MEGALOBLASTIC ANAEMIA OF PREGNANCY AND THE PUERPERIUM

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Investigation of patients with megaloblastic anaemia of pregnancy and the puerperium is handicapped by the urgency with which treatment must be carried out and by the tendency of the anaemia to remit spontaneously after delivery. Strauss and Castle (1933) suggested that this anaemia was due to a temporary reduction in the secretion of intrinsic factor, but the failure of parenteral liver extracts and vitamin B_{12} to bring about remission in most cases has made it clear that this cannot be the only explanation. Three cases have been described in which defective absorption of fat was discovered on subsequent admission to hospital (Davidson, 1948 ; Tuck and Whittaker, 1950 ; Thompson and Ungley, 1951), and Tuck and Whittaker (1950) have proposed that, in some instances at least, the underlying mechanism may be an occult idiopathic steatorrhoea, which is unmasked by pregnancy. In the present observations on nine patients, particular attention has been directed to the detection of abnormalities of gastric secretion and defects of the absorption of fat and labelled vitamin B_{12} from the intestine. We show that there was no evidence of reduction in the secretion of intrinsic factor or in the absorption of fat in these patients.

Clinical Features

The salient clinical features are presented in Table I. Four women were investigated before term and the remaining five were seen after delivery ; in all cases the diagnosis was confirmed by finding megaloblastic changes in the sternal marrow. Of particular interest is the high incidence of complications such as vomiting, diarrhoea, and haemorrhage, which might tend to decrease the supply of or increase the demand for haemopoietic factors during pregnancy and the puerperium. The tongue was sore in three patients. There was atrophy of the papillae in four patients—complete in two and confined to the edge of the tongue in two. Aphthous ulcers were present in four patients, three of whom had leucopenia. The spleen was palpable in two patients, in whom the level of haemoglobin was less than 5 g. No neurological abnormality was detected in any of the patients.

Treatment was with folic acid by mouth or vitamin B_{12} by injection. Folic acid was given in a dose of 20 mg. daily. Vitamin B_{12} was given on a single day only, in a dosage of 2,000 μg. ; this was the " flushing dose " which was employed in measuring the excretion of labelled vitamin B_{12} in the urine. In Case 8 only 100 μg. of vitamin B_{12} was given.

Of the three patients seen three weeks or more before delivery, one responded well to folic acid alone, another failed to respond to vitamin B_{12} but subsequently improved with folic acid, and the third showed no improvement up to the time of delivery with combined folic acid and vitamin B_{12} therapy. A fourth patient was treated with vitamin B_{12} and folic acid one week before delivery without apparent effect, but gradual improvement occurred during the puerperium.

In three patients the diagnosis was made early in the puerperium. An optimal response followed treatment with vitamin B_{12} in one and folic acid in another. The third received both vitamin B_{12} and folic acid, and showed a progressive increase in haemoglobin, although the reticulocytes did not rise above 3%. Since spontaneous remission is common following delivery, it is not certain that these responses were due to specific therapy.

Two patients were seen with severe anaemia six weeks after delivery. There was no response to vitamin B_{12} over a period of eight days in Case 8, but prompt symptomatic and haematological remission followed the administration of folic acid. Case 9 was transfused initially and then treated with vitamin B_{12} with an optimal reticulocytosis and rise in haemoglobin and the haematocrit reading.

Special Investigations

(A) Methods

1. *Gastric Secretion.*—Gastric acidity was measured directly in seven subjects and indirectly by the " diagnex " technique (Conway and Meikle, 1953) in one (Case 5). In two patients free acid was found in the resting juice and no stimulant was given. Fractional test-meal examinations were carried out on four patients with histamine and one patient with gruel. The urinary excretion of uropepsinogen over a 24-hour period was measured in seven subjects (Aitken *et al.*, 1951).

2. *Gastric Biopsy.*—Biopsy of the gastric mucous membrane was carried out in four patients, using Wood's flexible gastric biopsy tube (Wood *et al.*, 1949).

