white cells could have been studied. The white cell counts on the next two occasions were also low, being 3000 and 4350 cu./mm. respectively, the latter in June 1962, but when she was admitted this time in May 1964 the picture was that of acute myeloblastic leukemia. This was a rare presentation of acute myeloblastic leukemia, this diagnosis should be considered as a possibility whenever one is confronted with a case of erythema nodosum.

I wish to express my thanks to Drs. J. Ronald and J. Knox, under whose care the patient was admitted, for permission to publish this report: Dr. R. Saaedand, Sister Ross for all the help; Mr. I. Gordon for haematological investigations, and Mr. W. Rose for the photographs.

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ANAEMIA ASSOCIATED WITH PHENOBARBITONE

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IT HAS been established that treatment with phenobarbitone may produce a macrocytic blood picture. In 1958 Hawkins and Meynell noted macrocytosis in as many as 34 per cent of a group of epileptics receiving phenobarbitone alone. However only two well documented cases of megaloblastic anaemia due to this drug have been reported. (Chanarin, Laidlaw, Loughridge, and Mollin, 1960; Sherwin, Wait, and Cooper, 1960). The purpose of this paper is to present a third case.

Case Report

A woman aged thirty six was admitted to the Victoria Infirmary, Glasgow. She had been thought to be normal until sudden right-sided spasticity appeared at the age of four, and epilepsy at five. Since then she had taken phenobarbitone intermittently, and in the last four or five years had taken 180 mg. daily, with convulsions at about monthly intervals. She led a sheltered life and was well looked after at home. In 1950 severe burns of face and hands necessitated several plastic operations, and in 1958 she was operated on for deformities of the right arm and leg resulting from the spastic condition.

Three weeks before admission she complained of nausea, vomiting, diarrhoea and weakness. There was heavy menstrual loss with abdominal pain. Her general practitioner treated obvious anaemia, but there was no response to intramuscular iron. Pheno-

barbitone was continued in usual dosage and 100 mg. chlorpromazine given daily for a few days.

Investigations: On admission on September 16th, 1963 she was confused and febrile. There was heavy vaginal bleeding. Hb. 2.7 g./100 ml., RBC 0.69 mill./cu. mm., PCV 8 ml./100 ml., MCV 116 cu.µ, MCHC 34%, WBC 800/cu. mm., reticulocytes 1.2%, platelets 19,000/cu. mm. Films showed well-stained red cells, marked anisopoikilocytosis, and many macrocytes. Macropolycytes were present, and a few megaloblasts. Two pints of group A, rhesus positive blood were given, and serum specimens taken before and after transfusion for vitamin B₁₂ and folic acid activity estimation. Direct Coombs test was negative at a dilution of 1 in 40.

Progress: On the following day her condition allowed sternal marrow aspiration to be done before further transfusion of two pints of blood. Erythropoiesis was megaloblastic, with many extremely early forms, with fine nuclear structure, and obvious nucleoli. Few late forms were seen. Giant metamyelocytes and precursors were present, and the metamyelocytes had abnormal nuclear configuration. Mitotic figures were increased.

While serum estimations were awaited the patient was given 1000 µg. vitamin B₁₂ intramuscularly daily for four days with oral iron and her usual phenobarbitone. A chest infection was treated with intramuscular penicillin. Her condition improved, though heavy vaginal bleeding continued. On September 19th direct Coombs was positive at dilutions of 1 in 5 and 1 in 10, negative at 1 in 40. Hb. was 7.4 g./100 ml., reticulocytes 2%, WBC 1,800/cu. mm. (neutrophils 64%) megaloblasts present in blood film. On September 24th the platelet count was still extremely low at a level of 38,000 per

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c.mm. Urobilinogen was found in the urine, and serum albumin was low (2.92 g.).

The vitamin B₁₂ level before transfusion proved to be 225 µg./ml., and afterwards 280 µg. (Bioassay using the organism *L. leichmannii*). Serum folic acid activity was 1.4 mµg./ml., and 2.0 mµg. (Bioassay using the organism *L. casei*). The lower limit of normality was taken as 4.9 mµg. On September 24th folic acid was started. 20 mg. were given intramuscularly for two days, then orally. There was rapid improvement in the patient's general condition. Vaginal bleeding ceased on September 30th. By October 2nd Hb. was 8.6 g./100 ml., reticulocytes 16.2%, platelets 442,000/cu. mm.

Two days after treatment with folic acid was begun, the excretion of formimino-glutamic acid after oral histidine was estimated (Chanarin and Bennett, 1962). The result of 193 mg. during the 8-hour test period compared to the normal of less than 17 mg., confirmed folic acid deficiency. Further investigations showed normal osmotic fragility, direct Coombs positive at 1 in 5 and 1 in 20, normal urinary urobilinogen, serum proteins, urea, liver function tests and fat and nitrogen excretion. (Total fat excretion 3.8 g./day; total nitrogen excretion 1.6 g./day). No lupus erythematosus cells were found. There was no faecal occult blood. Barium meal and follow through were normal. Jejunal biopsy was normal. On two occasions oral glucose tolerance tests were normal. A survey of the patient's ordinary diet showed an excessive intake of over 4,000 calories daily. (Protein 111 g., fat 148 g., Carbohydrate 676 g., Ascorbic acid 56.8 mg.). However, the uncooked food would yield only 70 µg. folic acid daily. It is probable that 50-90% would be lost in cooking, so that at the most favourable estimate 35 µg. would be available. (McCance and Widdowson, 1960).

