml. of anahaemin had been given on three consecutive days before sternal biopsy was undertaken. Eight days later the blood count was slightly lower and the M.C.V. was 84 c. μ . The state of the bone marrow could not be ascertained, since the patient refused to have a second sternal puncture. The presence of an occasional megaloblast in the peripheral blood suggested that no change had occurred. Accordingly treatment with folic acid was started, a single injection of 30 mg. being given intramuscularly, followed by 10 mg. by mouth daily. This resulted in a reticulocyte peak of 26% on the fifth day, and an increase of 1,380,000 red cells and 12% haemoglobin in 18 days. At this date the colour index was 0.75, and the hypochromic appearance of the erythrocytes clearly indicated the need for supplementary iron therapy.

Case 3

A married woman aged 30 was transferred to our wards from the Simpson Memorial Maternity Pavilion on Feb. 26, 1947, on account of severe anaemia. She had given birth to a healthy son on Feb. 14 and had had no previous pregnancies. Labour had been uneventful except that there had been a moderately heavy blood loss after delivery of the placenta. There was no family history of anaemia or diarrhoea. Her appetite was good. The patient's dietetic history was satisfactory and she had never suffered from dysphagia, dyspepsia, diarrhoea, anaemia, or any serious illness. Physical examination revealed no abnormality of the heart, lungs, abdominal organs, or nervous system. There was some atrophy of the papillae of the tongue; neither koilonychia nor enlargement of lymphatic nodes was found. The blood pressure was 124/90. The urine contained a trace of albumin but no excess of urobilinogen. There was free hydrochloric acid in the gastric juice.

When we first saw the patient on Feb. 26 the blood count was: red cells, 1,800,000 per c.mm.; haemoglobin, 46%; colour index, 1.28; white cells, 6,800 per c.mm.; reticulocytes, 5.6%. The M.C.V. calculated on two occasions was 107 and 114 c. μ . The marrow was megaloblastic. The patient had been treated with 6 gr. (0.4 g.) of ferrous sulphate three times a day during pregnancy, but had never received liver by mouth or by injection. At the end of a control period of ten days the red cell count was unaltered and the reticulocyte count had fallen to 1.8%. Accordingly, 10 mg. of folic acid daily was given by mouth. She had to leave hospital on account of domestic difficulties, but continued to take the folic acid as an out-patient, reporting at regular intervals to the blood clinic for assessment of progress. A rapid improvement in her general clinical condition resulted, while a gain of 1,410,000 red cells and 10% haemoglobin occurred in 35 days. She was then given 18 gr. (1.2 g.) of ferrous sulphate daily and the blood count was restored to normal.

Case 4

This patient, an unmarried woman aged 38, was in the sixth month of pregnancy when we were asked to see her because of severe anaemia which had failed to respond to treatment with iron and various preparations of liver.

In 1940, at the age of 30, she had been admitted to the Royal Infirmary of Edinburgh suffering from severe anaemia. The following information was obtained from her case records. Before admission she had been getting increasingly pale, easily tired, and breathless, and vomiting and diarrhoea had occurred. There was oedema of the ankles, the skin had a lemon-yellow colour, and the conjunctival mucous membrane was very pale. Apart from atrophic glossitis, anaemia, and achlorhydria, no

abnormality was noted in any system. Her blood count on April 15, 1940, was: red cells, 1,720,000 per c.mm.; haemoglobin, 45%; colour index, 1.3. Intensive treatment with parenteral liver extract was given. She received an intramuscular injection of 5 ml. of "pernaemon" daily. As the response was poor, "campolon," one ampoule daily, was sub-

FIG. 2.—Bone marrow from Case 4, showing persistence of megaloblastic erythropoiesis despite administration of 32 ml. anahaemin, 6 ml. plexan, and 3½ oz. (115 g.) of hepamino over a period of 3 weeks. ($\times 1,400$.)

stituted. The response continued to be poor, and despite this intensive treatment the gain in red cells and haemoglobin over a period of two and a half months was only 1,500,000 red cells and 25% haemoglobin. After discharge from hospital the patient continued to have injections of liver extract from her doctor, at first daily and then weekly for the next two years.

FIG. 3.—Bone marrow from Case 4, showing reversion to normoblastic erythropoiesis 36 hours after the intramuscular administration of 60 mg. of folic acid. ($\times 1,400$.)

