appears to be a highly important factor, as do other post-operative causes of increased intra-abdominal pressure such as vomiting, distension, and ascites. Incisions in the upper abdomen, and vertical incisions, carry a high risk of bursting.

There is no evidence that the type of suture material used is of any importance.

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CLINICAL COMPARISON OF BARBITURATES AS HYPNOTICS

BY

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The classification of barbiturates by the duration of their action into long, intermediate, short, and ultra-short was based on the results of animal experiments by Fitch and Tatum (1932). They gave 60% of the minimum lethal dose of each barbiturate to rabbits and rats, and noted the time taken for the animals to wake. Over 40 animals were used to test each barbiturate, and the drugs were administered orally and intraperitoneally. A wide range of hypnotic action was noted. Nevertheless, Bleckwenn as early as 1930, using medical patients, reported little difference between intermediate- and short-acting groups.

It is widely accepted that phenobarbitone has less hypnotic action and is more likely to produce a hangover than intermediate and short-acting barbiturates. This is stated in several standard works (Wilson and Schild, 1959; Alstead, 1960; *British National Formulary*, 1960). Lasagna (1956), however, using medical patients, showed in a well-controlled trial that phenobarbitone in doses of 100 mg. could hardly be distinguished from quinalbarbitone or pentobarbitone in the same dose in respect of either sedation or hangover. Wayne (1960) has drawn attention to this and similar studies which have thrown doubt on the clinical relevance of the pharmacological classification of the barbiturate series into short-, intermediate-, and long-acting members and has suggested that the position should be reviewed. This problem has therefore been investigated using the relatively simple technique of sequential analysis.

Method

The trial has been conducted in general medical wards. A study was made of 173 patients—91 men and 82 women. Only those patients who had previously benefited from a hypnotic were included and no patient aged over 70 was used. Other sedatives were withheld. Six successive clinical trials were carried out using the same method. The drugs to be compared were dispensed as identical white tablets in containers marked A and B; their content was known only to the pharmacist. On the first night a number of patients would receive tablet A and the remainder tablet B. On the second night this was reversed. The order of giving tablets A and B was decided by random selection as described in a previous trial (Parsons and Thomson, 1961). In the morning after the second hypnotic each

patient was asked two questions. "On which of the last two nights did you have the better sleep?" and, "Have you had any hangover or drowsiness on waking after either of these drugs?" An identical form of question was used in every case.

The results were examined by the now familiar method of sequential analysis described by Bross (1952), and further explained by Armitage (1960). Only a preference between A and B is plotted as X; if the patient states there is "no difference" between treatments no entry is made on the chart. These trials have been so designed that a preference for A is charted vertically and for B is charted horizontally. When the X path crosses the upper border of the boxed area, tablet A is superior, and if it crosses the lower border then tablet B is superior. If the plotted results cross the boundary in the V shape between the 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 area.

Results

The results for trials 1-3 are shown in the figures and for trials 4-6 are reported only in the text. For convenience the contents of tablets A and B have been entered on the figures. The first trial (Fig. 1) showed that quinalbarbitone 100 mg. was superior to an inert tablet consisting of lactose and starch. To reach this conclusion nine patients were studied, of whom eight stated a preference and one could detect no difference. Two patients complained of hangover with quinalbarbitone. The second trial (Fig. 2) demonstrated no important difference between 100 mg. of quinalbarbitone and 100 mg. of phenobarbitone. In order to complete this study 47 patients were used, of whom 34 gave a preference and 13 no difference results. Five patients complained of hangover—two with quinalbarbitone and three with phenobarbitone—and one patient was restless after phenobarbitone. Fig. 3 shows the comparison of 100 mg. of butobarbitone and 100 mg. of quinalbarbitone carried out in the third trial. It shows no important difference after a total of 27 patients had been studied, five giving no difference results. Three patients complained of hangover with quinalbarbitone, none with butobarbitone.

The fourth trial showed 200 mg. of quinalbarbitone to have superior hypnotic effect when compared with 200 mg. of phenobarbitone. This conclusion was reached after 46

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patients had been studied, 35 of whom stated a preference and 11 could detect no difference. Seven patients complained of hangover with quinalbarbitone and four with phenobarbitone; a further two had hangover after both drugs. In the fifth trial 200 mg. of butobarbitone was shown to be a more effective hypnotic than 200 mg. of phenobarbitone. Twenty-two patients were studied, of whom 14 stated a preference and 8 could detect no difference. Eight patients complained of hangover—five after phenobarbitone, one after butobarbitone, and two after both the drugs. The sixth trial demonstrated the superior hypnotic action of 200 mg. of quinalbarbitone when compared with 200 mg. of butobarbitone. Twenty-two patients were required to complete this trial, of whom 20 gave a preference and 2 could detect no difference. Six patients complained of hangover—four after quinalbarbitone, one after butobarbitone, and one after both

the drugs. One patient complained of restlessness after quinalbarbitone.

Discussion

Many factors influence the result of a trial which compares the hypnotic effect of different drugs. Most people do not require a hypnotic to ensure sleep, and it is therefore preferable, as in this series, to use patients who had all required a hypnotic drug before being included in the trial. Inert tablets are well known to produce satisfactory sleep in about a third of the patients (Wilson, 1962), and this sleep may be little different in duration from that afforded by an active drug (Stewart, 1956). It is however, comparatively simple in a well-designed trial to show that the effective drugs are superior to "placebos." The absence of a single preference for inert tablets in trial I in this series is unusual but may depend on the small number of cases studied.

