THE RECENTLY INTRODUCED RAPIDLY-ACTING BARBITURATES; A REVIEW AND CRITICAL APPRAISAL IN RELATION TO THIOPENTONE

BY

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"Thiopentone is a well tried and reliable drug . . . to displace such a drug, a new compound must have clear cut advantages and should be assessed in the light of the hazards inherent in thiopentone". (Dundee, 1958.)

Since its introduction into clinical use 25 years ago, thiopentone has held pride of place amongst intravenous anaesthetics. However, during this time a search has gone on for more satisfactory compounds and judging by the number of reports in the literature, this search has been intensified in recent years. Much attention has been focused on nonbarbiturate compounds which, up to the present, have not offered serious competition to the barbiturates.

In this publication it is proposed to review the barbiturates which have been recently introduced into anaesthetic practice and those compounds which have been subjected to clinical trial, even though they have not proved suitable for everyday use.

It is first necessary to consider how thiopentone falls short of the ideal intravenous anaesthetic and then to see if any of the newer compounds overcome these deficiencies. It is also important to compare the toxicity of the newer compounds with that of thiopentone with awareness that any possible advantages they may have over the standard drug must not be "bought at too great a price".

UNDESIRABLE ACTIONS OF THIOPENTONE

It should be emphasized that many of the hazards associated with the use of thiopentone are due to a rapid onset of anaesthesia rather than to a specific action of this particular drug; such dangers as vomiting and regurgitation are probably present to the same extent with any rapidly-acting intravenous agent. The hazards associated with the use of thiopentone in porphyrics seem to be shared by all barbiturates and it is expected that this will apply to conditions in which undue sensitivity to the drug is manifest.

From the point of view of the practising anaesthetist the following seem to be inherent dangers associated with thiopentone.

Local irritation of tissues.
Perivenous injection can produce intense pain and even sloughing of subcutaneous tissues, depending on the concentration and volume of misplaced solution. The sequelae of intra-arterial injection can include nerve lesions, tissue damage and even gangrene of the limb. While these are minimized by the use of dilute solutions this necessitates the injection of greater volumes and the use of larger and more clumsy syringes.

Cardiovascular depression.
While this can be lessened by the slow injection of dilute solutions, it is an inherent toxic action of the drug which cannot be ignored.

Respiratory depression.
This likewise can be minimized by proper use of the drug, but its augmentation by opiate premedication is not always appreciated.

Other undesirable respiratory effects.
These include coughing, hiccough, laryngospasm, sneezing and bronchospasm which fortunately occur very rarely.

Lack of analgesia.
This limits the safe employment of the drug as the sole narcotic except for brief procedures.

Delayed recovery of consciousness and cumulative action.
Whether or not this is a disadvantage depends on the nature and duration of the operation and the part played by the drug in the anaesthetic
technique. When used as a basal narcotic for the induction of anaesthesia for major operations the duration of action of moderate doses of thio-pentone seems ideal. If a drug with a more rapid rate of recovery is used it may be necessary to revise many of our standard anaesthetic techniques to ensure a more rapid uptake of volatile and gaseous anaesthetics. However, for minor procedures, particularly on outpatients, the delayed recovery is a disadvantage. Irrespective of the circumstances attendant on its use, full return of mental faculties may be delayed for several hours.

Failure to produce muscular relaxation in safe doses.

With modern anaesthetic techniques this is not a major disadvantage of thiopentone and a drug which produces greater relaxation may well cause a greater degree of respiratory depression.

MODIFICATIONS OF THE BARBITURATE NUCLEUS

It is necessary next to consider those sites at which the barbiturate nucleus can be modified to produce compounds of use in anaesthesia (fig 1). This subject has been discussed at great length in the publications of Tatum (1939, 1940); Raventós (1954) and Richards and Taylor (1956) and is mentioned to explain the classification used in this review. The sites of substitution are as follows:

1. This is normally a hydrogen atom, which can be replaced by methyl or ethyl group. These changes frequently produce compounds with a more rapid recovery rate but they may have convulsant properties.