3. *Absorption of Vitamin B_{12}.*—The absorption of vitamin B_{12} was tested by measuring the amount of radioactivity which was found in the faeces after an oral dose of 0.5 μg. of vitamin B_{12} labelled with cobalt^{60} (Heinle *et al.*, 1952). This gave an indirect assessment of the secretion of

TABLE I

Case	Age	Previous Pregnancies	Diagnosis of Anaemia	Complicating Features	Hb Before Therapy (g./100 ml.)	Response to Therapy
1	22	4	Ante partum 4 weeks	Fifth pregnancy within 5 years	4·6	Transfused—Hb 6·8 g. Folic acid—good response
2	18	0	Ante partum 4 weeks	Twin pregnancy	9·8	B_{12}—no response 14 days. Folic acid—good response
3	20	0	Ante partum 3 weeks	Vomiting and anorexia throughout pregnancy	9·9	B_{12} and folic acid—no improvement up to time of delivery
4	23	1	Ante partum 1 week	Poor diet; hypertension	10·3	B_{12} and folic acid—no reticulocytosis, improved post partum
5	34	2	Post partum 1 week	Very poor diet; appendicectomy in first trimester	8·9	B_{12}—good response
6	28	2	Post partum 2 weeks	Anorexia, diarrhoea, mild toxaemia, and post-partum haemorrhage	3·9	Transfused—Hb 9·7 g. Folic acid—good response
7	20	2	Post partum 1 week	Post-partum haemorrhage; third pregnancy in 3 years	9·2	B_{12} and folic acid—moderate rise Hb, reticulocytosis 3%
8	22	0	Post partum 6 weeks	Post-partum vomiting; puerperal fever—? endometritis	5·3	B_{12}—no response 8 days. Folic acid—good response
9	29	1	Post partum 6 weeks	Ante-partum diarrhoea; breast abscess first week post partum	4·7	Transfused—Hb 9·6 g. B_{12}—good response

intrinsic factor. In six patients a parenteral injection of 2,000 μg. of non-radioactive vitamin B_{12} was given with the oral dose in order to rid the body of as much of the absorbed radioactivity as possible (Schilling, 1953). Normally 15% or more of the oral dose of 0.5 μg. of Co^{60}-vitamin B_{12} is excreted in the urine with this technique (Callender and Evans, 1955). The collection of stools was incomplete in Case 3, and only the radioactivity in the urine was measured.

4. *Absorption of Fat.*—The absorption of fat was estimated in six of the subjects by a four-day fat balance with a measured dietary intake of 70 to 100 g. of fat daily.

5. *Serum Vitamin B_{12}.*—The level of vitamin B_{12} in the serum was determined by microbiological assay, in two cases with *Euglena gracilis* and in four cases with *Lactobacillus leichmannii.*

TABLE II

Patient	Free Acid in Gastric Juice	Uropepsinogen Excretion (Units/24 hr.)	Percentage of Oral Dose of Co^{60}-vitamin B_{12} in Faeces	Fat Absorption (% of Dietary Intake)	Serum Vitamin B_{12} ($\mu\mu$g./ml.)
Normal values ..		50+	9–47	90+	100+
1	0	140	30 ; 17	—	—
2*	+	9	18	91	430
3	Not tested	—	(23)†	—	—
4	+	116	28	95	140 ; 110
5*	+	310	16	96	310
6*	0	161	42 ; 33	—	—
7	+	132	28	96	260
8*	+	164	36	95	190 ; 175
9	+	48	28	96	220

* Gastric biopsy. † Radioactivity in urine.

(B) Results (Table II)

1. *Gastric Secretion.*—The fractional test meal revealed achlorhydria in two patients, but in one of these (Case 1) the uropepsinogen excretion was within normal limits, and in the other (Case 6) the biopsy showed no atrophy of the gastric body glands. Uropepsinogen excretion was low in two patients, within the range encountered in pernicious anaemia, but in both of them free acid was present in the gastric juice.

2. *Gastric Biopsy.*—Histological examination of the gastric mucosa revealed no abnormality. There was evidence of superficial gastritis in Case 6, but no atrophy of the gastric body glands was noted.

3. *Absorption of Vitamin B_{12}.*—The absorption of vitamin B_{12} was normal in all nine patients, implying that the secretion of intrinsic factor was adequate.

4. *Absorption of Fat.*—The absorption of fat was within normal limits in the six patients tested. The low normal result on the basis of a four-day fat balance does not absolutely exclude the possibility of steatorrhoea in Case 2.

5. *Serum Vitamin B_{12}.*—Normal quantities of vitamin B_{12} were present in the serum of five patients. The values in Case 4 are just above the range observed in untreated pernicious anaemia, and might be explained by the grossly inadequate diet which she took throughout her two pregnancies and the intervening period.

