Hart and Rees (1950) on the influence of cortisone on the tuberculous lesion.

Granulomata of somewhat similar though not identical character to those under review have been found in other cases of phenylbutazone toxicity (Steinberg *et al.*, 1953; O'Brien and Storey, 1954). Associated vascular lesions of the hypersensitive type were present in both these cases, and when necrosis was found it was fibrinoid in type. Widespread microgranulomata were present. The changes in these patients are probably a direct hypersensitivity reaction to phenylbutazone, and they parallel those described by More *et al.* (1946) in persons dying from sulphonamide hypersensitivity. No vascular lesions were found in the patient in the present report, and the granulomata do not appear to originate from phenylbutazone hypersensitivity.

The interstitial myocarditis is non-specific and probably anaphylactoid. Apart from old paravascular fibrillar scarring, no rheumatic lesion was found. Similar myocardial lesions were also described by More *et al.*

The pulmonary histological changes, apart from the granuloma, have many of the characteristics of those described by Gouley and Eiman (1932) for "rheumatic" pneumonia of a proliferative type. These lesions are of a type which may occur in the lungs, independent of any form of therapy, during the course of an acute rheumatic attack. They draw attention to the importance of relating the findings in cases of drug toxicity to the known pathological findings in the diseased state for which the drug has been administered, as well as to the normal. Otherwise, toxic effects may be ascribed to the drug which it does not possess. The coincidence of acute rheumatic lesions and those of rheumatoid arthritis in the present instance also raises the question whether phenylbutazone may not be more toxic in such cases than in cases of simple rheumatoid arthritis.

It is reasonable to suggest that in this case the myocarditis, and the necrosis in the liver and possibly also in the kidney, were related to one another in so far as, with the development of the myocarditis, passive congestion supervened and the anoxia thus induced in the parenchymatous cells of the liver and kidney aided the development of necrosis by the toxic action of phenylbutazone.

Summary

A fatal case of rheumatoid arthritis in a woman of 73 who received phenylbutazone and cortisone is reported. Necropsy revealed multiple pathological lesions, among which hepatic and renal necrosis were prominent; these lesions are ascribed to toxic action by phenylbutazone. An interstitial myocarditis was probably due to hypersensitivity to phenylbutazone. Pleural and epicardial granulomata were most probably modified rheumatoid nodules. Other pulmonary changes conformed to those found in acute rheumatic disease. The importance of relating the pathological changes found in cases of drug toxicity to the known changes found in untreated cases of the disease for which the drug is administered, as well as to the normal, is indicated.

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MEGALOBLASTIC ANAEMIA DUE TO PHENYTOIN SODIUM

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The possibility that phenytoin sodium might produce a megaloblastic anaemia was first suggested by Badenoch (1954), who described two patients on phenytoin sodium therapy with a megaloblastic anaemia and with normal vitamin B_{12} absorption. A total of five further cases have been reported by Hawkins and Meynell (1954), Chalmers and Boheimer (1954), Rhind and Varadi (1954), and Webster (1954), although one of the two cases reported by Chalmers and Boheimer probably had pernicious anaemia. Hawkins and Meynell mention one further example brought to their notice by Dr. J. F. Wilkinson.

Recently we have had under observation two patients with a megaloblastic anaemia and normal gastric acidity who were on phenytoin sodium therapy. In order to determine the frequency of the condition, the records of 56 patients with megaloblastic anaemia who were admitted to Whiston Hospital during the last four years were studied, but no further cases were revealed. In addition, blood examinations were made on 102 epileptic patients in Rainhill Mental Hospital, all of whom had been taking phenytoin sodium for several years, and the laboratory records of 140 patients with a haemoglobin value below 70% in Rainhill Hospital during the last four years were surveyed. None of the 102 epileptic patients had a megaloblastic anaemia, but one possible case was discovered from the survey of the records (Case 3).