In 1942 she had two severe reactions following the injection of liver extract. When anahaemin was substituted for the previous liver extract no reactions followed. The doctor states, however, that the patient attended for treatment irregularly and at long intervals during the next five years. Throughout this period she was pale, breathless, and easily tired, but continued working

most of the time. In July, 1947, she reported to her doctor because she was pregnant, and was admitted to the Royal Infirmary on Dec. 22, 1947, because of severe anaemia.

The patient was extremely pale but showed no obvious loss of weight. She stated that her appetite was poor and that she frequently suffered from flatulent dyspepsia and had occasional attacks of diarrhoea. A dietary history indicated that her intake of animal protein and vitamin C in particular was very unsatisfactory. Glossitis and koilonychia were absent. There was no enlargement of liver, spleen, or lymph nodes. A test meal revealed histamine-fast achlorhydria. During her stay in hospital she had no diarrhoea. In view of her irregular and insufficient treatment with liver extract, particular attention was paid to examination of the nervous system. Although she stated that she had never had any paraesthesiae or ataxia, indubitable signs of involvement of the spinal cord were found—namely, grossly exaggerated reflexes in both lower limbs and a bilateral extensor plantar response. Apart from a mild degree of incoordination no evidence was obtained of involvement of the peripheral nerves or posterior columns of the cord.

Her blood count was: red cells, 1,200,000 per c.mm.; haemoglobin, 28%; white cells, 3,600; the M.C.V. on two occasions was 93.9 c. μ and 92.7 c. μ ; the blood picture was typical of pernicious anaemia, and her bone marrow was megaloblastic. In view of her grave clinical state she was given

FIG. 4.—Chart of Case 4. ----- indicates counts done before we saw the patient.

a transfusion of blood. During the next 14 days she received 3 gr. (0.2 g.) of ferrous sulphate three times a day, and 32 ml. of anhaemin, 6 ml. of "plexan," and 3½ oz. (115 g.) of proteolysed liver ("hepamin"). As no clinical or haematological improvement resulted a further transfusion of 4 pints (2.3 litres) of blood was given, and this raised her red cell and haemoglobin levels to 2,980,000 per c.mm. and 68% respectively. A second sternal puncture indicated that the marrow was still megaloblastic (Fig. 2). After a control period of six days, during which no therapy was given, the red cells had fallen to 2,480,000 per c.mm. and the haemoglobin to 58%. The reticulocyte count never exceeded 1%.

Accordingly, treatment with folic acid was started, a single injection of 60 mg. being given intramuscularly. A third sternal puncture carried out 36 hours later showed a remarkable transformation of the marrow to the normoblastic state (Fig. 3). This was followed by a rise in the reticulocyte count, the peak of 15.6% occurring on the eighth day, and a dramatic improvement in the patient's clinical condition. A gain of 600,000 red cells and 12% haemoglobin occurred in ten days. On the fourteenth day after the first injection of folic acid labour was induced. A second injection of 60 mg. of folic acid was given next day, and a third injection of the same quantity seven days later. Thereafter she received 10 mg. daily by mouth, and on the 59th day after the initial injection of folic acid her red cells amounted to 4,630,000 and haemoglobin to 90% (Fig. 4).

It is of interest to note that the patient's father had suffered from pernicious anaemia for nine years, and that there was a remarkable history of the premature development of white hair on the paternal side of the family. We have previously noted in other patients who have developed pernicious anaemia at a surprisingly early age that a family history of the disease is commonly obtained.

Discussion

The first large series of cases of pernicious anaemia of pregnancy in Great Britain was recorded by Stevenson (1938). As this investigation was carried out before sternal puncture became a routine haematological procedure it is possible that certain of the cases might not have fulfilled the essential criterion of having a megaloblastic bone marrow. The literature dealing with pernicious anaemia of pregnancy has been fully reviewed by Callender (1944), who described 25 cases which she observed personally. In 1942 Davidson, Davis, and Innes described 16 cases, and Davidson and Davis (1947) drew attention to four points of particular importance. (1) The diagnosis of pernicious anaemia of pregnancy depends essentially on the demonstration of typical megaloblasts in the bone marrow, since the peripheral blood picture may be quite unlike that of Addisonian pernicious anaemia, the colour index may be below unity, and the M.C.V. within normal limits. (2) Although free hydrochloric acid is often present in the gastric juice, in a number of cases a histamine-fast achlorhydria is found. In such cases it may be difficult or impossible to decide whether the case should be classified as pernicious anaemia of pregnancy or Addisonian pernicious anaemia complicated by pregnancy unless the effect of stopping all forms of liver therapy is observed for a period lasting up to two years. (3) The response to parenteral liver therapy may be normal, poor and delayed, or absent. (4) Cases refractory to parenteral liver therapy will respond promptly to oral treatment with proteolysed liver (hepamin) or to cooked liver (Fullerton, 1943).