Discussion

The preceding investigations do not provide conclusive evidence of the nature of the disturbance of haemopoiesis in megaloblastic anaemia of pregnancy and the puerperium or of its pathogenesis. The secretion of intrinsic factor, as determined by the absorption of radioactive vitamin B_{12}, was normal and there is therefore no support for the theories of Strauss and Castle (1933). The absorption of fat was also normal in our patients, as it was in six cases of megaloblastic anaemia of pregnancy recently studied by Moore *et al.* (1955). It must therefore be concluded that, though megaloblastic anaemia in pregnancy may occasionally be due to adult coeliac disease, this is by no means a common cause.

Although the absorption of vitamin B_{12} is normal the possibility exists of a deficiency of the vitamin in the diet. This is probably not uncommon in India (Das Gupta, 1954), and it has been described in Europe. Nieweg *et al.* (1954) report two patients responding to vitamin B_{12} therapy in whom the evidence favours a deficiency of the vitamin. In one the serum vitamin B_{12} was very low (40 $\mu\mu$g. per ml.), and in the other the blood folic acid was normal. In 20% of a group of patients studied during pregnancy and lactation, Heinrich (1954) found low serum vitamin B_{12} levels and reduced excretion of vitamin B_{12} in the urine, although there was no evidence of macrocytic anaemia. Oral administration of vitamin B_{12} was effective in restoring normal serum levels and urinary excretion in these patients, and Heinrich suggested the existence of a state of hypovitaminosis-B_{12} due to increased demands for the vitamin during pregnancy and lactation.

However, Mollin and Ross (1954) report serum vitamin B_{12} levels in 31 cases of megaloblastic anaemia of pregnancy and the puerperium, and in only two were the levels as low as is seen in untreated cases of pernicious anaemia. In our cases, likewise, the level of vitamin B_{12} in the serum was within normal limits. Hence it would appear that, although vitamin-B_{12} deficiency may occur in Europe, it is not commonly responsible for the development of megaloblastic anaemia in pregnancy. In the two women who improved with vitamin B_{12} therapy in the present series the response may have been mediated by some indirect mechanism, related to the massive size of the dose, for in both of them the serum levels of vitamin B_{12} were normal. This conclusion is supported by the work of Moore *et al.* (1955), who obtained a satisfactory response to vitamin B_{12} in 13 out of 17 cases of megaloblastic anaemia of pregnancy by giving massive doses, of the order of 1,000 μg. Five of their patients were treated before delivery and 12 after. The four women who did not respond to vitamin B_{12}, which in two instances was pushed to 5,000 μg., responded to folic acid.

At present it is difficult to assess the folic acid status of the organism other than by the response to treatment. Folic acid in large doses is usually effective in the megaloblastic anaemia of pregnancy, both before and after delivery. This observation favours a folic acid deficiency, though this deficiency, like that of vitamin B_{12}, is more likely to be relative than absolute, for remission may occur after delivery in patients who receive no treatment at all.

It seems likely that patients with megaloblastic anaemia of pregnancy and the puerperium do not represent a homogeneous group, and this may explain the variable findings and response to therapy. Complications of pregnancy and the puerperium occur frequently in relation to megaloblastic anaemia. Toxaemia and infection may interfere with the utilization of haemopoietic factors; haemorrhage and multiple or rapidly repeated pregnancies may increase the demands; while poor diet and gastro-intestinal upsets reduce the natural supply. However, in some patients pregnancy alone may induce the anaemia, and in such cases the cause appears to be the development of resistance to vitamin B_{12} and folic acid.

Summary

Nine patients with megaloblastic anaemia of pregnancy and the puerperium have been studied. The incidence of complications of pregnancy and the puerperium was high.

No abnormality in the secretion of intrinsic factor or the absorption of fat was discovered in any case.

The serum vitamin B_{12} levels were normal.

In women treated before delivery folic acid was more effective than vitamin B_{12}.

Although an absolute deficiency of folic acid cannot be excluded, the anaemia seems more likely to be due to resistance to the action of the haemopoietic factors than to deficiency.

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MEGALOBLASTIC ANAEMIA FOLLOWING ANTICONVULSANTS

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Two cases of megaloblastic anaemia occurring in epileptics who had been taking phenobarbitone and phenytoin were reported by Badenoch (1954), who suggested that the anticonvulsants might have played a part in the production of the anaemia. Other cases have been reported by Hawkins and Meynell (1954), Chalmers and Boheimer (1954), and Rhind and Varadi (1954).

