MEGALOBLASTIC ANAEMIA OCCURRING DURING PRIMIDONE THERAPY

BY

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In 1954 Badenoch described the cases of two epileptic patients who developed megaloblastic anaemia while under treatment with phenytoin sodium, and subsequently 10 further such cases were recorded (Hawkins and Meynell, 1954; Chalmers and Boheimer, 1954; Rhind and Varadi, 1954; Webster, 1954; Berlyne *et al.*, 1955; Ryan and Forshaw, 1955). All the patients had received phenytoin sodium; in all but one instance, where no mention is made of the fact, phenobarbitone had been given in addition, and sometimes other anticonvulsant drugs had supplemented therapy. In two instances primidone was given in addition to the phenytoin sodium and phenobarbitone (Chalmers and Boheimer, 1954; Berlyne *et al.*, 1955).

In nine instances it is reported that free hydrochloric acid was present in the gastric juice; the serum vitamin-B_{12} level was measured and found to be normal in four; the absorption of labelled vitamin B_{12} was normal in the three cases in which it was measured; fat absorption was normal in three and reported as low during a three-day period in one. In three instances gastric mucosa was examined following biopsy and was found to be normal. Four patients showed haematological improvement while under treatment with cyanocobalamin, but in two (Webster, 1954; Ryan and Forshaw, 1955) it is possible that the improvement was due rather to the cessation of anticonvulsant therapy. In one of the cases (Chalmers and Boheimer, 1954) the authors themselves considered that the patient had coincidental pernicious anaemia, while in the fourth patient (Badenoch, 1954) there is insufficient information for a possible explanation to be given. In six instances folic acid therapy was successful where cyanocobalamin had been ineffective.

In all the cases referred to above, the various authors have considered it likely that phenytoin sodium was the agent responsible, but the mechanism of production of the anaemia has not been established. However, in a paper giving a general survey of the megaloblastic anaemias (Girdwood, 1956) an account is given of a patient who did not receive phenytoin sodium and who developed megaloblastic anaemia on two occasions while under treatment with primidone and phenobarbitone.

The present report is of another patient who developed megaloblastic anaemia while receiving primidone ("mysoline") and phenobarbitone for epilepsy.

Case Report

A 42-year-old married woman was admitted to hospital in June, 1955. For about five months she had been feeling tired and generally unwell. Her diet had been satisfactory and there was no history of diarrhoea. She had not been abroad. For about 26 years she had suffered from epilepsy, and for this had been receiving phenobarbitone, ½ gr. (32 mg.) thrice daily, and primidone, 250 mg. twice daily, for the period of seven months before admission to hospital. During January, February, and March, 1953, phenytoin sodium, 1½ gr. (100 mg.) thrice daily, and phenobarbitone, ½ gr. (32 mg.) thrice daily, were given, but no phenytoin sodium was administered in the 25 months before admission.

The patient was obviously severely anaemic. No abnormality was found in the chest or abdomen, and at no time was there subjective or objective evidence of any neurological abnormality. The haemoglobin level was 4.1 g. per 100 ml.; red cells, 1,300,000 per c.mm.; P.C.V., 17%; M.C.V., 130 cubic microns; M.C.H.C., 24%; reticulocytes, 1%; and the marrow was megaloblastic. Owing to her poor general condition the doctor who first saw the patient in hospital transfused her with 2 pints (1,140 ml.) of blood and gave 100 µg. of cyanocobalamin intramuscularly without first taking blood for serum vitamin-B_{12} estimation: cyanocobalamin in the same dosage was given on the two following days. To this treatment there was no reticulocyte response, and the marrow remained megaloblastic. Free hydrochloric acid was present in the gastric juice. A differential test for urinary folic-acid excretion (Girdwood, 1953) was carried out, and this did not give evidence of malabsorption of synthetic folic acid, the results being: (*a*) output after 5 mg. of folic acid subcutaneously, 1.16 mg.; (*b*) output after 5 mg. of folic acid given by mouth, 1.52 mg. At the time of this test the patient was receiving 250 mg. of primidone twice a day and 1 gr. (65 mg.) of phenobarbitone three times a day. (The addition of 250 mg. of primidone and 1 gr. (65 mg.) of phenobarbitone to 1,000 ml. of urine did not interfere with the recovery of 5 mg. of added folic acid.)

