Megaloblastic Anemia from Methophenobarbital

By R. J. CALVERT, E. HURWORTH AND A. L. MACBEAN

THE OCCASIONAL DEVELOPMENT of megaloblastic anemia during the administration for months or years of certain anticonvulsant drugs (phenytoin sodium and/or primidone, with or without phenobarbital) has been reviewed by Gydell and Newman and Sumner. Our report concerns an epileptic patient who presented as a gynecologic emergency with this blood disorder after eight years of treatment with phenyl-methyl barbituric acid ("Rutonal") in standard dosage. This drug has not previously been incriminated.

CASE REPORT

A 39-year-old spinster was admitted to this hospital in a state of prostration on January 24, 1957 with a 10-day history of unremitting menorrhagia. From the age of 10 she had had frequent, major epileptic seizures for which she began taking methophenobarbital (0.2 Gm. t.d.s.) in 1949. This therapeutic dose had been taken regularly up to the day of admission. Apart from iron tablets no other drug had been taken recently.

Her diet was low in first-class protein. Her menstrual history was normal. Her records showed that in December 1954 her hemoglobin level was 12.4 Gm. per 100 ml.; and in July 1956 it was 8.0 Gm. per 100 ml., with an erythrocyte count of 2,950,000 per cu. mm. and color index of 0.95. Iron tablets were then prescribed.

Examination

She was of spare build with extreme pallor and sighing respirations. She had moderate jugular venous distension, but no icterus, oedema or palpable lymph nodes. Her tongue and fingernails were normal. Her pulse rate was 106 per minute, with poor volume but regular rhythm. Her heart was not enlarged; its sounds were of fair quality, and a hemic murmur was heard. Blood pressure was 85/40 mm.Hg. Her abdomen was normal except for a palpable nontender spleen extending 4 cm. below the costal margin. There was a steady vaginal loss of clots and "watery" blood. Vaginal and rectal examinations disclosed no abnormality. The only other unusual feature was many round and oval retinal hemorrhages.

Investigation and Treatment

Immediate blood examination revealed a hemoglobin level of 4.3 Gm. per 100 ml.; erythrocytes, 730,000 per cu.mm.; reticulocytes, 3.6%; PCV, 11%; MCHC, 39%; MCV, 150 cu. μ; leukocytes, 4,200 per cu.mm. with normal proportions and appearances; and platelets, 104,000 per cu. mm. The blood film was typical of a megaloblastic anemia. The sternal marrow smear was confirmatory. The direct Coombs' test was negative. On paper electrophoresis, the pigment migrated with the albumin, as we have found in another patient with methemalbuminemia. Surprisingly, the concurrent serum bilirubin level was only 0.9 mg. per 100 ml. The urine also was dark brown and contained an excess of urobilin and urobilinogen, but no bilirubin; these features persisted for one week. Spectroscopic examination of the urine on the fourth day showed no blood pigment.

Blood transfusion was begun soon after admission. During the first 24 hours she received
MEGALOBLASTIC ANEMIA FROM METHOPHENOBARBITAL

one pint of whole blood and two pints of packed red cells. By then her hemoglobin level had merely risen to 5.0 Gm. per 100 ml. Persistent, though diminishing, vaginal bleeding necessitated intermittent blood transfusion in the next two days. All barbiturates were prohibited. Bromide or, occasionally, paraldehyde was given as temporary anticonvulsant treatment. On each of the first two days folic acid (15 mg.) and cyanocobalamin (250 μg.) were given intramuscularly. She was now fit for gastric aspiration. Analysis showed ample free hydrochloric acid. Folic acid (15 mg. i.m., daily) alone was continued. During the second week she was given "Imferon" (an iron-dextran complex), 2 ml. i.m., daily.

Further investigation revealed normal values for serum electrolytes, blood urea (19 mg. per 100 ml.) and hepatic tests (thymol turbidity, 2 units; zinc sulphate turbidity, 4 units; serum albumin, 3.9 Gm. and globulin 1.4 Gm. per 100 ml.; and serum alkaline phosphate, 8.9 King-Armstrong units per 100 ml.). The prothrombin index was 87%. The Wassermann reaction was negative. Although slight but definite porphyrinuria was demonstrated for two successive days early in the second week, it was not detected later; nor was there any hint that it had occurred previously.

