infiltration of the organ by carcinoma or leukaemia. Such functional disturbances quite likely initiate the gross structural changes in the liver. Anaesthesia used during biopsy does not modify liver cell metabolism.

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MEGALOBlastic ANAEMIA AND VITAMIN-B₁₂ DEFICIENCY AFTER ANTICONVULSANT THERAPY

REPORT OF TWO CASES

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In 1952 Mannheimer and his colleagues described leucopenia and megaloblastic anaemia in an epileptic patient receiving treatment with hydantoin. Macrocytosis and hypersegmented polymorphs were present in the blood films of other patients, but only scanty haematological details were given. Badenoch (1954) reported detailed studies in two epileptic patients who developed a megaloblastic anaemia while being treated with phenobarbitone and phenytoin sodium ("epanutin") and suggested that the megaloblastic anaemia might be due to the anti-convulsant drug. Since then megaloblastic anaemia has been reported in 21 other patients receiving phenytoin sodium and/or primidone ("mysoline") (Hawkins and Meynell, 1954; Chalmers and Boheimer, 1954; Rhind and Varadi, 1954; Webster, 1954; Berlyne *et al.*, 1955; Fuld, 1955; Ryan and Forshaw, 1955; Vaishnav, 1955; Girdwood and Lenman, 1956; Girdwood, 1956; Christenson *et al.*, 1957; Gydell, 1957; Newman and Sumner, 1957) and in one non-epileptic patient receiving large doses of quinalbarbitone sodium and amylobarbitone sodium (Hobson *et al.*, 1956).

The cause of the megaloblastic anaemia in these patients is uncertain. Most patients have responded only to treatment with folic acid, but there has rarely been evidence of intestinal malabsorption. Although some patients have taken an inadequate diet (Gydell, 1957; Newman and Sumner, 1957), in most the diet has been adequate. It has therefore been suggested that the megaloblastic anaemia is due to interference with the tissue metabolism of folic acid. In none of the patients hitherto reported has there been definite evidence of vitamin-B₁₂ deficiency.

The purpose of this paper is to give details of two epileptic patients who developed a megaloblastic anaemia while being treated with anticonvulsant drugs. In both there was evidence of vitamin-B₁₂ deficiency due to dietary inadequacy.

Case 1

A 41-year-old woman had been treated for epilepsy since childhood. She had received phenobarbitone, 2 gr. (0.13 g.) daily, for many years, and for the last two years she had received, in addition, phenytoin sodium, 100 mg. daily. She lived with her mother in poor circumstances, subsisting on a meagre diet which at times consisted of little more than bread, buns, and boiled sweets. Two months before admission she was found by her family doctor to be suffering from bleeding gums, purpuric blotching of the skin, and swollen ankles. He diagnosed scurvy and treated her with 200 mg. of ascorbic acid daily for six weeks. The bleeding stopped and the purpura rapidly disappeared, but she became progressively more anaemic, and was admitted to hospital on August 25, 1955.

On examination she was found to be of low intelligence and retarded in speech and behaviour. The only abnormal physical signs were gross pallor and severe gingivitis. Chest x-ray examination revealed no abnormality.

Investigations.—Red cells, 1,100,000 per c.mm.; Hb, 4.5 g. per 100 ml.; packed cell volume, 13%; mean cell volume, 118 cubic microns; leucocytes, 1,700 per c.mm., of which 1,122 were polymorphs. Stained films showed macrocytosis, anisocytosis, and poikilocytosis. Sternal marrow films showed severe megaloblastic haemopoiesis. The vitamin-B₁₂ concentration of two samples of serum taken before treatment, measured with the Euglena assay, was 50 and 40 µg. per ml. respectively (normal range 100 to 900 µg. per ml., Mollin and Ross, 1954). The low serum concentration was not due to a growth inhibitor, for similar values were obtained at various dilutions. Furthermore, when vitamin B₁₂ was added to the serum and the serum was re-assayed, 83 to 94% of the added vitamin B₁₂ was recovered. The serum iron was 90 µg. per 100 ml. Direct Coombs test was negative.

