Case 8.—This patient was suffering from malignant hypertension. The initial blood urea was 200 mg. per 100 ml. Following 12.5 mg. of pentacynium the patient complained of drowsiness and a dry mouth. Thirty minutes later she became unconscious, with a systolic pressure of 95 mm. Hg. Elevation of the foot of the bed raised the blood pressure to 130/95. Over the next 12 hours, with a constant pressure reading, consciousness returned. At the end of 18 hours after the injection the blood pressure had reached 250/140. Subsequent doses of 1.25 mg. of pentacynium subcutaneously reduced the B.P. to 140/110. The blood urea, however, rose to 419 mg. per 100 ml. and the patient died in coma three weeks later. Permission for necropsy was not obtained.

Case 9.—This patient, who had severe essential hypertension, cardiac enlargement, and a left-sided hemiplegia, had received a low-protein and low-salt diet for 18 months before admission. His blood pressure had not been controlled by large doses of parenteral pentolinium or mecamylamine by mouth. The initial blood urea was 180 mg. per 100 ml. A satisfactory fall in blood pressure occurred initially with 25 mg. of pentacynium subcutaneously, and normal blood pressure was later achieved with 6.25 mg. subcutaneously each morning. The patient's general condition improved over the next two weeks, and before discharge his blood urea was 80 mg. per 100 ml. He had not experienced any side-effects, and was back at light work.

The incidence of side-effects in our series appears high, and may be partially explained by the dose of drug used and the incidence of renal damage. Nausea and vomiting were probably aggravated by the water drunk in an attempt to maintain urinary flow. The fall in urine flow was marked in all instances and water intoxication might be precipitated under these circumstances.

Drowsiness occurred in all nine subjects, and does not seem to have been commented on previously. It appeared earlier than the maximum fall in blood pressure. This effect, which was not associated with hypotension, has not been recorded with other ganglion-blocking drugs, and may be due to a central action, possibly on the hypothalamus.

Eight patients of this series have been followed up for six months after the study. Blood pressures were still well controlled with 6.25–12.5 mg. of pentacynium once daily, combined with a reserpine preparation three times a day.

Summary

The effect of pentacynium methylsulphate (presidal) on the renal circulation in nine subjects with hypertension has been studied.

A fall in blood pressure to normal levels occurred in all subjects and persisted for at least 16 hours.

Reduction in E.R.B.F. and G.F.R. occurred initially in all subjects by 30 minutes. In four subjects the mean E.R.B.F. and G.F.R. had risen to 50% of the mean control value by 60 to 110 minutes. In two subjects with severe renal damage the values for E.R.B.F. and G.F.R. had risen to greater than their control values by 110 minutes.

The significance of these findings is discussed, and it is noted that satisfactory control of blood pressure may be obtained with a single daily injection of pentacynium.

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FOLIC-ACID STUDIES IN MEGALOBLASTIC ANAEMIA DUE TO PRIMIDONE

BY

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It is well known that a megaloblastic anaemia may develop in patients being treated with barbiturate-like anticonvulsants such as phenytoin sodium (Badenoch, 1954; Hawkins and Meynell, 1954), primidone (Fuld and Moorhouse, 1956), and, very occasionally, other barbiturates (Hobson, Selwyn, and Mollin, 1956). The cause of the anaemia is uncertain. The patients resemble patients with folic-acid deficiency in that their serum vitamin B_{12} concentrations are normal, and they fail to respond, or they respond suboptimally, to treatment with vitamin B_{12}, while responding excellently to treatment with folic acid. However, as there is no evidence of malabsorption of folic acid in these patients it has been generally assumed that the drugs act by interfering with the metabolism of folic acid. In this paper we report studies made on the utilization of folic acid in a patient who developed severe megaloblastic anaemia while receiving primidone (" mysoline ").