Special investigation was arranged to clarify the basis of the megaloblastic anemia. The initial serum-vitamin-B12 level, measured by the euglena assay, was 130 μg. per ml. (normal range 100–900 μg. per ml., Mollin and Ross'). The absorption of radioactive vitamin B12, using the fecal excretion technic (Heinle et al.), was normal, since our patient absorbed 0.5 μg. from an oral dose of 1.0 μg. of vitamin B12 labeled with Co" (specific activity 1.0 mc. per mg.). The urinary excretion of folic acid was measured by Dr. I. Chanarin (Postgraduate Medical School of London), using Strep. faecalis, after the patient had been treated with folic acid for 13 days. The procedure was that described by Girdwood. The patient excreted 1.7 mg. of folic acid in 24 hours, after an oral dose of 5 mg. This result falls within the range found in control subjects. The standard oral glucose tolerance test, using capillary blood, gave a normal curve (fasting level, 103 mg. per 100 ml.; 171 mg. and 116 mg. per 100 ml. at 30 and 180 minutes, respectively, after the ingestion of 50 Gm. of glucose). The serum-calcium levels (8.5, 8.6, 9.3, and 9.4 mg. per 100 ml. at weekly intervals) were fairly constant, even though slightly below normal limits. The serum inorganic phosphate value was normal (2.6 mg. per 100 ml.). The fat-absorption test, using a 50 Gm. fat intake daily for the 2 days before and for the 6 days of the test, showed 90.3% absorption, which lies just within the normal range. The barium-meal study revealed a normal small intestinal pattern.

Response to Treatment.

The vaginal bleeding stopped after one week, during which time the patient received ethinyl oestradiol (0.5 mg. t.d.s.). The retinal hemorrhages had disappeared one week after admission. Splenomegaly persisted unchanged. Brief grand mal attacks occurred about 3 or 4 times a week until treatment with methophenobarbital was resumed. Thereafter, she was free of fits.

The hematologic response to folic acid (15 mg. i.m. daily) was satisfactory with a maximal reticulocyte count of 6.4% on the fifth day of treatment; the corresponding hemoglobin level was 7.5 Gm. per 100 ml. At the end of the first fortnight, when it was verified that her bone marrow cytology was normal, the hemoglobin value was 11.0 Gm. per 100 ml. (reticulocytes, 2.0%) and reached 12.1 Gm. per 100 ml. (reticulocytes, 0.8%) three weeks later when she was discharged from the hospital on March 2, 1957. One week before leaving the hospital she resumed treatment with methophenobarbital (0.2 Gm. t.d.s.), and folic acid (5 mg. t.d.s.) was continued by mouth.

Follow-Up.

Two months after leaving the hospital she was in excellent health and had remained free from fits. Her spleen was as large as it was on admission. Blood examination now showed a hemoglobin level of 13.2 Gm. per 100 ml.; erythrocytes, 4,010,000 per cu.mm.; PCV, 41%; MCHC, 32%; MCV, 102 cu.μ; and leukocytes, 6,000 per cu. mm., with a normal differential count. The dose of folic acid was reduced to 5 mg. b.d. and a fortnight
later to 5 mg. daily, since her hemoglobin level was then 14.3 Gm. per 100 ml. At the time of writing (November 1957) her hematologic picture is normal.

DISCUSSION

Megaloblastic anemia can only be designated drug-induced after the exclusion of other recognized causes. Since our patient had ample free hydrochloric acid, a normal jejuno-ileal pattern, a normal capacity to absorb radioactive vitamin B\textsubscript{12}, a normal initial serum-vitamin-B\textsubscript{12} level and (apparently) normal hepatic function, it seems certain that an impaired vitamin B\textsubscript{12} mechanism was not responsible for the anemia.

The alternative explanation of deranged folic acid metabolism will now be considered. Our patient could absorb folic acid normally. If it is argued that prolonged mild intestinal malabsorption could have been a contributory cause of the anemia then it is difficult to explain her normal capacity to absorb folic acid. Nevertheless, the slight hypocalcemia and the border-line-normal fat absorption leave this conclusion equivocal. The probable explanation is that dietary deficiency of folic acid or interference with folic acid metabolism by methophenobarbital, or both, had over a period of years produced her severe megaloblastic anemia. The anemia had been intensified by persistent vaginal hemorrhage, and perhaps by an intravascular hemolysis, more closely coincident with the time of admission to hospital.

The dietary history merits separate mention. She had seldom had a cooked meal, contenting herself with a monotonous diet of bread and butter, biscuits and cake, and many cups of tea. There is little evidence that in the United Kingdom dietary deficiency of folic acid per se is ever sufficiently gross to cause megaloblastic anemia. It is of interest that, in contrast to the earlier related literature, several recent reports (Girdwood,\textsuperscript{4} Christenson et al.,\textsuperscript{1} Forshaw,\textsuperscript{2} Cydell, case 3,\textsuperscript{6} Newman and Sumner, case 2\textsuperscript{11}) clearly stated that a poor diet had preceded the discovery of megaloblastic anemia associated with anti-convulsant therapy.