The serum protein was 6.3 g. % (albumin 3.55 g., globulin 2.75 g.); serum bilirubin 0.7 mg. per 100 ml.; thymol turbidity 1 unit; colloidal gold 0; alkaline phosphatase 4.5 King-Armstrong units per 100 ml.

Quinine test meal (with histamine) showed free HCl to be present. The fat-balance study had to be abandoned because the patient was uncooperative, but the amount of faecal fat was within normal limits, being 18% of dried stool.

The radioactivity of the plasma after an oral dose of 1 µg. of ⁵⁵Co vitamin B₁₂ (specific activity 5.0 mc. per mg.) was maximal at eight hours, when 1.5% of the administered dose was present in the plasma (normal range 1 to 2%, Booth and Mollin, 1956). This indicated that the patient was able to absorb vitamin B₁₂ normally.

Treatment.—On August 30 she was given an intramuscular injection of 100 µg. of vitamin B₁₂. Three days later her serum iron was unchanged, being 97 µg. per 100 ml., and the marrow obtained by sternal puncture was still grossly megaloblastic. The haemoglobin concentration was now 3.6 g. per 100 ml.; red cells were 1,020,000 per c.mm., and the reticulocyte count was 4.8%. She was then given 10 mg. of folic acid three times daily; five days later the reticulocytes had reached a peak of 36%. The serum iron had fallen to 28 µg. per 100 ml. By September 21 the red cells were 2,400,000 per c.mm.; the haemoglobin concentration was 7.8 g. per 100 ml.; packed cell volume was 26.6%; and the mean cell haemoglobin concentration was 29%. Folic acid was reduced to 10 mg. twice daily, and a proprietary preparation of colloidal ferric hydroxide ("neoferrum") 8 ml. twice a day, and ascorbic acid (50 mg. daily) were also given. On October 21 the red cells were 4,600,000 per c.mm.; the haemoglobin concentration was 13.3 g. per

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100 ml., and the packed cell volume 44%. Treatment with phenytoin sodium, 100 mg. daily, and phenobarbitone, 1 gr. (65 mg.) three times a day, had been continued throughout. The patient continues to take 10 mg. of folic acid daily, and there has been no sign of haematological relapse to date.

Comment.—This patient appeared to be suffering from deficiency of both vitamin B₁₂ and folic acid, for although her serum vitamin-B₁₂ concentration was as low as that found in patients with untreated vitamin-B₁₂ deficiency she failed to respond to treatment with vitamin B₁₂ alone. Her sternal marrow was grossly megaloblastic three days after an injection of 100 µg. of vitamin B₁₂, whereas in patients with uncomplicated vitamin-B₁₂ deficiency erythropoiesis would be proceeding on essential normoblastic lines by this time. Her serum iron was also unchanged three days after the injection. Houghton and Doan (1941) and Hawkins (1955) have emphasized that a fall in the serum iron is an early and valuable sign of response to treatment in patients with megaloblastic anaemia. Her anaemia responded completely when folic acid was given, in spite of the fact that treatment with phenytoin sodium was continued.

Case 2

A feeble-minded female epileptic aged 34 was admitted to hospital on June 9, 1956, *in extremis* and died with acute pulmonary oedema two hours later. On admission the red cell count was 650,000 per c.mm. and the haemoglobin 2.7 g. per 100 ml. The blood film was typical of severe megaloblastic anaemia, and sternal marrow aspirated before death was grossly megaloblastic.

The patient had been receiving phenobarbitone, 1½ gr. (0.1 g.) daily, for many years. In May, 1955, phenytoin sodium, 100 mg. daily, was started and given in addition to phenobarbitone, and from October, 1955, primidone, 250 mg. daily, later increased to 500 mg. daily, was also given. About two months before admission the dose of phenytoin sodium had been reduced to 30 mg. daily.

Two months before admission she had undergone an emergency hysterectomy for intractable menorrhagia of one month's duration. Before a transfusion of 4 pints (2.3 litres) of blood the haemoglobin concentration was 5.9 g. per 100 ml. At this time, although she appeared well nourished, great difficulty was found in persuading her to eat whilst in hospital, and she had taken a grossly inadequate diet before admission. Her mother stated that she had had very little to eat since her discharge.