Case Report

An Anglo-Indian woman aged 44 was admitted to Hammersmith Hospital on May 28, 1957, under the care of Dr. J. G. Scadding. She had lived in India until August, 1956, when she was brought to England. She had a bilateral hemiplegia, probably due to a birth injury, and at 13 years of age began to have major and minor epileptic fits. She was looked after at home, and until two years before admission had been given bromides and various barbiturates for her fits. Two years before admission treatment with primidone (1 to 2 g. daily) was started and treatment with other barbiturates was stopped. Until six months before admission she was reasonably well and took a well-balanced diet. Shortly after arriving in England she became lethargic, lost interest in her surroundings and refused food, and from this time until the time of admission she ate only tea, bread, biscuits, Horlicks' milk, and an occasional banana. She became progressively weaker and paler, had episodes of diarrhoea, and shortly before admission became incontinent of urine and faeces.

Examination.—The patient was a well-nourished Anglo-Indian, crying out incomprehensibly but able to respond to simple commands. Her mucous membranes were very pale, but there were no skin lesions, purpura, or haemorrhages, and her gums were normal. The lymph nodes were not enlarged and the spleen was not palpable. Her temperature was 97° F. (36.1° C.), she was slightly dyspnoeic, the jugular venous pressure was 10 cm. above the sternal angle, but there was no oedema. Her pulse rate was 120 a minute and blood pressure 110/30. Her heart was not grossly enlarged, but there was a soft apical systolic murmur. Signs of a bilateral hemiplegia were present, more marked on the left than on the right side. There were scars around the left eye, and the left retina appeared disorganized.

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Investigations.—A blood count showed red cells, 600,000/c.mm.; Hb, 2.9 g./100 ml.; P.C.V., 9%; reticulocytes, 3.9%; M.C.V., 150 cubic microns; M.C.H.C., 32%; leucocytes, 4,500/c.mm. (neutrophils 68%, lymphocytes 28%, monocytes 4%); platelets, 95,000/c.mm. A stained film revealed macrocytosis, poikilocytosis, anisocytosis, with occasional polychromatic megaloblasts and myelocytes. A sternal-marrow biopsy showed severe megaloblastic change. The serum vitamin-B_{12} level measured by the *Euglena* assay, was 190 $\mu\mu$g./ml. (normal range, 100 to 900 $\mu\mu$g./ml., Mollin and Ross, 1954). The serum protein was 6.6 g./100 ml. (albumin 3.6 g., globulin 3 g.), serum bilirubin 0.6 mg./100 ml., and urea 28 mg./100 ml. The fractional test meal showed the presence of free acid in the gastric juice; and the absorption of radioactive vitamin B_{12}, measured by the hepatic uptake method of Glass (1954), was normal, an estimated 0.4 μg. being absorbed from a 1-μg. dose of ^{56}Co-vitamin B_{12}. A three-day fat balance was normal, the patient excreting 4.3 g. daily while on a 50-g. fat diet. Fat absorption, using ^{131}I-labelled fat, was studied by Dr. K. Ibbertson; the blood level of iodine in the patient was similar to that found in normal subjects. Vitamin-A absorption was also normal, the blood level rising from 38 to 584 I.U. after a dose of 300,000 units. A glucose-tolerance test and a barium-meal examination revealed nothing abnormal. The urine contained numerous pus cells, and culture gave a heavy growth of *Escherichia coli.*