The patient continued to receive these anticonvulsants together with 5 mg. of folic acid thrice daily by mouth. To this there was a satisfactory haemopoietic response, the reticulocyte peak being 18%. The haemoglobin level rose to 7.7 g. per 100 ml. and the red-cell count to 2,440,000 per c.mm. in 10 days.

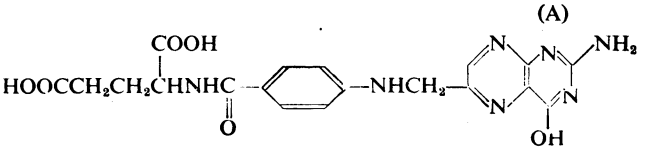
After three weeks' treatment with folic acid the excretion test was repeated and the results were (*a*) 1.98 mg. and (*b*) 1.90 mg.; the patient continued to receive the same anticonvulsants during the test. Two months later she was seen again. She had continued with phenobarbitone, 1 gr. (65 mg.), three times a day, and primidone, 250 mg., twice a day, but had received no folic acid for three weeks. The blood levels were: haemoglobin, 11.4 g. per 100 ml.; red cells, 4,410,000 per c.mm. The marrow was normoblastic, the serum vitamin-B_{12} level (*L. leichmannii* assay) was 140 µµg. per ml. (normal), liver-function tests revealed no abnormality, and there was normal absorption of glucose from the alimentary tract. A further test for folic acid absorption gave normal results—(*a*) 2.53 mg., (*b*) 2.56 mg.—on anticonvulsant therapy, and when the test was repeated after 48 hours without anticonvulsants the results were again normal: (*a*) 1.94 mg., (*b*) 2.19 mg. While in hospital the patient would not co-operate in eating the diet for a fat-balance test.

Discussion

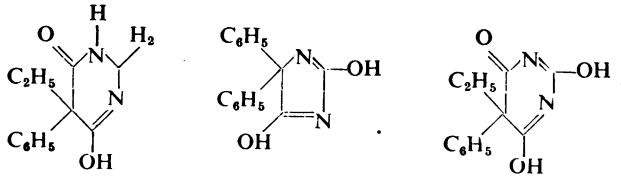
It seems likely that primidone or the combination of primidone and phenobarbitone was responsible for the development of megaloblastic anaemia in this patient as in the other one referred to above.

The chemical structure of pteroylglutamic acid is as follows:

(A)



For comparison the structures of the anticonvulsants mentioned above, in the enol forms, are:



Primidone Phenytoin Phenobarbitone

It will be seen that in primidone and in phenobarbitone there is a six-membered pyrimidine ring, and that there is also a pyrimidine ring in the pteridine nucleus of pteroylglutamic acid—at (A). In phenytoin there is a five-membered hydantoin ring, but the general structural similarity of all four substances can be seen above. Epilepsy is a common disorder and anticonvulsant drugs are used in large quantities; megaloblastic anaemia from the use of phenobarbitone alone has not been recorded and its occurrence after phenytoin or primidone therapy is very rare. Nevertheless, in view of the structural similarities it is possible that in certain circumstances these last two substances act as competitive inhibitors of some enzyme system normally involving folic acid as a co-factor. Whether or not the coincidental administration of phenobarbitone is important has not been established, but it is surprising that primidone therapy should lead to megaloblastic anaemia while prolonged administration of the closely related phenobarbitone alone does not appear to do so.

