Although the side-effects may be described as unpleasant rather than dangerous they do represent a drawback to treatment with the drug. A number of patients find them intolerable, and considerable persuasion is necessary on occasion to maintain the patient on the drug even though he may have responded well as regards his depressive illness.

Summary and Conclusions

A six-months follow-up study of 97 patients included in a clinical trial of imipramine confirms that this drug is an effective method of treatment of both endogenous and reactive depression.

A strict comparison with the effects of E.C.T. in endogenous depression was not carried out, but from figures obtained in another trial it is clear that the relapse rate among cases showing a good immediate response to E.C.T. is so high that after six months the effects of E.C.T. and of imipramine are of a similar order.

It appears that even though the initial response to imipramine is dramatic and the maintenance dose seemingly adequate, relapse may occur in occasional cases. This seems most likely to occur within two months of the initial improvement. Regular surveillance of all cases under treatment with imipramine is rendered all the more necessary because of this possibility.

The duration of treatment with imipramine necessary to avoid relapse is very variable and is likely to be an individual matter. It may be related to the natural periodicity of depressive illness. The mean duration of treatment was about six months, with a range of one to more than 14 months.

Although an initial daily dosage of 250 mg. was used, experience with patients not included in this trial suggests that 150 to 200 mg. of imipramine a day is sufficient in a substantial number of patients, but the larger amount is necessary in some. Once maximal improvement has been obtained the dose can be reduced to 75 to 100 mg. daily. In a few patients higher maintenance doses are necessary (150 to 200 mg.), and any attempt to reduce the dose below this level leads to a return of symptoms.

In cases responding to imipramine, improvement occurred in five days to six weeks, with a mean of 18 days. Maximal improvement was seen after periods of treatment varying from 1½ to 24 weeks, the mean being seven weeks. There was no indication of why such large variations in the individual responses should exist. It is not possible to declare treatment with imipramine a failure unless it has been given for six weeks, though after three weeks the chances of success show a steady decline with the passage of time. It must be accepted that when the response to the drug is so protracted, unless the symptoms are relatively mild, the advantages of drug treatment over E.C.T. become questionable, for the latter form of treatment can be relied upon to provide speedy, though not necessarily permanent, relief of the patient's symptoms.

Side-effects were produced in 83% of patients treated with imipramine. These are seldom dangerous, but the discomfort engendered often leads to refusal by the patient to continue with treatment, even though the presenting symptoms have been relieved. The most serious side-effect seen in this trial, though the rarest, was an attack of grand mal. From experience with

other patients it appears that some caution is necessary in giving imipramine to epileptics, and it may be necessary to increase the amount of anticonvulsant drugs. In patients known to have suffered from epilepsy in the past but no longer on medication, it would seem to be a wise precaution to cover the period of imipramine administration with anticonvulsants. An occasional patient in whom there is no history of fits may suffer one or more attacks of epilepsy while taking imipramine.

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METHAQUALONE AS A HYPNOTIC

BY

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Methaqualone ("melsedin"; 2-methyl-3-o-tolyl-4-quinazolone hydrochloride) is a synthetic non-barbiturate hypnotic. Ravina (1959) reported on its value given as an oral dose of 150 mg.: in 54 out of 100 patients the hypnotic effect was superior to that of previously administered hypnotics; placebo tablets were not used in Ravina's series.

The present investigation was designed to assess the relative merits of methaqualone and a standard dose of cyclobarbitone; an inert tablet was used as a control. The design of the trial was similar to that used by Thomson (1958).

Method

The patients were in general medical wards and presented the usual wide range of diseases; there were 79 women and 21 men, and their ages ranged from 32 to 74 years. Only those who required hypnotic drugs were included in the trials. All other sedatives were withheld during the period of observation; when any patient developed a new symptom which in itself might have caused insomnia during a trial, he was excluded from the series. Three clinical trials were carried out using the same plan of investigation. The two drugs to be compared were dispensed as white sugar-coated

tablets identical in appearance. These were labelled A, B, C, or D, their content being unknown to the patients, the nurses, and the clinicians.