By October 8th direct Coombs test was only weakly positive. The patient went home on 15 mg. folic acid and 180 mg. phenobarbitone daily, with oral iron. When seen on November 11th she was in excellent health. Hb. was 13.2 g./100 ml. with normal reticulocyte, platelet and white cell counts and negative direct Coombs test. The patient had no convulsions while in hospital or after return home.

Discussion

This patient had definite folic acid deficiency. Serum folic acid activity was low, urinary excretion of formiminoglutamic acid high, and the megaloblastic anaemia responded completely to folic acid. There was no deficiency of vitamin B₁₂. Apart from diet, other causes of folic acid deficiency were excluded. Phenobarbitone was the only drug she had taken for more than a few days. A positive direct Coombs test, becoming negative during treatment, is not unusual in megaloblastic anaemias. (Hawkins and Meynell, 1958), and has been recorded in another epileptic with megaloblastic anaemia due to anticonvulsants. (Chalmers and Boheimer, 1954). Gross thrombocytopenia and severe haemorrhage are also occasionally found in megaloblastic anaemia. (Smith, Smith and Fletcher, 1962). In 1957 Varadi described specific marrow changes in megaloblastic anaemia due to anticonvulsant drugs, but marrow appearances in this case seemed consistent with the severity of the anaemia, and not specific.

The suggestion of Dawson and Johnson (1958) that lack of vitamin C and protein is necessary for "full blown" megaloblastic anaemia was not confirmed.

It has been suggested that anticonvulsant drugs act as competitive inhibitors of cellular enzyme systems which normally involve folic acid, by virtue of structural similarity (Girdwood and Lenman, 1956). Sherwin and his colleagues draw attention to the fact that it is difficult to determine the relative importance of anticonvulsant drugs and dietary deficiency. Folic acid is found in many animal tissues, and particularly in liver, yeast and green vegetables. The minimal daily intake for an adult is probably 50 µg. (Zalusky and Herbert, 1961; Gough, Read, McCarthy and Waters, 1963). The two patients with megaloblastic anaemia previously reported had been on poor diets, but this patient, whose diet appeared excessive on ordinary enquiry, had a daily intake of available folic acid below the minimum. The rarity of megaloblastic anaemia due to a drug in common use suggests that the drug alone is not the cause. Dietary deficiency of folic acid probably must also be present. A recent report has shown that nutritional deficiency of folic acid is more common in temperate zones than previously realised. (Gough and others, 1963) and suggests that phenobarbitone may have been associated with dietary deficiency in two cases of megaloblastic anaemia. An expert dietary assessment is therefore essential when anaemia associated with an anticonvulsant is investigated.

Summary

An epileptic woman, who had been on constant phenobarbitone therapy for several years, developed megaloblastic anaemia with gross thrombocytopenia and severe haemorrhage. It is shown that this was due to folic acid deficiency, and that the patient's diet was low in folic acid. It is suggested that dietary deficiency and phenobarbitone are both necessary to produce megaloblastic anaemia in such cases, and emphasised that an expert assessment of the diet must be made.

I thank Dr. Ian Murray and Dr. Ian Wang for advice and criticism, Dr. Ian W. Pinkerton who performed the jejunal biopsy, Miss M. Banks and Miss P. M. Sweeney, dietetic department, Victoria Infirmary, who assessed the patient's diet, and the patient's general practitioner for his assistance.

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THE ADULT FANCONI SYNDROME

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THE following case demonstrates the clinical features of this condition and also the excellent response to vitamin D therapy. The patient, a woman of 44, had multiple defects of tubular function, osteomalacia and numerous pseudo-fractures. In addition, slit lamp examination revealed a number of conjunctival and corneal crystals. She has now been followed up for fourteen months and radiological cure is almost complete. The cause of this condition in this patient remains uncertain. The urine from nine close relatives has been examined, but no abnormal amino-aciduria has yet been discovered. She has lived all her life in the same area on the north side of Sheffield, and it may be that her diet has long been poor.

Case History

The patient was first seen in October, 1963, having been referred to the medical unit by a rheumatologist. For four years she had suffered from increasingly severe bone pain affecting her shoulders, rib cage, spine and legs. Any movement, especially sitting up from a lying position was difficult. For eighteen months her gait had become waddling in character. Some two years previously she had been on small doses of prednisolone as treatment for her "rheumatism". She had complained of thirst and polyuria for four months, and she also suffered from occasional attacks of unexplained fever with headache.

There was no past history of rickets or coeliac disease. However, her obstetric history was important. She has six live children ranging from eighteen to eleven. Her first baby died aged one month with broncho-pneumonia. In February 1950, a contraction ring developed during labour and her fifth child was delivered by Caesarean Section. Proteinuria and a trace of sugar in her urine had been found one month prior to this delivery. In May 1952, on account of an

oblique lie, her sixth child was also delivered by Caesarean Section and her tubes were then tied. Moderate proteinuria was frequently noted during this pregnancy, in the absence of obvious infection. However, there was no ankle oedema and her blood pressure was 130/70 mm.Hg. Radiographs of her chest and pelvis in 1950 and 1952 showed no evidence of osteomalacia.

Examination (See Fig. 1.) revealed a thin, red faced woman, who was rather deaf. She had a waddling gait. There was some shortening of her spine so that her arm span was disproportionately great. Her ribs were tender and compression of her pelvis was painful. The remaining systems were normal and her blood pressure was 130/110 mm.Hg.

FIG. 1.—Photograph of patient. Height 4 ft. 10 ins. Span 4 ft. 10 ins. (former height 5 ft. 2 ins.) Weight 33 Kg.

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