It will be noted that Cases 1, 3, and 4 all failed to respond to the parenteral injection of large amounts of well-known liver extracts of various types, both crude and refined, but responded promptly to folic acid given either parenterally or orally. No liver therapy was given to Case 3 prior to the administration of folic acid. Case 4 failed to respond to proteolysed liver, but the quantity given was inadequate and the period of treatment (5 days) too short for the attainment of a successful therapeutic effect.

No satisfactory explanation is as yet available of the mechanism underlying the development of a megaloblastic anaemia in pregnant women. The anaemia could develop as a result of defective intake of some factor necessary for normal blood formation, from a failure in the production of Castle's intrinsic factor, or from a defect in absorption from the alimentary tract. We were particularly interested in the possibility of malabsorption because of our past experience of a case diagnosed as pernicious anaemia of pregnancy and two cases diagnosed as idiopathic refractory megaloblastic anaemia which were subsequently shown to be cases of idiopathic steatorrhoea, although diarrhoea was absent in all three patients throughout the period of investigation in hospital (Davidson, 1948). Although none of the patients in this series had diarrhoea or fatty stools during their stay in hospital, a fat-balance test was carried out in Cases 1 and 4. The results showed no evidence of defective malabsorption of fat. We realize, of course, that this finding does not rule out the possibility of a selective malabsorption of other factors required for the continuation of normoblastic blood formation.

Folic acid would seem to be the best agent available at the present time for the treatment of pernicious anaemia of pregnancy because it can be administered orally in the

form of a small tasteless tablet and because of the rapid clinical and haematological improvement which results even in cases refractory to parenteral liver therapy. Since the duration of treatment with folic acid is limited to a few weeks, the danger of producing subacute combined degeneration of the cord is greatly reduced as compared with Addisonian pernicious anaemia. Further time must elapse, however, before it can be stated confidently that neurological features will not occur in patients with pernicious anaemia of pregnancy receiving folic acid.

As many cases of pernicious anaemia of pregnancy are suffering from a dual deficiency of iron and the factor required for maintenance of normoblastic blood formation it is desirable that both deficiencies be corrected simultaneously. While our patients were receiving folic acid iron was deliberately withheld in order to simplify the interpretation of the therapeutic response.

(Anaheamin is a refined liver extract, and "plexan" and "campolon" are crude extracts.)

Summary

Three cases of pernicious anaemia of pregnancy and one case of Addisonian pernicious anaemia complicated by pregnancy responded excellently to treatment with folic acid. Three of the cases had failed to respond to the parenteral injection of liver extracts prior to the administration of folic acid.

We wish to thank Prof. Kellar, Dr. Fahmy, and others of our colleagues in the Simpson Memorial Maternity Pavilion of the Royal Infirmary, Edinburgh, for permission to investigate and treat the above cases.

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FOLIC ACID*

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Idiopathic Steatorrhoea and Coeliac Disease

A number of reports have now appeared on the excellent effect of "folic acid" in the treatment of tropical sprue (Darby and Jones, 1945; Darby *et al.*, 1946a, 1946b; Spies, 1946a, 1946b; Spies *et al.*, 1946; Manson-Bahr and Clarke, 1946; Morrison and Johnston, 1947); while Davidson and Girdwood (1947) and Weir and Comfort (1947) have described their results using it on patients with non-tropical sprue, particularly those with normoblastic marrows.

*The conclusion of the lectures (abridged) given to the Section of Experimental Medicine of the Royal Society of Medicine on May 13, 1947, and to the Medical Society of London on Feb. 9, 1948.

The following four cases illustrate my results when pteroylglutamic acid is used on patients with idiopathic steatorrhoea (non-tropical sprue) and coeliac disease (Table V).

Idiopathic Steatorrhoea

The diagnostic criteria for patients with idiopathic steatorrhoea (non-tropical sprue) were: (1) a macrocytic anaemia with a megaloblastic or normoblastic marrow; (2) frequent loose, bulky, offensive stools, often yellowish in colour; (3) high total fat content of stools with or without a prior fat test meal; (4) achlorhydria gastrica or normal acidity; (5) soreness or ulceration of the mouth or tongue; (6) severe loss of weight; and (7) a flat glucose-tolerance curve.