Content of Tablets A, B, C, and D in the Trials

Trial No.	A	B	C	D
1	150 mg. methaqualone	Placebo		
2	200 mg. cyclobarbitone	150 mg. methaqualone		
3	150 mg. methaqualone	150 mg. methaqualone	Placebo	200 mg. cyclobarbitone

The Table lists the contents of the tablets used in the three trials. If tablet A was given on the first night tablet B was prescribed on the second, and vice versa. To avoid bias the order of giving tablet A or B on the first of the two test nights was decided by random selection; after mixing 20 labels marked A and 20 of B, the order in which they were drawn from a box was listed and this determined the order of administration. In the second trial 43 patients were required to complete the study, and the order of administration of the test tablets in the last three patients was determined by the same method of random selection. The appropriate tablet was given with a small draught of water at 10 p.m.—three hours after the evening meal. Each patient was informed that he was receiving "a sleeping tablet"; he was not told that a comparative study was in progress. In the morning after the second hypnotic one of us asked each patient, "On which of the two nights did you have the better sleep?" The question was framed with the deliberate intention of eliciting a comparison, and on each occasion the same form of words was used.

The results were examined statistically by sequential analysis as described by Bross (1952). The outstanding feature of this method is that observations are charted as soon as they become available. If we take Fig. 1 as an example, only a stated preference by the patient between A and B is plotted as X; if a patient answers the question by saying that there is "no difference" between the treatments, no entry is made on the chart. If the patient preferred tablet A, a mark X is placed in the square to the right of the last entry on the chart. If the preference is for B, a mark is placed on the square above the last entry. When the path of these symbols travels "east," and emerges from the boxed area, treatment A is superior. If the data as plotted fall into the zone between the two boxed areas, this denotes "no important difference between treatments." The clinical trial—to compare A and B—ends when the X path crosses any boundary of the boxed areas.

Results

The results are shown in Figs. 1 to 3, which should be read in conjunction with the Table. The first trial demonstrated that 150 mg. of methaqualone was superior to a placebo containing 90 mg. of starch, 90 mg. of lactose, and 60 mg. of sucrose. In order to complete this study 28 patients were required, as 17 stated a preference for tablet A and 11 "no difference" results were obtained. The second trial (Fig. 2) demonstrated no important difference between 200 mg. of cyclobarbitone and 150 mg. of methaqualone. To reach this conclusion 43 patients were studied, of whom 30 stated a preference and 13 found no difference between the treatments. Trial 3 was planned to allow a comparison to be made between 300 mg. of methaqualone

and a 200-mg. tablet of cyclobarbitone which was given with a placebo tablet; this avoided "patient bias" arising from the administration of a different number of tablets on consecutive nights. The results (Fig. 3) indicated that 300 mg. of methaqualone was superior to 200 mg. of cyclobarbitone; the "northern" boundary was crossed after 20 preferences and there were 9 "no difference" results.

In trial 2, three patients volunteered the information that 150 mg. of methaqualone made them restless before they fell asleep; these patients stated a preference for 200 mg. of cyclobarbitone. One patient in this trial complained of restlessness after taking cyclobarbitone.

Summary

The effectiveness of methaqualone has been determined by a double-blind clinical trial. The investigation

Fig. 1.—Sequential plan in trial 1, showing 150 mg. of methaqualone superior to placebo.

Fig. 2.—Trial 2, in which there was no important difference between 200 mg. of cyclobarbitone and 150 mg. of methaqualone.

was designed to answer two questions: (1) Is methaqualone a reliable hypnotic? (2) Is the action of this drug comparable with that of the usual dose of cyclobarbitone? Other aspects of the pharmacological action of methaqualone were not studied. It is emphasized that the conclusions reached depend entirely on patients' opinions; but the reliability of their assessments was checked by the technique of investigation, and this included the use of a placebo.

FIG. 3.—Trial 3, showing 300 mg. of methaqualone to be superior to 200 mg. of cyclobarbitone.