Summary

An account is given of a patient who developed megaloblastic anaemia while under treatment with primidone and phenobarbitone. There was no response to injections of cyanocobalamin, but a good response occurred to folic acid therapy. Tests for folic acid excretion gave no evidence of malabsorption of synthetic folic acid. It is possible that primidone or phenytoin may in certain circumstances act as competitive inhibitors of some enzyme system normally involving folic acid as a co-factor.

Our thanks are due to Dr. J. K. Slater for allowing these investigations to be carried out on this patient, who was under his care.

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In the Invalid Children's Aid Association's annual report for 1954–5 it is stated that 1,503 delicate children were placed in Homes during the year. Of these, 1,107 went to recuperative holiday homes, 213 to boarding special schools, and 183 to convalescent homes belonging to regional hospital boards. The majority of the applications reach the association through health or education authorities. The association's case department has continued its work of helping children who are suffering from ill-health, emotional disturbance, or physical handicap. The work has been carried out from headquarters and from 17 local offices in London and the Home Counties by the association's 29 trained social workers, experienced both in family case work and in tackling the special problems presented by a sick or crippled child in the family. These workers have been assisted by a number of experienced voluntary workers, including several who have married or otherwise retired from their professional social work.

NYLON STOCKING DERMATITIS

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Although many millions now wear nylon stockings, contact dermatitis from them is extremely rare. The first reference to dermatitis from dyed nylon stockings was by Dobkevitch and Baer (1947a, 1947b). They described 13 cases seen in the United States; all these patients were found to be sensitive to the dye but did not react to pure nylon. In France the condition has been reported by Sidi and Dobkevitch-Morril (1951) and Vial-Weissenbach (1954), but there have been no previous case reports from this country. Failure, however, to recognize the characteristic pattern of a stocking dermatitis may cause the diagnosis to be missed, as happened in most of the present cases.

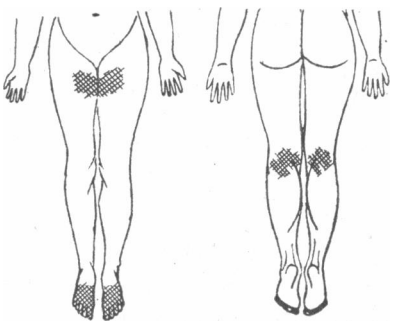

FIG. 1.—Diagrammatic representation of areas usually affected.

Three sites are commonly affected—the dorsa of the feet and toes, the backs of the knees, and the inner part of the upper thighs (Fig. 1). The eruption may also involve the heels, the soles, and the plantar surfaces of the toes. It is usually symmetrical and may be acutely vesicular and exudative, or dry and scaly.

Case Reports

Case 1.—A housewife aged 51 complained of patches of eczema on the right side of the forehead and the nape of the neck for the past seven weeks. Four weeks later she developed a rash on the thighs, the bends of the knees, and the feet. It was noticed that the distribution of the rash conformed to the areas contacted by her nylon hair-net and nylon stockings. It was particularly marked where the strap of her shoes had pressed the stockings against the skin of the feet. She was told to wear no more nylon and was treated with a bland cream. The rash slowly faded in the course of the next year. During this time she tried wearing nylons on several occasions. Each time an exacerbation of the rash occurred after about three days.

Case 2.—A housewife aged 46 had suffered from a retroauricular dermatitis for the past 10 weeks. This was followed by a weeping dermatitis behind the knees and an erythematous rash on the inner surfaces of the thighs and on the dorsal surfaces of the toes. The rash behind the ears cleared when she stopped wearing her hair-net, but relapsed when she wore it again a week later. She had suffered from urticaria in the past, but had no other skin disease.

Case 3.—A factory worker aged 44 had been treated for tinea pedis intermittently over a period of two years. One month previously she developed a rash which began over the soles of the feet on both sides. It spread up the legs, being particularly severe on the medial surfaces of the thighs and producing weeping patches behind the knees. She was