Case 1

A man aged 32 was admitted to Whiston Hospital in February, 1953; he had had dyspnoea on exertion and lassitude for three months. His diet had been adequate, and there was no history of haemorrhage. He had previously been healthy except for attacks of grand mal, which started in 1939. During the last five years he had been taking 1 gr. (65 mg.) of phenobarbitone and 300 mg. of phenytoin sodium daily, which completely controlled the epilepsy. On examination he was thin (weight 8 st. 1 lb.—51.3 kg.), there was pallor of the skin and mucous membranes, ulcers were seen on both legs, and his temperature was 102° F. (38.9° C.). The tongue and gums were normal, the spleen was not palpable, and there were no abnormal neurological signs. The chest *x*-ray examination showed consolidation in the left mid-zone.

Laboratory Investigations.—R.B.C., 770,000 per c.mm.; Hb, 36% (5.2 g.%); W.B.C., 8,500 per c.mm. (normal differential count); P.C.V., 9%; M.C.V., 128 cubic μ; reticulocytes 2%. Blood films showed macrocytosis, and the sternal marrow contained megaloblasts. Serum bilirubin, 0.7 mg. per 100 ml. Occult blood tests on three specimens of faeces were negative. No excess of faecal fat. A fractional test meal showed the normal amount of free hydrochloric acid.

Treatment.—Vitamin B_{12}, 100 μg., was given daily by the intramuscular route for the first week, and then twice weekly for six weeks. There was a small reticulocyte response of

11.8%, but the haemoglobin rose to 82% (12.1 g.%) within six weeks of the beginning of treatment. He was also given 500,000 units of crystalline penicillin eight-hourly for ten days for the pneumonia, which resolved completely. Phenytoin sodium was stopped at the time of his admission to hospital, but he continued to take ½ gr. (32 mg.) of phenobarbitone daily. In November, 1954, nineteen months after cessation of the vitamin B_{12} therapy, he was feeling very well and had not had any further attacks of grand mal. His weight was 9 st. 3 lb. (58.5 kg.); the blood count was: R.B.C., 4,620,000 per c.mm.; Hb, 112% (16.6 g.%); W.B.C., 8,900 per c.mm.

Case 2

A single woman aged 28 was admitted to Whiston Hospital in July, 1954, having had dyspnoea and lassitude for one week. Her appetite was good, but she had been on a weight-reducing diet. Menstruation was normal and there was no history of haemorrhage. She had previously been healthy except for attacks of grand mal, which had started at the age of 4 years. During the last eight years she had been taking 2 gr. (130 mg.) of phenobarbitone and 300 mg. of phenytoin sodium daily, and the epilepsy had been completely controlled during the previous four years. Examination revealed pallor of the skin and mucous membranes, oedema of the feet, and bruising on both arms and the left buttock; temperature, 103.8° F. (39.9° C.); weight 11 st. 9 lb. (73.9 kg.). The tongue and gums were normal, the spleen was not palpable, and there were no abnormal neurological signs. Chest *x*-ray films showed nothing abnormal.

Laboratory Investigations.—R.B.C., 1,090,000 per c.mm.; Hb, 26% (3.7 g.%); W.B.C., 5,200 per c.mm. (normal differential count); platelets, 98,000 per c.mm.; P.C.V., 13%; M.C.V., 130 cubic μ; M.C.H.C., 29%; reticulocytes, 3%. Blood films showed macrocytosis, and the sternal marrow contained megaloblasts. Serum bilirubin, 1.6 mg. per 100 ml.; red-cell fragility test normal. Direct Coombs test negative. No excess of faecal fat. A fractional test meal showed the normal amount of free hydrochloric acid.

Treatment.—Crystalline penicillin, 500,000 units, was given twice daily for 18 days, but this had no effect on the pyrexia, which settled slowly during the following month as the anaemia improved. One and a half pints (750 ml.) of blood were given on the day after admission, and the haemoglobin value rose to 36%. One week later treatment with 45 mg. of folic acid daily by mouth was started, being continued for two months. This produced a reticulocyte response of 29%, and one month after treament was started the haemoglobin value had risen to 71%. Phenytoin sodium was stopped at the time of her admission to hospital, but she continued to take 3 gr. (0.2 g.) of phenobarbitone daily. In January, 1955, four months after cessation of the folic-acid treatment, she was feeling well and the haemoglobin value was 90% (13.3 g.%).