2. The substitution of a sulphur for an oxygen atom in this position produces compounds with an appreciably shorter duration of action. This is sometimes erroneously attributed to more rapid detoxication whereas alteration in distribution in the body plays the main part. In the case of pentobarbitone (O) and thiopentone (S), the onset of anaesthesia with the latter drug is more rapid (Dundee, 1957) and equilibration with brain tissue occurs more quickly (Mark et al., 1958; Goldstein and Aronow, 1960). The degree of plasma binding is greater with the sulphurated compound, which also has a greater affinity for fat (Brodie, 1952). It has been stated by Cope and Hancock (1939) and Knoefel (1945) that conversion of a barbiturate to a thiobarbiturate makes stimulant properties appear frequently. Richards (1951) however, has observed a marked species difference in this effect.

5 & 5'. These have been the most popular sites of attack by research chemists and substitution has been with aliphatic, aromatic or heterocyclic radicals as well as halogenated and sulphurated aromatic radicals. Optimum results seem to be achieved with one short and one long chain substituent, containing from 4 to 8 carbon atoms in toto. Double bonds (allyl, pentyl) produce compounds which are more vulnerable to tissue oxidation and may be shorter acting.

For the purpose of this review, the drugs have been divided into four groups as follows:


Most of the compounds which are either in clinical use or have been subjected to clinical trial are listed in table I. Another group, the spiro-thiobarbiturates is not included above but is mentioned for the sake of completeness.

A graphic representation of the side chains of the drugs to be discussed in detail is given in figure 2. It can be seen from this figure and table I that the number of radicals in the 5 and 5' positions of the various drugs is not very great and thus the differences to be expected between some of the compounds cannot be marked.

An attempt has been made to assess the
THE RECENTLY INTRODUCED RAPIDLY-ACTING BARBITURATES

Table I
Classification of various barbiturates, according to changes in the 1 and 2 positions of the side chains and their approximate potency relative to thiopentone.

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>Side chains</th>
<th>Approximate induction potency compared with thiopentone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pentobarbitone</td>
<td>Ethyl</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Amylobarbitone</td>
<td>Ethyl</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Quinalbarbitone</td>
<td>Allyl</td>
<td>1.0-1.2</td>
</tr>
<tr>
<td>2</td>
<td>Hexobarbitone</td>
<td>Methyl</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Narconumal</td>
<td>Allyl</td>
<td>1.0-1.2</td>
</tr>
<tr>
<td></td>
<td>*Methohexital</td>
<td>Bromallyl</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>*Inactin</td>
<td>Allyl</td>
<td>1.0-2.5</td>
</tr>
<tr>
<td></td>
<td>*Buthalitone</td>
<td>Methyl-thioethyl</td>
<td>0.6-0.7</td>
</tr>
<tr>
<td>3</td>
<td>Thiopentone</td>
<td>Ethyl</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Thiamylal</td>
<td>Allyl</td>
<td>1.0-1.2</td>
</tr>
<tr>
<td></td>
<td>*Inactin</td>
<td>Allyl</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>*Buthalitone</td>
<td>Allyl</td>
<td>0.7-0.8</td>
</tr>
<tr>
<td></td>
<td>*Methitural</td>
<td>Methyl-thioethyl</td>
<td>0.6-0.7</td>
</tr>
<tr>
<td>4</td>
<td>Methyl-thiopentone</td>
<td>Ethyl</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Methyl-thiamylal</td>
<td>Allyl</td>
<td>1.0-1.2</td>
</tr>
<tr>
<td></td>
<td>*B.137</td>
<td>Allyl</td>
<td>0.7-0.8</td>
</tr>
<tr>
<td></td>
<td>*B.82</td>
<td>Allyl</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* Only these drugs are reviewed in this publication.

