Discussion

Although mid-diastolic apical murmurs may be heard in cases of anomalous pulmonary venous drainage (Gardner and Oram, 1953 ; Whitaker, 1954), a confident diagnosis of mitral stenosis was made in this patient because of the presence of an enlarged left atrium fluoroscopically, and a well-marked opening snap clinically. In view of the grave condition of the patient it was decided to perform a mitral valvotomy before undertaking any special investigations such as cardiac catheterization. The findings at subsequent cardiac catheterization confirmed the presence of partial anomalous pulmonary venous drainage into the right atrium via the superior vena cava.

In a patient with mitral stenosis the presence of anomalous pulmonary venous drainage would probably add to the disability by increasing the pulmonary artery pressure. Relief of the mitral stenosis would be expected to result in improvement in the patient's condition, though perhaps not to the same extent as in a patient with normal pulmonary venous drainage. The result in this case has been excellent and most gratifying.

Taussig (1947), Snellen and Albers (1952), and Whitaker (1954) noted that the typical " figure-of-8 " or " cottage-loaf " cardiovascular shadow was diagnostic of total anomalous pulmonary venous drainage into a left superior vena cava. Grishman *et al.* (1951) reported a case of partial anomalous pulmonary venous drainage, and the teleradiogram reproduced in their report showed the typical " figure-of-8 " appearance. However, as the difference in oxygen content between blood from the right atrium and the femoral artery was only 0.5 vol.%, which might be within the range of experimental error, it is possible that their patient in fact had total pulmonary venous drainage into a left superior vena cava. The normal arterial oxygen saturation in their patient would not exclude this possibility, as a similar finding was noted in a proved case by Gardner and Oram (1953). In the case reported here, although only part of the venous drainage of the lungs was into the left superior vena cava, the typical " cottage-loaf " cardiovascular shadow was present and was explained by the additional presence of tricuspid incompetence with subsequent increased prominence of the superior vena caval shadow.

Summary

A case is reported of the association of mitral stenosis and partial anomalous pulmonary venous drainage into a left superior vena cava. An excellent result was obtained by mitral valvotomy.

The radiological appearance was suggestive of total drainage of pulmonary veins into a left superior vena cava, and was explained by the additional presence of tricuspid incompetence.

I thank Dr. K. Shirley Smith, in whose department the cardiac catheterization was performed, and Mr. J. R. Belcher for permission to record this case.

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Opuscula Medica, a new Swedish monthly journal, contains short papers and records cases of interest discussed at staff meetings of the Södersjukhuset, Stockholm. It is edited by Dr. Sixten Kallner, head of the Department of Medicine at the Södersjukhuset. At present papers are in Swedish, but it is hoped shortly to include brief summaries in other languages.

OBSERVATIONS ON MEGALOBLASTIC ANAEMIAS AFTER PRIMIDONE

BY

H. FULD, M.D., M.R.C.P.Ed.
Consultant Physician, Sefton General Hospital, Liverpool

AND

E. H. MOORHOUSE, M.R.C.S., L.R.C.P.
Pathologist, Sefton General Hospital, Liverpool

Since Badenoch (1954) reported " a hitherto undescribed form of megaloblastic anaemia " in two young epileptic women receiving anticonvulsants, including phenytoin sodium and phenobarbitone, a number of papers on megaloblastic anaemia during anticonvulsant therapy have appeared.

Hawkins and Meynell (1954) remarked that this would be the first instance of drug-induced megaloblastic alteration of the bone marrow. Their case was a male epileptic who had taken phenytoin sodium, 4½ gr. (0.29 g.) daily for 13 years. Folic acid succeeded after vitamin B_{12} had failed to cure the anaemia. Phenytoin sodium was continued throughout the treatment. Chalmers and Boheimer (1954) described the case of a patient who over a period of five years had taken barbiturates, phenytoin sodium, and, for some months, primidone before the discovery of a megaloblastic anaemia. They could not come to definite conclusions about the particular drug which caused the anaemia, there having been no previous report on possible effects of primidone on blood formation. Their patient kept well on a combination of folic acid and primidone. Rhind and Varadi's (1954) and Webster's (1954) papers both dealt with megaloblastic anaemia after phenytoin sodium, the former's patients responding to folic acid, and Webster's case being successfully treated with vitamin B_{12}. Berlyne, Levene, and McGlashan (1955) published the histories of two epileptics developing megaloblastic anaemia, the first after taking phenytoin sodium and phenobarbitone, and the second after taking primidone for three months in addition to phenytoin sodium and phenobarbitone which had been prescribed over four years. The patients did well on folic acid. Ryan and Forshaw's (1955) paper dealt with three cases of megaloblastic anaemia following phenobarbitone combined with phenytoin sodium for the treatment of epilepsy. Vaishnava (1955) added two further cases of megaloblastic anaemia due to phenytoin sodium. Girdwood and Lenman's (1956) patient developed a similar anaemia while receiving primidone and phenobarbitone for epilepsy.