In April, 1954, we first encountered a megaloblastic anaemia in a patient who had been receiving phenytoin and phenobarbitone. In the absence of any obvious cause we speculated whether anticonvulsant drugs could have had any causative relationship. Our suspicions were strengthened when in July a further epileptic patient under our care developed a megaloblastic anaemia which had no obvious cause. The cases reported recently, together with the cases we now record, seem to indicate that megaloblastic anaemia may arise after the prolonged use of anticonvulsant drugs, and that this anaemia is probably due to phenytoin.

Case 1

A man aged 28 was admitted to Prestwich Hospital with an epileptic psychosis in August, 1952. He had suffered from major and minor fits for seven years and had been taking both phenytoin and phenobarbitone for at least eighteen months. At the time his anaemia was detected he was taking phenytoin 1½ gr. (100 mg.), and phenobarbitone, ¾ gr. (50 mg.), thrice daily. He was a good eater and was on a full mixed diet. There was no history of steatorrhoea.

On April 23, 1954, he was noted to be pale and he complained of weakness. Physical examination revealed nothing beyond pallor of skin and mucous membranes and a loud apical systolic murmur. A blood count showed: haemoglobin, 50%; red cells, 2,660,000 per c.mm.; white cells, 6,800 per c.mm. (polymorphs 48%, lymphocytes 50%, monocytes 2%). Anisocytosis and poikilocytosis were present. A fractional test meal revealed a small quantity of free acid. Sternal marrow puncture revealed megaloblastic erythropoiesis, the predominant cells being early and intermediate megaloblasts. The white-cell series showed early forms, some of which were larger than normal.

On May 4 vitamin B_{12} was started (100 μg. daily), but in spite of this his blood picture continued to deteriorate and there was no reticulocyte response. By May 10 the blood count was: haemoglobin, 25%; red cells, 1,800,000 per c.mm.; white cells, 3,200 per c.mm.; and reticulocytes, 3%. His physical condition was unaltered. He had a smooth tongue but no active glossitis, a loud apical systolic murmur, and high pulse pressure (B.P. 110/50). There was no evidence of subacute combined degeneration of the cord or any clinical evidence of steatorrhoea or liver disease.

On May 10 he was put on oral folic acid, 5 mg. four times a day. On the 11th his reticulocytes were 5%, and by the 13th they had reached 8%. In addition to folic acid, 20 mg. daily, he received a crude liver preparation ("hepatex T," 4 ml. daily) from May 11 to 13. Otherwise he was maintained solely on folic acid.

On the 13th he was transferred to the Manchester Royal Infirmary under the care of Dr. J. F. Wilkinson. His reticulocytes reached a peak of over 30%, and on his return to Prestwich Hospital on June 2 his haemoglobin had reached 70%. By July 9 the blood count showed: haemoglobin, 90%; red cells, 5,000,000 per c.mm.; white cells, 13,600 (normal differential).

He was discharged home in August, his mental state having improved. He remained on phenytoin and phenobarbitone throughout his illness, and at the time of discharge was taking folic acid, 20 mg. daily.

Case 2

A 26-year-old male epileptic had suffered from epilepsy following a head injury at the age of 5 which had left him with a left hemiparesis. He was also suffering from an epileptic psychosis. He had been on phenobarbitone and phenytoin since 1950. In May, 1954, he was put on to primidone, 0.25 g. thrice daily, in addition to phenytoin, 1½ gr. (100 mg.), and phenobarbitone, ½ gr. (32 mg.), thrice daily to obtain better control of his fits. He was a good eater and was on a full mixed diet. There was no history of steatorrhoea.

Physical examination on August 24, 1954, revealed intense pallor, a left hemiparesis, an apical systolic murmur, and a blood pressure of 140/70 mm. Hg. He had mild hypertrophy of the gums but no significant glossitis. There was no evidence of subacute combined degeneration of the cord or any clinical evidence of steatorrhoea or liver disease. A blood count showed: haemoglobin, 28%; red cells, 1,620,000 per c.mm., white cells, 3,600 per c.mm. (polymorphs 31%, lymphocytes 64%, monocytes 3%, eosinophils 3%). Anisocytosis, poikilocytosis, punctate basophilia, Howell-Jolly bodies, and Cabot rings were obvious in the blood film. Sternal marrow puncture showed a megaloblastic marrow, early and intermediate megaloblasts predominating. No abnormality was noted in the white-cell series.

A fractional test meal with histamine showed free acid present. There were no fat globules in the faeces, and faecal-fat estimation showed total fat 28%, with a normal split/unsplit ratio. The glucose-tolerance test showed normal