Case I.S.—A housewife aged 53 had an eight-months history of tiredness, lack of energy, palpitation, intermittent soreness of the tongue, increasing pallor, and frequent loose, bulky, offensive, yellowish stools up to eight in 24 hours. She had lost at least 3 st. (19 kg.) in weight. The bone marrow was very cellular and active, with a mixed megaloblastic (5%)—normoblastic (27%) hyperplasia. A blood count showed: R.B.C., 2,610,000; Hb, 72%; C.I., 1.33; W.B.C., 6,600 (polymorphs, 73%, lymphocytes 22%, large monocytes 3%, eosinophils 2%); marked anisocytosis and poikilocytosis; reticulocytes, 3.2%. Stools: total fat, 55% (split fat 83%, unsplit 17%). She was given 20 mg. of pteroylglutamic acid orally per day. There was slight reticulocytosis (4.2% on the 8th day) and the haematological response was slow but ultimately (after 64 days) reached R.B.C. 4,140,000, Hb 82%, C.I. 1, W.B.C. 7,100, with a normal differential white cell count. The stools rapidly improved, became formed, and ceased to be frequent, bulky, or offensive; total fat, 28% (split 84%, unsplit 16%). Clinically the patient had improved very much indeed; she was free from symptoms and was gaining weight steadily when discharged from hospital.

Case B.C.—A housewife aged 35 had had tetany intermittently since the age of 24; she had bilateral cataracts and frequent bulky offensive stools in addition to the usual general symptoms. Examination revealed achylia gastrica, a flat glucose-tolerance curve, a negative Wassermann reaction, and normal C.S.F.; serum calcium varied between 6.4 and 9.8 mg. per 100 ml., blood urea 22 mg. per 100 ml., urea clearance 85%, serum phosphorus 3.6%, plasma alkaline phosphatase 4–14 units; radiologically there was some generalized osteoporosis of the long bones; weight, 4 st. 12 lb. (30.84 kg.); blood pressure, 100/70. A blood count on June 27, 1946, showed: R.B.C., 3,210,000; Hb, 74%; C.I., 1.16; W.B.C., 3,600 (polymorphs 59%, lymphocytes 36%, large monocytes 4%, eosinophils 1%); anisocytosis and poikilocytosis marked; platelets 97,000. The marrow was very active and cellular and showed a mixed megaloblastic (4.7%)—normoblastic (9.7%) reaction. Stools: total fat, 41% (split fat 82%, unsplit fat 18%). Bacteriological examination of faeces did not disclose any abnormality.

The patient had 15 mg. of pteroylglutamic acid intramuscularly daily for 10 days without any clinical or haematological response, and was then given 1 oz. (28 g.) orally of proteolysed liver extract daily without improvement, the blood count on Aug. 9 being rather worse: R.B.C., 2,820,000; Hb, 62%; C.I., 1.11; W.B.C., 7,200. At this stage the sternal marrow showed a normoblastic (49.25%) hyperplasia. Continued treatment with liver extract parenterally, supplementary synthetic vitamins of the B complex, hog's stomach, etc.,

TABLE V.—*Idiopathic Steatorrhoea*

Case	Sex	Age	Marrow	Gastric Acidity	R.B.C. × 10 ⁶	Hb %	W.B.C.	Folic Acid
I.S.	F	53	Mbl 5% Nbl 27%	Achylia	2.61 4.14 (69)	72 82 (69)	6,600 7,100	20 mg. orally
B.C.	F	35	Mbl 4.7% Nbl 9.7% Mbl 0 Nbl 49.25%	Achylia	3.21 3.11 (14) 3.49 4.31 (32) 2.80 (187) 3.08 (201)	74 72 (14) 70 84 (32) 74 (187) 64 (201)	3,600 5,200 (14) 9,700 7,400 (32) 9,000 (187) 12,800 (201)	15 mg. [10] i.m. 50 mg. [2] i.v. 50 mg. [25] i.v. 40 mg. [187] orally
H.C.	F	27	Mbl 10.4% Nbl 10.4%	Normal	1.97 5.35 (107)	50 108 (107)	3,200 5,700	20 mg. [107] orally
J.M.	F	3	Mbl 2.25% Nbl 2.5%	Normal	3.12 3.81 (129)	63 44 (129)	4,500 4,300 (129)	5 mg. [129] orally

Reticulocytes: Case I.S. 4.3% (8); Case H.C. 25.4% (7). Nbl = Normoblasts. Mbl = Megaloblasts.) Day after beginning treatment. [] No. of days on treatment