From this review of the literature, it appears that most cases of megaloblastic anaemia after anticonvulsants were caused by a combination of phenytoin sodium and phenobarbitone. Only three cases are reported of megaloblastic anaemia in which primidone may have played a part, and a letter from one of us (Fuld, 1955) contains the only evidence so far of the development of megaloblastic anaemia in patients who for a considerable time have received primidone only. It occurred to us while observing these patients that an opportunity offered itself to study the relationship between primidone and the development of megaloblastic anaemia.

Case 1

A spinster aged 37 was seen on May 1, 1954, with a history of temporal lobe epilepsy since 1951. Barbiturates and bromide had little effect on frequent attacks of grand mal and petit mal. Primidone, 750 mg. daily, was started on May 4. Four and half months later her private doctor (Dr. Goldberg) referred her for consultation on account of lassitude, anorexia, weight loss, and ulcerative gingivitis and stomatitis. The fits had ceased, but she appeared rather ill when seen on September 15. She had an acute glossitis, stomatitis, and macrocytic anaemia (red cells 1,420,000, Hb 37%, colour index 1.3) and a white cell count of 4,550. Megaloblasts were seen in the blood film. The bone marrow was megaloblastic. The gastric juice contained free hydrochloric acid. Glucoce-tolerance, fat-balance, and liver-function tests were all normal.

Primidone was stopped and folic acid, 20 mg. daily, was begun on September 17. The reticulocyte response was good. Clinical and haematological recovery (red cells 4,500,000, Hb 91%, colour index 1.0) was complete on November 23. Folic acid was then stopped and primidone withheld. The blood count on December 28 was : red cells, 4,840,000 ; Hb 97% ; colour index, 1. On that date primidone, 500 mg. daily, was started. No folic acid was prescribed. All was well until March 1, 1955, when macrocytosis reappeared in the blood film. The blood count was : red cells, 4,000,000 ; Hb, 87% ; colour index 1.1. Monthly clinical examination and blood counts were carried out. Macrocytosis persisted and the red-cell count and haemoglobin level slowly went down. On July 19 the blood count was: red cells, 3,130,000 ; Hb, 67% ; colour index, 1.1. Sternal marrow examination on August 9 confirmed reversion to megaloblasia. A few days later 5 mg. of folic acid was added to the primidone, which was now increased to 750 mg. daily for more effective control of her fits. On October 11 her general condition had much improved and she had gained one stone (6.4 kg.) in weight since folic acid had been added to the primidone. The blood count was : red cells, 3,850,000 ; Hb, 75% ; colour index, 0.97. The red cells had become normocytic. On November 22 the count had improved to: red cells, 4,570,000 ; Hb, 94% ; colour index, 1. Her general health remained good.

Case 2

A married woman aged 44 had a history of Jacksonian type of epilepsy since 1950 caused by an oligodendroglioma proved by biopsy and treated by irradiation. Epilepsy persisted, but was much better controlled when she was put on primidone, 500 mg. daily, in October, 1952. From January, 1953, she took 1,000 mg. daily, and in December, 1954, the dose was stepped up to 1,250 mg. No other drug besides primidone was taken by this patient after September, 1952. In Autumn, 1954, she felt tired, lost her appetite, and complained of dizziness and dyspnoea. Her private doctor (Dr. Gibson) ordered a blood count. This was : red cells, 1,200,000 ; Hb, 32% ; colour index, 1.3. Megaloblasts were seen in the film. She was thought to be suffering from pernicious anaemia and received "cytamen" and later "anahaemin" injections without benefit. On February 2, 1955, her blood count was : red cells, 1,030,000 ; Hb, 22% ; colour index, 1.1 ; white cells, 4,850.

