Summary

Results of 750 estimations of serum leucine aminopeptidase on 671 subjects do not support claims that a normal level would exclude the diagnosis of a carcinoma of the pancreas. In our hands the test did not distinguish between carcinoma of the pancreas and other causes of jaundice; it merely denoted the presence of an obstruction to the biliary flow, without reference to the cause of obstruction.

Only extremely rarely does this test yield information not already supplied by the established tests of serum bilirubin and serum alkaline phosphatase.

ADDENDUM.—Of six further patients with carcinoma of the pancreas, tested since the compilation of this paper, five had raised values and one was within normal range.

Our thanks are due to Dr. E. M. Darmady and to the Board of the Portsmouth and Isle of Wight Area Pathological Service for enabling us to obtain a supply of the substrate before it was available in this country. We have also to thank the many clinical colleagues who co-operated in this investigation.

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Medical Memoranda

Granulocytopenia after Treatment with Phenytoin Sodium

Phenytoin sodium ("epanutin") has been used in the treatment of epilepsy for 21 years (Merritt and Putnam, 1938). During this time numerous side-effects have been described—skin rashes, cerebellar incoordination, gastro-intestinal symptoms, hirsutism, and hyperplasia of the gums. Unlike the closely related drug methoin ("mesontoin"), it rarely causes suppression of the bone-marrow. Bernhardt (1950) has described granulocytopenia after treatment with phenytoin, but his patient was also receiving methoin, so that the responsibility for bone-marrow suppression does not necessarily lie with the former.

In view of the rarity of this important side-effect after the use of phenytoin in an epileptic patient, the following case is presented.

CASE REPORT

The patient, a man aged 34, was admitted to hospital with a history of frequent epileptic attacks for about a year. There were no abnormal physical signs, but arteriography demonstrated a small angioma in the Rolandic fissure on the left side. This was successfully removed at operation, without sacrifice of brain tissue. After the operation he was dysphasic and had a right hemiparesis, but these had improved considerably within a week. He had not received

any anticonvulsant therapy before admission, but after operation phenytoin, 100 mg., and phenobarbitone, 50 mg., were given six-hourly. After one week this regime was changed to eight-hourly administration of the same dose of the two drugs, and two weeks later he was discharged to convalescence with this anticonvulsant therapy.

He was readmitted 12 days later in status epilepticus. Intramuscular paraldehyde was given at frequent intervals to bring the fits under control, and phenytoin, 100 mg. three-hourly, and phenobarbitone, 100 mg. six-hourly. On the next day he received 400 mg. of phenytoin and 400 mg. of phenobarbitone, and this was continued till the fourth day after admission, when he complained of a sore throat. On examination he had a temperature of 101° F. (38.3° C.), angular stomatitis, hypertrophic gums, and a profuse growth of monilia over his palate, buccal mucosa, and gums. Haematology showed: haemoglobin, 78%; white-cell count, 2,500/c.mm.; neutrophils, 6%. Phenytoin was stopped immediately, and methoin and primidone ("mysoline") were given, the dose of the latter being increased over the next three weeks, while the methoin was reduced and finally discontinued. Phenobarbitone was continued unchanged. His monilial infection responded satisfactorily to nystatin lozenges. On the day after the cessation of phenytoin, his neutrophil count was 30/c.mm., with a platelet count of 280,000/c.mm. Twenty-four hours later his white-cell count had increased to 3,500, with neutrophils 32%, and bone-marrow examination showed normal regeneration. After a further two days his white-cell count was 7,750/c.mm., with neutrophils 75%, and subsequently remained within normal limits.

COMMENT

That phenytoin was responsible for the granulocytopenia in this patient is suggested by the rapidity with which his white-cell count returned to normal after the cessation of therapy with this drug. The condition was fortunately recognized before irreversible damage had been done to the bone-marrow.

Thirty-eight days elapsed between the beginning of treatment with phenytoin and the onset of symptoms due to granulocytopenia. The maximum daily dose that he received was 400 mg., and for more than three weeks the dose was only 300 mg. daily. The optimal dose-level is said to vary between 200 and 600 mg. daily (Goodman and Gilman, 1955). At no time, therefore, was he receiving a dosage that would be regarded as dangerous.

Methoin (5-ethyl-3-methyl-5-phenylhydantoin) has a well-marked depressant action upon the bone-marrow. Abbott and Schwab (1954) showed that in 23% of their 79 patients treated with it neutrophil counts fell below 2,500/c.mm. In view of the toxicity of this drug, it is surprising that phenytoin so rarely causes granulocytopenia. Its occurrence in this patient probably represents an uncommon constitutional sensitivity to this widely used anticonvulsant drug.

I thank Dr. Michael Kremer and Mr. Valentine Logue for their permission to publish this case.

PAUL TURNER, M.B., B.S., B.Sc.,
 Medical Unit, Royal Free Hospital, London;
 Lately Neurological House Officer,
 The Middlesex Hospital, London.

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