Hare (1955) found great variation in individuals' response to different barbiturates, but he also showed that patients respond consistently to any one barbiturate. His method allows a comparison of response to be based on a single night's sleep. The present trials have not sought to define the time of onset of hypnotic action, or its duration, or the presence of alarming dreams. The results have been assessed on the patients' overall impression of the quality of the night's sleep. In the great majority of cases this subjective approach has been found to compare accurately with the objective impression of nurses (Stewart, 1956; Thomson, 1958).

The incidence of side-effects is low with barbiturates, even if the normal therapeutic dose is doubled (Lasagna, 1956). In this series only the occurrence of hangover (undue drowsiness, headache, or dizziness on waking) has been recorded. The few patients reporting undue restlessness during the night have been separately noted. The resumption of sleep after breakfast has not been included as hangover because the patients did not usually consider it unpleasant. A possible source of error is that the patients' overall preference may have been influenced by the occurrence of hangover. In fact, of the 32 patients with hangover on one of the nights, 15 gave a preference

FIG. 1.—Sequential chart in trial 1.

FIG. 2.—Sequential chart in trial 2.

FIG. 3.—Sequential chart in trial 3.

for the drug which caused the hangover. No cases of skin rash or other hypersensitivity phenomena were reported.

The results show that in a dosage of 100 mg., phenobarbitone, butobarbitone, and quinalbarbitone have similar hypnotic power. This agrees with the work of Lasagna (1956). A similarity of hypnotic effect in this dosage has previously been noted between quinalbarbitone and pentobarbitone (Goldstein, 1953; Belleville and Fraser, 1957) and between butobarbitone and amylobarbitone sodium (Stewart, 1956). In the present series a hangover was reported in 6.4% of patients taking 100 mg. of phenobarbitone and in 12.5% (average over three trials) of patients after taking 100 mg. of quinalbarbitone. No hangover was reported after 100 mg. of butobarbitone had been given to 27 patients.

When the dose was doubled subjects found quinalbarbitone more effective than both butobarbitone and phenobarbitone. The superiority of quinalbarbitone over phenobarbitone was less convincing than that of quinalbarbitone over butobarbitone. Butobarbitone was found to be more effective than phenobarbitone. The incidence of hangover calculated for each drug over two trials had increased, though it was less with butobarbitone (11.3%) than with quinalbarbitone (21.3%) and phenobarbitone (22.4%).

The similarity of hypnotic power of these drugs in the normal dose and the low incidence of hangover with phenobarbitone are contrary to general teaching. Physicians' opinion on the comparative merits of barbiturates have recently been shown to mimic the views expressed in influential medical textbooks (Lasagna, 1962). Thus little account has been taken of the now considerable evidence supporting the similarity of hypnotic effect. Failure to recognize the position earlier has been attributed to the difficulties inherent in carrying out true comparative trials in human subjects, making allowance for the presence of placebo reactors: and also to neglect of detailed clinical

observation after the administration of barbiturates in hypnotic doses.

Summary

The hypnotic effects of phenobarbitone, butobarbitone, and quinalbarbitone have been compared by sequential analysis using a method which involved inert tablets and the double-blind technique. With doses of 100 mg. no differences were demonstrated. With doses of 200 mg. the order of effectiveness in descending order was quinalbarbitone, butobarbitone, and phenobarbitone.

With both doses butobarbitone gave rise to least hangover. With 100-mg. doses phenobarbitone caused less hangover than quinalbarbitone.

There seems little justification for classifying barbiturates into short-, intermediate-, and long-acting groups.

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CONTROLLED COMPARISON OF FOUR SEDATIVE DRUGS IN ELDERLY PATIENTS

BY

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The evaluation of hypnotics has always been made difficult by lack of agreement on the importance of the parameters measured. One review (*Brit. med. J.*, 1962) states: "The estimation of what constitutes 'sound sleep' is in itself a major problem"; while Hinton and Marley (1959) point out that the perfect solution to the problem of measuring the depth of sleep remains elusive.

The methods of evaluating hypnotics can be divided into the two main groups of objective and subjective. Objective methods include measurement of nocturnal motility by mechanical means or, more commonly, the observation of patients at intervals by attendant staff who note whether or not the patient is asleep. Satisfactory correlation between both of these methods has been shown by Hinton and Marley (1959), Cox and Marley (1959), and Hinton (1961).

Subjective methods entail questioning the patient on the night's sleep. An overall evaluation of the night's sleep has

often shown poor correlation with objective assessments (Straus *et al.*, 1955; Hinton and Marley, 1959; Cox and Marley, 1959), although other workers have found some degree of correlation (Foltz *et al.*, 1955; Hare, 1955; Lasagna, 1956; Stewart, 1956). This apparent unreliability of patients' opinions has tended to discredit such subjective assessment, and in many studies inquiries are limited to the presence or absence of actual side-effects. It is unfortunate that this should have occurred, for, as mentioned by Lasagna (1954), "subjective evaluation is important, if for no other reason than that the clinical use of hypnotic agents is most frequently concerned with the alleviation of patients' complaints."

We agree that the patient's own evaluation of the night's sleep is an important measure of an hypnotic. Indeed, we consider that it must be the most important single assessment because the patients alone can judge the measure of success of what is, after all, mainly symptomatic treatment.