She was admitted to hospital on the following day. Her condition was critical and she was given several pints of blood during the first week. The bone marrow was megaloblastic. The gastric juice contained free hydrochloric acid. Fat-balance and liver-function tests were within normal limits. She received 20 mg. of folic acid daily and 750 mg. of primidone from the day of admission. Reticulocyte response was good and there was an uninterrupted clinical and haematological recovery. The blood count on April 22 was: red cells, 4,500,000 ; Hb, 89% ; colour index, 1 ; M.C.V., 93 cubic microns ; M.C.H. 29 $\mu\mu$g. ; M.C.H.C., 31%. She left hospital on April 25. Folic acid was stopped in June and primidone was increased to 1,000 mg. daily. Phenobarbitone, 1½ gr. (0.1 g.) was also taken by her from time to time for headaches. It was decided to continue this treatment well beyond the period of protective action of the folic acid previously prescribed and to carry out physical and haematological examinations at monthly intervals. The patient maintained her good general state, and her blood count has been normal since she left hospital. The last count, on December 8, was: red cells, 4,680,000 ; Hb, 94% ; colour index, 1. The red cells were normocytic. We intend to observe this patient regularly in order to detect early any reversion to megaloblastic anaemia, which, after seven months of primidone without additional folic acid, has so far not occurred.

Discussion

These case reports differ in some aspects from those published so far. They deal with patients who, for varying periods prior to development of megaloblastic anaemia, had taken no drugs besides primidone. In the first case it took a little over four months for a dangerous degree of megaloblastic anaemia to develop. The second patient, however, had taken primidone for two years before the severe megaloblastic anaemia appeared.

Both patients have been followed up under conditions which have allowed us to assess more clearly the relationship between primidone and megaloblastic anaemia and its control by folic acid. In the first case the anaemia relapsed when primidone was restarted and folic acid withheld, and there was a second prompt response to folic acid. The protective effect of folic acid when added to primidone was also proved for the second time. The other patient, who had taken large doses of primidone without damage for almost two years, has so far not relapsed. This is perhaps not surprising when comparing her case history with that of the first patient, who had developed anaemia within a little over four months of taking primidone and whose anaemia could be reproduced in three-quarters of that time (three months). The comparable time for reappearance of anaemia in Case 2 would be 18 months. Only seven months have elapsed so far.

The experiences of other writers coincide with our own in that we find that folic acid protects safely those very few epileptics who develop megaloblastic anaemia after anticonvulsants. Phenytoin sodium and primidone are too valuable to withhold even in patients who develop a megaloblastic anaemia, and a change over to another anticonvulsant is unnecessary provided the patient continues the anticonvulsant and folic acid combination indefinitely.

Various theories have been put forward about the action of an anticonvulsant in producing a megaloblastic anaemia, and about the relationship between folic acid, phenytoin, or primidone and haemopoiesis. Girdwood and Lenman (1956) pointed out "the general structural similarity" of folic acid, primidone, phenytoin, and phenobarbitone, and the possibility of interference by phenytoin and primidone in some enzymatic process normally involving folic acid as co-factor. Even if it is agreed that certain anticonvulsants can inhibit the effects of the active form of folic acid as a co-factor for single carbon unit transfers in the formation of pyrimides and of nucleic acids, there still remains the question why phenytoin and primidone should act this way in certain rare instances while scores of epileptics take these drugs for many years without any effect on haemopoiesis.

Summary

Two cases of megaloblastic anaemia during treatment with primidone are reported. Folic acid had a curative effect and also protected against anaemia when added to primidone. In one patient megaloblastic anaemia recurred three months after primidone treatment was resumed. Again folic acid brought about a rapid recovery.

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Medical Memoranda

Favism in an English-born Child

Favism is a form of acute haemolytic anaemia caused by ingestion of broad beans (*Vicia faba*) or by inhalation of the pollen of that plant. A good review of the subject in English is that of Luisada (1941). The disease usually occurs in members of susceptible families, and the susceptibility seems to be inherited as a Mendelian dominant factor with variable expression, though about 40% of the cases appear to be sporadic (Marcolongo *et al.*, 1953). It is common only around the Mediterranean basin, and the few cases recorded in the Americas have been in families of Sardinian or Sicilian origin (Marcolongo, 1951). Two cases in families from Cyprus living in England have been recorded by Diggle (1953), and McCarthy (1955) has reported a case in an autochthonous British child.