The pigment disorders observed defy ready explanation and have not previously been recorded in the literature on megaloblastic anemia during anti-convulsant treatment. Methemalbuminemia of the magnitude we report is rare except in blackwater fever and other conditions with hemoglobinuria. However, neither hemoglobinemia nor hemoglobinuria was detected in our patient. In the first week she had excessive urobilinuria and urobilinogenuria, compatible with the occurrence of intravascular hemolysis\textsuperscript{*}; the fecal excretion of urobilinogen was not determined. Presumably, the hemoglobin moiety of the methemalbumin was released and broken down in the reticuloendothelial system to products for excretion by the hepatoenteric route. If so, this would imply good hepatic function since neither hyperbilirubinemia nor bilirubinuria was detected. The later transient demonstration of small quantities of porphyrin in the urine (not specifically tested for in the first week) did not

\textsuperscript{*}A direct relation cannot be glibly assumed since London and West\textsuperscript{6} suggested that in untreated pernicious anemia much of the bile pigment does not come from the hemoglobin of mature circulating red cells.
Megaloblastic anemia from methophenobarbital

897

coincide with barbiturate medication. Further discussion here of these aspects would be over-speculative.

The exact mechanism by which the prolonged administration of certain anticonvulsant drugs occasionally causes a megaloblastic anemia is uncertain. Girdwood and Lenman pointed out that structurally pteroylglutamic acid, primidone and phenobarbital have each a six-membered pyrimidine ring, whereas phenytoin has a five-membered hydantoin ring. They postulated that primidone or phenytoin might act as a competitive inhibitor of an enzyme system which normally involved folic acid as a co-factor. Recent investigators (Girdwood and Lenman, Chanarin, cited by Christenson et al., Broquist, cited by Forshaw, using microbiologic technics, were unable to demonstrate any interference by primidone or phenytoin in the utilization of folic acid by Streptococcus faecalis. This indirect negative evidence, although interesting, still leaves the question unsettled.

The development of megaloblastic anemia during the use of this class of drugs probably depends inter alia on dosage. Although phenobarbital alone has still to be reported as a cause, the explanation may be the low dose conventionally used to avoid drowsiness. Whereas the usual maximal daily dose of phenobarbital is 0.2 Gm., primidone is invariably, and phenytoin is often, prescribed in much larger doses. Similarly, as stated, our patient had for eight years taken 0.6 Gm. of methophenobarbital daily. Moreover, it is noteworthy that this drug differs structurally from phenobarbital only by the substitution of a methyl for an ethyl radical.

Therapeutically, folic acid is the drug of choice, and recovery will be hastened by the suspension of the anticonvulsant drug(s). Our observation adds to the evidence (Girdwood and Lenman, Hobson et al.) that these patients can absorb folic acid normally. Hence, small maintenance doses should ensure complete hematologic remission when the previously required dosages of the anticonvulsant drugs are reinstituted.

Summary

A 39-year-old spinster presented with a severe megaloblastic anemia after treatment of her epilepsy for eight years with the barbiturate, methophenobarbital, taken regularly and alone in therapeutic dose. This drug appears to have caused the anemia, which may have been conditioned by a folic-acid-poor diet. Hematologic remission followed the administration of folic acid, which she has since continued to take along with her previous dose of methophenobarbital. Disordered pigment metabolism, including methemalbuminemia, is reported and discussed.

Summary in Interlingua

Un innupta de 39 annos de etate se presentava con un sever anemia megaloblastic, manifeste post octo annos de tractamento pro epilepsia con le barbiturato methophenobarbital in administration regular e non combineate in dosage therapeutic. Il pareva que iste droga habeva causate le anemia, possibilemente conditionate per un dieta a basse contento de acido folic. Remission hematologic sequeva le administration de acido folic. Depost ille tempore le
patiente ha continuado prender acido folic insimul con su previe doses de methophenobarbital. Le presentia de disordines del metabolismo de pigmentos, incluse methemalbuminemia, es reportate e discuitite.

ACKNOWLEDGMENTS

We are indebted to: Mr. K. A. K. Hudson and Dr. R. Kempthorne for the opportunity to investigate and treat this patient; Dr. D. L. Mollin, Department of Hematology, Postgraduate Medical School of London, for advice and for the results of the microbiological and radiobiological assays; Dr. D. Dangerfield for supervision of the biochemical studies; Dr. G. M. Shaw-Smith for provision of details of the patient’s earlier medical history and treatment.

REFERENCES

Megaloblastic Anemia from Methophenobarbital

R. J. CALVERT, E. HURWORTH and A. L. MACBEAN