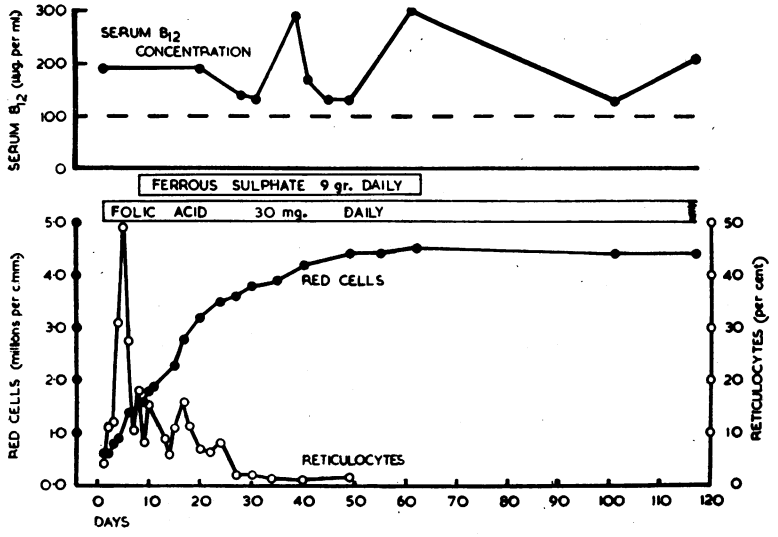

FIG. 1.—Haematological response to treatment.

Course and Treatment

Haematological Response.—The haematological response to treatment is shown in Fig. 1. On the day of admission and on the following day 0.69 mg. of folic acid was injected intravenously. Then 15 mg. of folic acid was given twice daily, by intramuscular injection during the first week, and subsequently by mouth. A third intravenous injection of 0.69 mg. of folic acid was given on the ninth day. A single dose of ascorbic acid (500 mg.) was given on the second day. Treatment with primidone was continued until the third day.

There was a reticulocyte response with a peak of 49% on the fifth day. The red-cell count rose rapidly, but evidence of iron deficiency appeared at the end of the first week with a fall in the M.C.H.C. to 24%. Ferrous sulphate, 3 gr. (0.2 g.), was given three times a day. Seven weeks after admission the blood count was: red cells, 4,600,000/c.mm.; Hb, 14.4 g./100 ml.; P.C.V. 44%; M.C.H.C., 33%.

Other Treatment.—On the fourth day after admission she developed a temperature of 101° F. (38.3° C.), which was due to a urinary infection. She was then given sulphafurazole ("gantrisin"), 2 g. at the start of treatment and 1 g. three times a day for 10 days. With this treatment her fever subsided and her urine became sterile. Phenobarbitone, ½ gr. (32 mg.) three times a day, was also given, and on this regime her fits appeared to be well controlled.

Folic-acid Studies

The absorption of folic acid was studied by measuring the changes in the concentrations of folic acid in the serum after an oral dose of 3 mg. (Chanarin *et al.*, 1958a).

The utilization of folic acid was assessed by measuring the rate of disappearance from the blood of a small dose of folic acid given by intravenous injection (Chanarin *et al.*, 1958b). The dose used for this test was 15 μg. per kg. body weight.

Folic acid in serum was estimated by microbiological assay, using *Streptococcus faecalis R* as the test organism, as described by Teply and Elvehjem (1945), Jukes (1955), and Chanarin *et al.* (1958a).

Absorption.—The peak serum folic-acid level in the patient after the oral dose was normal (73 μmg./ml.) (Fig. 2). The peak serum folic-acid concentrations in 55 normal subjects ranged from 40 to more than 140 μmg./ml. The results of three normal subjects and three patients with treated folic-acid deficiency associated with idiopathic steatorrhoea are included in Fig. 2 for comparison.

Utilization.—The rate of clearance of folic acid from the plasma was studied after an intravenous dose of 15 μg./kg. body weight (0.69 mg.): (1) before treatment was started, while the patient was still receiving primidone; (2) on the following day, when treatment with primidone had been stopped and after the patient had received a large dose of ascorbic acid; and (3) on the ninth day, after the patient had received large doses of folic acid. Fig. 3 shows that the clearance of folic acid in all three tests was similar to the clearance found in normal subjects and unlike the very rapid clearance found in patients with a megaloblastic anaemia due to folic-acid deficiency.