Similar anaemias have been reported as being due to inhalation of the pollen of spring flowers (Bagdad spring anaemia: Lederer, 1941), of the broom (*Genista scoparia*) (Luisada, 1936a, 1936b), and of the odorous product of stinkwood (*Anagyris foetida*) (Carcassi *et al.*, 1950); to the ingestion of berries of the bog-bilberry (*Vaccinium uliginosum*) (often called whortleberry in England) (Frankiel, 1931–2), of the mushroom (*Morchella esculenta*, the morel), of male fern (*Dryopteris filix-mas*) (Gasser, 1951), and of peas (*Pisum sativum*) by a member of a favist family (Carcassi *et al.*, 1951); and as of unknown aetiology by several authors (Brill, 1926; Lederer, 1930; Giordano and Blum, 1937; Bernard, 1950a, 1950b; Fois, 1950). These odd cases suggest that favism is a special form, albeit the commonest, of a disease process which might be called, following Italian example, "allergic icterohaemoglobinuria" (Marcolongo, 1954). It is commonest probably because broad beans have been a staple food (except among the adherents of Pythagoras), whereas morels and bog-bilberries are not, so that repeated exposure to the one is usual, to the others rare. Although this disease is commonest in Sardinia and Sicily, it is familial, so that the migrations and military expeditions of the last 3,000 years will have ensured that it is widely distributed between the Pillars of Hercules and the banks of the Indus.

In 1952 it became necessary to make a diagnosis of favism in an English-born child.

CASE HISTORY

A female child aged 2½ years had had a feverish illness for a day or two, but when seen on June 16, 1952, no abnormal signs were detected. During the evening of the next day there was slight scleral icterus but no enlargement of lymphatic glands, liver, or spleen, and no purpura. On June 18 she was pale and increased urobilinogenuria was noted. Laboratory tests showed: haemoglobin, 4.4 g./100 ml. (30%); erythrocytes, 1,500,000; leucocytes, 55,000 per c.mm. (42% neutrophils and 46% lymphocytes); normoblasts, 2,200 per c.mm.; marked polychromasia and some anisocytosis were present.

Haemolytic anaemia of unknown aetiology was diagnosed and a transfusion of the packed cells from 450 ml. of blood was given. The patient thereafter made an uninterrupted recovery, the haemoglobin rising to 71% on the 19th and jaundice having disappeared by the 23rd. A marrow film taken on the 18th showed 33.8% lymphocytes, and a leuco-erythrogenetic ratio of 4.25 (normal less than 2.65), thus showing increased erythropoietic activity.

The clue to the diagnosis was given by the appearance of the father, who was obviously of Mediterranean anthropological type. The suggestion of favism was made to him. Inquiries at home revealed that the patient had eaten heartily of broad beans at midday on the 17th, a few hours before the scleral icterus had been noted; and she had probably eaten small quantities of beans a day or two before.

The father was born in Bagdad into a family of Mesopotamian origin. The mother was born in Wales, but both her parents had been born in Bagdad into families of Mesopotamian origin unrelated to each other or to that of the father. No blood relations on either side had ever had any disease which could be described as favism, Bagdad spring anaemia, or Lederer's anaemia—and an account was obtained of all four grandparents, nine uncles and aunts, and eight more distant relatives.

There is no absolute proof that this child has suffered from favism, although the evidence would suffice for most observers. Obviously it would be unethical to try to prove it by inducing another attack. The real value of such cases is to indicate how the present *Völkerwanderungen* are bringing to our shores examples of disease which once had to be sought half a world away.

GEORGE DISCOMBE, M.D., B.Sc.,
W. MESTITZ, M.D.,
Central Middlesex Hospital, London, and
Royal Alexandra Hospital for Sick Children, Brighton.

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Radiological Demonstration of a Pyelo-chylous Fistula

The condition of chyluria is unusual and the successful demonstration of a lymphatic leak into the renal pelvis more so. These facts would seem to justify publishing this somewhat incomplete case.

CASE HISTORY

A naval rating aged 21 was referred for urinary investigation. He complained that for the last five days he had noticed that his urine was milky and that he had a slight ache in his left groin. There were no other symptoms. Routine urine examination made at a civilian hospital had shown the presence of albumin in quantity as well as numerous red cells and some white cells; no crystals or casts were seen. Some twenty-six months earlier he had noticed the same condition and had been admitted to a Service hospital in the Mediterranean. The onset of his illness at that time was identical with that of his present condition, but in the earlier illness his urine had become pink from blood-staining on the third or fourth day. He was told at this time that his urine contained fat, and his illness was labelled chyluria. Investigations failed to discover any cause and he was invalided home for further