The main conclusions are that methaqualone in a single dose of 150 mg. is a reliable hypnotic; and no important difference can be detected between the hypnotic action of 150 mg. of methaqualone and 200 mg. of cyclobarbitone.

We are grateful to Professor S. Alstead for permission to study the patients under his care. We are pleased to acknowledge assistance from Mr. P. S. Waldie, who prepared the figures. The tablets used in the trials were kindly supplied by Boots Pure Drug Company Limited.

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Applications of radioisotopes in the study of tropical diseases were reviewed at an international symposium held jointly by the International Atomic Energy Agency and W.H.O. in Bangkok from December 12 to 16, 1960. The meeting showed that the nature and causes of certain types of anaemia widely prevalent in tropical areas are now being investigated with radioactive isotopes of iron and chromium, while radioactive iodine has become indispensable in efforts to determine the causative factors of endemic goitre. As for diseases caused by insects such as malaria or those caused by parasites such as hookworm, radioisotopes help the study of the physiology, biochemistry, and behaviour pattern of insects and parasites concerned and in devising effective methods of attacking them. The application of isotopes in the investigation of disorders due to nutritional deficiencies was also discussed at the meeting.

FURTHER EXPERIENCE WITH METHOTREXATE IN CHORIONCARCINOMA

BY

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The demonstration of the inhibition of oestrogen-induced growth of the female genital tract in the experimental animal by folic-acid antagonists (Hertz and Sebrell, 1944; Hertz, 1948a, 1948b; Hertz and Tullner, 1949) and the effect of aminopterin in inducing foetal death *in utero* (Thiersch, 1952) was followed by the use of the folic-acid antagonist methotrexate (4-amino-N-10-methylpteroylglutamic acid), in the treatment of chorioncarcinoma (Li *et al.*, 1956, 1958). Since that time, reports have come from America on the use of this drug in a larger series of cases (Hertz *et al.*, 1958, 1959), and a small number of cases have been recorded from this country (Doniach *et al.*, 1958; Buckle, 1959; Bagshawe and Brooks, 1959; Bagshawe and McDonald, 1960).

In a previous paper (Buckle, 1959) a case was recorded in which an initial response to the drug was followed by drug resistance and death, the plea being made at that time for the collection of such cases in suitable centres in this country in order that this form of therapy could be assessed. A similar suggestion has also recently been made (*Brit. med. J.*, 1960). Although the value of recording single cases of tumour chemotherapy is generally of little value, exception may be made in the case of chorioncarcinoma in view of its rarity, and a further case is recorded.

Case Report

A gravida-2, aged 20, was admitted to hospital on December 17, 1959, at 30 weeks pregnancy, with painless, bright-red vaginal bleeding. She had had an idiopathic thoracic scoliosis at the age of 14 which had not progressed, although she had backache intermittently, especially during pregnancy. She had also been under investigation in 1958 for headaches and disturbances of consciousness, at which time she had been found to have bilateral rotatory nystagmus and diminished sensation to pin-prick on the left half of the body. Investigations had been inconclusive and there had been no change in the physical findings since that time. Her previous pregnancy, in 1958, was normal with the delivery of a live male infant, weighing 6½ lb. (2,950 g.).

Her last menstrual period began on May 10, 1959, and she was admitted to hospital at 16 weeks with vaginal bleeding. No abnormal findings were recorded and she was discharged nine days later. Pregnancy continued uneventfully until December 17, when she was admitted to hospital with a painless ante-partum haemorrhage. Apart from the vaginal bleeding, no abnormal findings were recorded and expectant treatment was adopted. Despite rest and sedation, the slight vaginal loss continued and she went into labour, delivering herself of a living premature female infant, weight 3 lb. (1,360 g.), seven days after admission. Examination of the placenta revealed no abnormality.

On the fifth day after birth the infant developed severe cyanotic attacks and died, necropsy showing minimal intracranial haemorrhage. Death was recorded as due to prematurity.