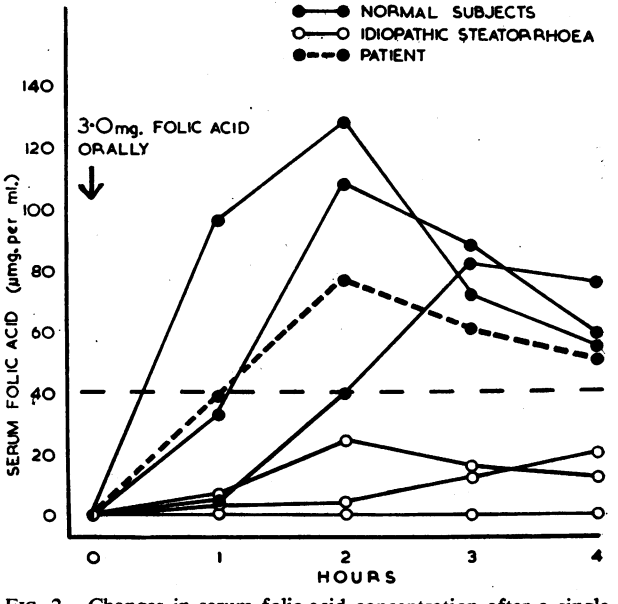

FIG. 2.—Changes in serum folic-acid concentration after a single oral dose of 3 mg. in three normal control subjects, three patients with idiopathic steatorrhoea, and the patient. Interrupted horizontal line denotes lowest peak level (40 μmg. per ml.) of folic acid found in 55 control subjects.

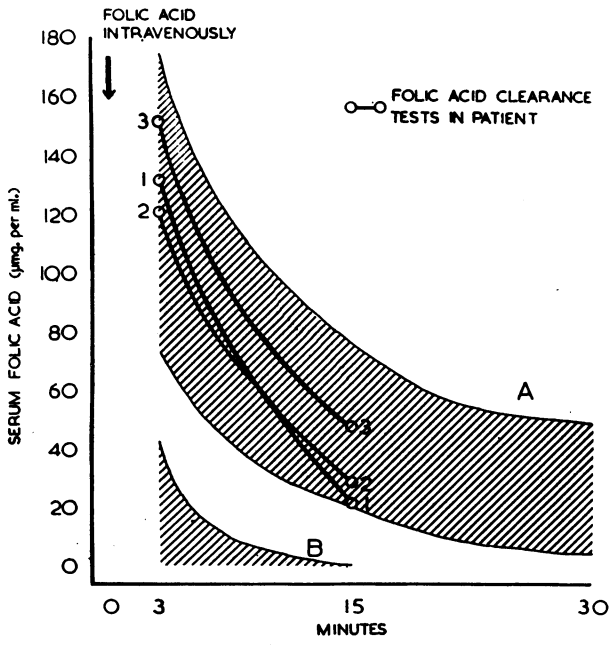

FIG. 3.—Rate of clearance from plasma of an intravenous dose of folic acid: in the patient 1——1=before withdrawal of primidone; 2——2=after a large dose of ascorbic acid; 3——3=after treatment with folic acid. A, In 35 control subjects. B, In 11 patients with megaloblastic anaemia due to folic-acid deficiency.

Discussion

The megaloblastic anaemia in this patient appeared to be due to the anticonvulsant drug primidone. She was not suffering from a gastro-intestinal malabsorption syndrome, for she absorbed vitamin B_{12}, folic acid, fat, vitamin A, and glucose normally. Although her diet was probably defective in vitamin B_{12}, there was no evidence of vitamin-B_{12} deficiency and her serum vitamin-B_{12} concentration was normal.

