Agranulocytosis after Imipramine and Meprobamate

We have lately observed the fatal outcome of agranulocytosis in a patient after treatment with imipramine ("tofranil") and meprobamate ("equanil") for involutional depression. As both drugs have the reputation of low toxicity and a low incidence of fatality, this case is of interest.

CASE REPORT

A multipara aged 56 was admitted to hospital on April 9 with a history of depression of varying severity and of at least four months' duration. She had been treated for 41 days with meprobamate in 400-mg. doses t.d.s. and imipramine, 25 mg. t.d.s., the dosage of the latter being increased to 50 mg. t.d.s. 10 days before her admission.

She was drowsy and restless and looked critically ill. She complained of sore throat and dysphagia lasting three to four days, was running a temperature of 100.4° F. (38° C.), and had large necrotic ulcerations of the palates and fauces, with bilateral tenderness of the cervical glands.

Investigations.—Urine: albumin +++; deposit nil. Hb, 72% (10.7 g./100 ml.); R.B.C., 4,000,000/c.mm. (reticulocytes, 0.2%); platelets, 120,000/c.mm. Total white cells, 2,100/c.mm. (neutrophils 2%, lymphocytes 83%, monocytes 15%). Liver-function tests: direct bilirubin, 1.2 mg./100 ml.; total bilirubin, 2.1 mg./100 ml.; alkaline phosphatase, thymol turbidity, and flocculation, normal values. Swabs from throat grew coliforms in a mixed culture.

The clinical picture was one of agranulocytosis. Antibiotics, blood transfusion with packed cells, vitamin B_6, and cortisone were given. However, the white-cell count fell to 1,400/c.mm. and the neutrophils to 1%. Terminal bronchopneumonia with right ventricular failure ensued, and she died on her sixth day in hospital.

The histology showed central necrosis with pigment deposits in degenerate cells of the liver; oedema, haemorrhages, and areas of necrosis in the lungs; toxic nephrosis; necrosis of the mucosa covered by heavy growth of fungi in the oesophagus; hypoplasia and fatty infiltration of the bone-marrow, the granulocytes being mainly affected.

COMMENT

Attention has been drawn to the toxic side-effects and hazards of meprobamate (*British Medical Journal*, 1958) and its various idiosyncratic manifestations (Charkes, 1958). Only one fatal case of blood dyscrasia can be traced in the literature (Meyer *et al.*, 1957).

Imipramine can also give rise to numerous untoward side-effects (Fullerton and Boardman, 1959; Segal and Howarth, 1960), and in overdoses to epileptiform convulsions (Brooke and Weatherly, 1959; Levene and Lascelles, 1959) leading to death (Manners, 1960). Leyberg and Denmark (1959) report on a man of 60 who, after four months on imipramine, developed transient leucopenia with stomatitis. Four cases of agranulocytosis have so far been published. The first one (Rothenberg and Hall, 1960), that of a 64-year-old man who manifested the first symptoms after 38 days of taking the drug, recovered. The second reported case ended fatally (Morgan-Hughes and Heald, 1960). It concerned a 72-year-old woman who had been ingesting the drug for 45 days with *Rauwolfia canescens* and amylobarbitone. In the third and fourth reported cases the patients recovered. The former (Bird, 1960), a woman of 44, fell ill after taking the drug for eight weeks, along with salicylates and steroids for her rheumatoid arthritis. The latter (Cohen, 1960), a woman of 70, had been treated for her depressive illness with a daily imipramine dosage of 225 mg. and occasional small infrequent doses of quinalbarbitone for eight weeks, with some interruption, before the clinical picture of a mild agranulocytosis developed. Our patient took the drugs, as mentioned, for 41 days.

It is difficult to say whether meprobamate or imipramine was the culprit, but it is more likely to be imipramine, as it was the common drug used in the cases mentioned above with similar symptomatology and identical aetiology.

Segal and Howarth (1960) raised the question of serious effects of synergic action of other such drugs as chloral and aspirin in large doses on the one hand and the monoamine oxidase inhibitor type of antidepressant drugs in normal doses on the other.

It is striking that the ill-effect of imipramine alone or in combination, in almost all the cases cited above, occurred in elderly persons. Furthermore, the onset of agranulocytosis was manifest in five to eight weeks after the first ingestion of the drug. In the case of severe but reversible leucopenia (Leyberg and Denmark, 1959) the clinical symptoms began even four months after the drug was first given. One would expect an allergic reaction to a drug at the beginning of its ingestion rather than after five to eight weeks. The pathology of our case and that of others indicates toxic aetiology.

Conclusions.—Even if the patient has no side-effects during the first two or three weeks of administration, all is not necessarily well. It would therefore be advisable to carry out white blood counts, at least after four to five weeks of taking the drug and at intervals of two to three weeks thereafter, especially in the elderly, as a low white blood count—say around and below 3,000/c.mm.—may give warning of an impending catastrophe. The administration of imipramine, and particularly its combination with other drugs, needs caution.

We are indebted to Dr. W. Doran, pathologist, for his report on the pathological histology of the case.

T. P. CURRAN, M.B., B.Ch., D.P.M.
E. BARABAS, M.D.
St. George's Hospital, Stafford.

REFERENCES

Bird, C. E. (1960). *Canad. med. Ass. J.*, **82**, 1021.
Brit. med. J., 1958, **2**, 1586.
Brooke, G., and Weatherly, J. R. C. (1959). *Lancet*, **2**, 568.
Charkes, N. D. (1958). *Arch. intern. Med.*, **102**, 584.
Cohen, S. I. (1960). *Lancet*, **2**, 1194.
Fullerton, A. G., and Boardman, R. H. (1959). Ibid., **1**, 1209.
Levene, L. J., and Lascelles, C. F. (1959). Ibid., **2**, 675.
Leyberg, J. T., and Denmark, J. C. (1959). *J. ment. Sci.*, **105**, 1123.
Manners, T. (1960). *Lancet*, **2**, 932.
Meyer, L. M., Heeve, W. L., and Bertscher, R. W. (1957). *New Engl. J. Med.*, **256**, 1232.
Morgan-Hughes, J. A., and Heald, I. N. S. (1960). *Lancet*, **1**, 552.
Rothenberg, P. A., and Hall, C. (1960). *Amer. J. Psychiat.*, **116**, 847.
Segal, M , and Howarth, E. (1960). *Brit. med. J.*, **1**, 348.

The effect that variations in pressure, temperature, and humidity have on radiation dosimeters—whose unit of measurement, the roentgen, is defined in relation to standard air conditions—is discussed in a recent publication of the National Physical Laboratory, *The Effect of Variations in the Ambient Air on the Calibration and Use of Ionization Dosemeters.* Tables of correction factors are given which, particularly in relation to humidity variations, are a valuable aid in precision dosimetry. (By G. P. Barnard, G. H. Aston, and A. R. S. Marsh. H.M.S.O., price 2s. 6d., by post 2s. 10d.)