Case 3

A single woman aged 27 developed lassitude and dyspnoea in March, 1952, when she was an in-patient in the epileptic ward at Rainhill Mental Hospital. She had had attacks of both petit mal and grand mal since 1943, and in addition there was considerable mental deterioration. No history of any other illness was elicited. At the time of her admission to Rainhill Hospital in February, 1951, she was taking 200 mg. of phenytoin sodium and 3 gr. (0.2 g.) of phenobarbitone daily, but it is not known for how long she had been taking phenytoin sodium before admission to hospital. The phenytoin sodium was stopped one month after admission, which was a year before the symptoms of anaemia were first noted. On examination there was pallor of the skin and mucous membranes, the tongue was normal, and the spleen was not palpable; her weight was 13 st. 4 lb. (84.4 kg.).

Laboratory Investigations.—R.B.C., 1,820,000 per c.mm.; Hb, 42% (6.2%); W.B.C., 7,900 per c.mm. (normal differential count); P.C.V., 21%; M.C.V., 115 cubic μ; M.C.H.C., 30%; reticulocytes, 0.5%. Blood films showed a few late megaloblasts, and the sternal marrow contained megaloblasts. The van den Bergh reaction was negative. The faecal fat content and gastric acidity were not estimated.

Treatment.—Vitamin B_{12}, 100 μg., and folic acid, 15 mg., were given daily by the intramuscular route, and 6 tablets of "ferro-redoxon" daily for two months. This produced a reticulocyte response of only 8.5%, but the haemoglobin rose to 90% (13.3 g.%) within the two months. Treatment was continued with 2 ml. of "plexan" intramuscularly twice weekly, and in July, 1952, the haemoglobin level was 95%.

In August, 1952, she died during an attack of status epilepticus. Post-mortem examination revealed congestive changes in the lungs, liver, spleen, and kidneys, but no other abnormality.

Discussion

It seems probable that phenytoin sodium was the aetiological factor in the first two patients, in whom none of the known causes of megaloblastic anaemia were evident. Unfortunately, the third patient was not investigated sufficiently to rule out the possibility of pernicious anaemia or steatorrhoea, but in view of her age and good nutritional state these diagnoses are unlikely. It is improbable that phenobarbitone produced the anaemia, for in two patients its administration was continued for 18 months and four months respectively after cessation of treatment for the anaemia without a relapse occurring. In addition, the absence of a relapse after stopping treatment makes it unlikely that these were cases of idiopathic megaloblastic anaemia, such as those described by Davidson (1948).

Only two (3.4%) out of 58 cases of megaloblastic anaemia admitted to Whiston Hospital in the last four years could be attributed to phenytoin sodium. The rarity of the condition is demonstrated further by the fact that no cases were discovered from a survey of 102 patients who were taking phenytoin sodium, and only one possible case was revealed by a study of the Rainhill Mental Hospital laboratory records for the last four years. In view of the rarity of this condition and the excellent response to treatment the use of this drug is not contraindicated. It is probably wiser, however, to change to another anticonvulsant drug in those patients who develop a megaloblastic anaemia.

Of the total of 10 cases which have been described, seven were treated initially with vitamin B_{12}, but only four showed a good response. On the other hand, there was a good response in the two patients treated with folic acid initially and in three patients who were given folic acid after vitamin B_{12} had failed. Badenoch (1954) showed that the serum vitamin B_{12} level and the vitamin B_{12} absorption were normal in his two patients, and yet one of them who was treated with vitamin B_{12} responded well. In view of these findings it is difficult to explain the pathogenesis of the condition, and further study is required.

Summary

Three cases of megaloblastic anaemia, which were probably produced by phenytoin sodium, are described.

This condition is rare, and no further cases were discovered from a survey of 102 epileptic patients on phenytoin sodium therapy. The anaemia is corrected by folic acid, but the response to vitamin B_{12} is variable.

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