The megaloblastic anaemia in these patients resembles that seen in pregnancy and in certain patients with intestinal malabsorption syndrome who develop uncomplicated folic-acid deficiency. The serum vitamin-B_{12} concentration in each of these three groups of patients is usually normal and the patients respond optimally only when they are treated with folic acid. In a general sense, therefore, patients developing a megaloblastic anaemia on treatment with anticonvulsants may be considered to be suffering from "folic-acid deficiency." Our results, however, suggest that the pathogenesis of the "folic-acid deficiency" in these patients is different from that in the pregnant patients and in the patients with folic-acid deficiency associated with intestinal malabsorption syndrome. These latter patients clear a small intravenous dose of the vitamin from their plasma very rapidly (Chanarin *et al.*, 1958b), and this has been interpreted as indicating true folic-acid deficiency with depleted tissue stores. In this patient, however, the rate of clearance of intravenously injected folic acid was normal. Hence it seems that there was no tissue deficiency of folic acid in this patient. The anaemia is thus probably not due to deficiency of folic acid but to interference by the anticonvulsant drug with the action of available folic acid in cellular metabolism. That tissue stores of folic acid are present in these patients is supported by the observation that the withdrawal of primidone will itself bring about relief of the anaemia (Christenson *et al.*, 1957).

The development of megaloblastic anaemia in patients receiving anticonvulsants is analogous to the megaloblastic change which develops in patients with leukaemia who are treated with 6-mercaptopurine or with various folic-acid antagonists. As one would expect, the folic-acid clearance in patients with leukaemia who develop such megaloblastic change remains unaltered (Chanarin *et al.*, 1958c).

The action of folic acid in producing a response in patients with megaloblastic anaemia associated with anticonvulsants is also presumably analogous to the action of folic or folinic acid in reversing the megaloblastic change in patients being treated with folic-acid antagonists, and similar to the action of *para*-aminobenzoic acid in overcoming sulphonamide inhibition in micro-organisms.

Although these observations provide a satisfactory explanation for the action of the anticonvulsant drugs, they do not explain why relatively few patients develop frank megaloblastic anaemia. The observations of Hawkins and Meynell (1957) suggest that about one-third of patients receiving anticonvulsants develop a macrocytosis which responds to folic acid. The effectiveness of these drugs in converting these minimal haematological changes into frank megaloblastic anaemia must depend on other factors such as associated vitamin-B_{12} deficiency (Kidd and Mollin, 1957), associated ascorbic-acid deficiency (Gydell, 1957; Kidd and Mollin, 1957), and probably the dietary intake of folic acid.

Summary

Folic-acid studies were carried out on a patient who developed a severe megaloblastic anaemia while being treated with the anticonvulsant drug primidone.

The absorption of folic acid was found to be normal.

However, by contrast with megaloblastic anaemia due to folic-acid deficiency the tissue stores of folic acid were normal.

It is concluded that the anaemia was not due to folic-acid deficiency but to interference with the tissue metabolism of folic acid.

We thank Dr. J. G. Scadding for permission to carry out these studies on his patient; Professor J. V. Dacie for his interest and advice; Dr. K. Ibbertson for carrying out an ^{131}I-labelled fat-absorption test; and Miss B. B. Anderson for help with folic-acid assays.

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Speaking at the opening of the Commonwealth Chest Conference in London on July 10, the MINISTER OF HEALTH, Mr. Derek Walker-Smith, said that the advances of recent years had brought total eradication of tuberculosis increasingly within the range of possibility. During the ten years since the start of the National Health Service, new cases of tuberculosis had fallen in England and Wales by 38% and deaths by 78%. This striking decline had brought both social and economic benefit, reflected not only in enhanced well-being of individuals but also in freeing hospital resources for the treatment of other ills. In tuberculosis more than in most diseases, continued the Minister, Government action could claim a good deal of credit. As Sir William Osler had said, tuberculosis was a social disease with medical aspects. The recent history of tuberculosis in this country illustrated the value of preventive measures. In England and Wales 27 million *x*-ray examinations had been carried out since the introduction of M.M.R. in 1943; and in recent years over 20% of all cases of tuberculosis had been detected by this means. Since 1949 over a million people had received B.C.G. vaccination.