Post-mortem Examination.—Necropsy was performed 11 hours after death, little being found other than acute pulmonary oedema and the usual stigmata of gross anaemia. No focal lesion was found in the brain. The marrow in the ribs, sternum, and lumbar vertebrae was pinkish grey in colour and grossly hyperplastic on histological examination. The gastric mucosa was of normal thickness and structure. The serum vitamin-B₁₂ concentration of a sample of right auricular blood taken at necropsy was 40 µµg. per ml.

Comment.—This patient was also suffering from vitamin-B₁₂ deficiency, for her serum vitamin-B₁₂ concentration was very low. The fact that her serum was obtained from blood taken after death does not invalidate this result, for our experience has been that the serum vitamin-B₁₂ concentration is never subnormal in the 24 hours after death unless the subject suffered from vitamin-B₁₂ deficiency (Mollin and Ross, unpublished observations). The fact that the gastric mucosa was normal excludes the possibility of Addisonian pernicious anaemia, but intestinal malabsorption syndrome was not excluded. Nevertheless, it seems probable that her condition was similar to that found in the first patient.

Discussion

Both these patients had serum vitamin-B₁₂ concentrations as low as those seen in severe Addisonian pernicious anaemia. As neither of them was suffering from this condition, and as there was no evidence of intestinal malabsorption

of vitamin B₁₂ or of fat in the one patient in whom detailed studies were made, it is probable that the deficiency of vitamin B₁₂ was due to inadequate diet. It is unlikely that these low serum levels were due to the anticonvulsant drugs, for while it is possible that these drugs might interfere with the metabolism of vitamin B₁₂ it is difficult to see how this could deplete the serum of its vitamin.

The previously published reports suggest that the megaloblastic anaemia found in patients receiving anticonvulsant drugs is due to interference with the metabolism of folic acid in the tissues. In at least one of the patients described above (Case 1) there was evidence of deranged folic acid metabolism, for the anaemia did not respond until folic acid was also given. However, the dietary deficiency of vitamin B₁₂ may have helped to precipitate the megaloblastic anaemia in both patients.

Vitamin-B₁₂ deficiency does not appear to be common in the patients so far described with this type of megaloblastic anaemia.

Apart from the patient described by Newman and Sumner (1957), few if any of the patients were taking a diet grossly deficient in vitamin B₁₂ and there has been little direct evidence of vitamin-B₁₂ deficiency. The serum vitamin-B₁₂ concentration was within the normal range in the nine patients in whom it was measured and was also normal in four others whose sera we have recently assayed. Although some patients were reported to have responded to treatment with vitamin B₁₂ the responses have been slow, and the anticonvulsant drugs were also stopped or changed before or at the same time as treatment with vitamin B₁₂ was started.

One of our two patients had also suffered from deficiency of ascorbic acid, and it is possible that the intractable menorrhagia in the other was due to this deficiency. Ascorbic acid deficiency was also reported by Gydell (1957) in two of his three patients, and one of the two patients described by Newman and Sumner (1957) may well have suffered from this condition. Gydell (1957) suggests that ascorbic acid deficiency may be more common in this type of megaloblastic anaemia than has been suspected. He points out, for instance, that both patients described by Badenoch (1954) and one of the patients described by Fuld and Moorhouse (1956) suffered from oral lesions, and that Kimball (1939) found evidence of ascorbic acid deficiency in patients who developed these lesions on phenytoin sodium. Furthermore, the ascorbic acid saturation test in the patient described by Chalmers and Boheimer (1954) was abnormal, although there were no other signs of ascorbic acid deficiency.

It is known that a scorbutic diet may produce a megaloblastic anaemia in animals (May *et al.*, 1950) and that a megaloblastic anaemia may be found in scurvy (Brown, 1955), so it is possible that ascorbic acid deficiency may also be a precipitating factor in some of the patients with megaloblastic anaemia associated with anticonvulsant therapy. It is unlikely that it is ever the sole or principal cause of the anaemia in these patients, for treatment with ascorbic acid did not relieve the anaemia in our own patients or in those described by Gydell (1957). The megaloblastic anaemia associated with scurvy alone responds rapidly to treatment with vitamin C (Brown, 1955; Booth and Mollin, 1956, unpublished observations).

There was a clear-cut history of dietary deficiency of vitamin C in all the patients mentioned above who gave a definite history of bleeding, but not in the patients with oral lesions or in the patients described by Chalmers and Boheimer (1954). It is therefore possible that the administration of anticonvulsants may itself tend to precipitate deficiency of ascorbic acid.

Summary

Two epileptic patients, one of whom was treated with phenytoin sodium, the other with phenytoin sodium and primidone, developed megaloblastic anaemia.

The serum vitamin-B₁₂ concentrations of both patients were very low, but neither suffered from Addisonian pernicious anaemia. Both had been taking a very inadequate diet, and one had recently suffered from scurvy.

Vitamin-B₁₂ deficiency was not the sole cause of the megaloblastic anaemia in the one patient in whom serial observations were made.

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KNOCK-KNEE IN CHILDREN

BY

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To learn more of the natural history of knock-knee over 1,000 examinations were made on unselected normal children from infant welfare clinics and from a school in North-west London. It was considered that a greater understanding of the natural history would simplify the management of children with knock-knee and avoid unnecessary treatment. The methods used were simple, and were applicable in any clinic.

Two groups of children were studied. Those with any defect or disease which might affect their lower limbs—for example, spastics—were excluded.

Material

From Three Infant Welfare Clinics.—Any child who was old enough to walk unaided was seen, and all children were invited to reattend in six months for remeasurement. Studies were made of 451 children aged 1 to 4 years inclusive. Of these, 245 were seen once, 146 on two occasions, and 60 on three occasions, making a total of 717 examinations. Thirty-nine examinations were also made on children aged 5 years and over. The results of two or three examinations on the same child have been used, provided that the child was in a different age group on each occasion. Return visits appear to have been made by a representative sample of the children, as the incidence of knock-knee found at the first examinations is similar to that of the whole series.

Likewise, the proportion of children immunized and receiving vitamin supplements is similar at the first examination and in the complete series.

From an L.C.C. Junior Modern and Infant School.—318 children, aged 5 to 11 years inclusive, were examined. All children in certain classes were seen, provided that their parents had given written permission for examination. These children were not re-examined, and no history was available, as the parents were not present.

History and Examination

In infant welfare clinics, where the child's mother was usually present, the following history was obtained: birth weight; age at which the child first walked unaided; details of diet, including the duration of breast-feeding and whether the child had vitamin supplements; illness as judged by the number of days the child had spent in bed since it started to walk; any habitual sleeping or sitting posture noticed by the mother; whether the mother had ever noticed anything wrong with the child's legs, feet, or back; if she had, details including any treatment received were noted.

In both the infant welfare clinics and the school the following facts were recorded.

Age in Months.

Weight.—Children in school wore vest and pants only, as did the majority of children in infant welfare clinics. If they were weighed naked or in any other clothes the weight was adjusted accordingly. The actual weights were used in calculations on children under 5 years old, but not enough children were seen for this to be satisfactory in the school age groups. For this reason the indices of Sutcliffe and Canham (1950) were used when calculating average heights and weights of children aged 5 years and over. (These indices are corrected for age and sex, and have a standard deviation of 15. The indices range from 65 to 135, with 100 representing the mean. Children in this series are rather heavier, after allowing for weight of vest and pants, and taller than Sutcliffe and Canham's subjects. However, it is reasonable to use these indices to compare different groups within this series.)

Height.—This was measured with the children standing barefoot against a vertical tape or rule. The actual heights were used in calculations on children under 5 years, and the indices of Sutcliffe and Canham for older children.

Knock-knee.—This was measured as the child lay or sat with the length of its legs supported on a couch. The legs were held with the patellae facing vertically upwards, the feet dorsiflexed to a right angle, and the inner surfaces of the knees just touching; the distance between the medial malleoli was then measured. In clinical work the amount of knock-knee recorded is usually less than this, as some pressure is applied to approximate the ankles. Four grades of knock-knee were used: Intermalleolar distance of less than 1 in. (2.5 cm.); 1 in. (2.5 cm.) but less than 2 in. (5 cm.); 2 in. (5 cm.) but less than 3 in. (7.5 cm.); and 3 in. (7.5 cm.) and over.

FIG. 1.—Method of grading footprints (see text).