Approved name | Other names | Side chains      |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Methohexital</td>
<td>Lilly 25398 Brevital Brietal</td>
<td>CH₃ 0 H₃C—CH=CH—CH₃ H₆C₃—C≡C—CH=CH—</td>
</tr>
<tr>
<td>Inactin</td>
<td>H S H₃C—</td>
<td>CH₃CH₃—CH—CH=CH₃</td>
</tr>
<tr>
<td>Buthalitone</td>
<td>H S CH₃=CH—CH₃</td>
<td>CH₃—CH₃—CH—CH=CH₃</td>
</tr>
<tr>
<td>Methitural</td>
<td>H S CH₃—S—CH₃—CH₃</td>
<td>CH₃CH₃—CH=CH—CH=CH₃</td>
</tr>
<tr>
<td>B.137</td>
<td>CH₃ S H₃C</td>
<td>CH₃CH₃—CH—</td>
</tr>
<tr>
<td>B.82</td>
<td>CH₃ S CH₃=CH—CH₃</td>
<td>CH₃—CH₃—CH—CH=CH₃</td>
</tr>
</tbody>
</table>

Fig. 2
Graphic representation of side chains.
relative potency of induction doses, as compared with thiopentone, in table I. Since all workers are not unanimous in their opinions on this subject, most of the values quoted are based on the authors' own experiences with the drugs.

Published reports frequently give different values for the pH of the same drug in the same concentration, presumably due to different methods of measurement. Table II lists readings obtained by the authors at room temperature using the same apparatus for all drugs. Since all are strongly alkaline, it is to be expected that the incompatibilities which Dundee (1956) gives for thiopentone will apply to all the drugs under review.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength of solution</th>
<th>1%</th>
<th>24%</th>
<th>5%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexobarbitone</td>
<td></td>
<td>11.05</td>
<td>11.39</td>
<td>11.50</td>
<td></td>
</tr>
<tr>
<td>Narconumul</td>
<td></td>
<td>10.70</td>
<td>10.82</td>
<td>10.93</td>
<td></td>
</tr>
<tr>
<td>Narcodorn</td>
<td></td>
<td>9.95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methohexital</td>
<td></td>
<td>11.11</td>
<td>10.95</td>
<td>11.03</td>
<td></td>
</tr>
<tr>
<td>Thiopentone</td>
<td></td>
<td>10.81</td>
<td>10.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamylal</td>
<td></td>
<td>10.60</td>
<td>10.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalbarbitone</td>
<td></td>
<td>10.25</td>
<td>10.30</td>
<td>10.40</td>
<td></td>
</tr>
<tr>
<td>Inactin</td>
<td></td>
<td>10.50</td>
<td>10.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buthalitone</td>
<td></td>
<td>10.60</td>
<td>10.55</td>
<td>10.47</td>
<td></td>
</tr>
<tr>
<td>Methitural</td>
<td></td>
<td>10.42</td>
<td>10.42</td>
<td>10.40</td>
<td></td>
</tr>
<tr>
<td>B.137</td>
<td></td>
<td>11.25</td>
<td>11.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.82</td>
<td></td>
<td>10.55</td>
<td>10.55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Claims are frequently made as regards the more rapid onset of a particular preparation. Using reactive hyperaemia to produce maximum forearm blood flow (Dundee and McArdle, 1959) the authors have found that adequate doses of all drugs to be discussed later can cause loss of consciousness within one arm-brain circulation time.

Each drug will now be discussed in the order set out in figure 2, and consideration will be given to their merits and demerits, using thiopentone as the standard.

**Methohexital**

**History.**

This compound was first described by Stoelting in 1957. Previous studies with a similar compound (Lilly, 22451) had shown that it was more potent than thiopentone and that recovery was more rapid (Chernish et al., 1956). However, this drug was found to have undesirable convulsive properties, but was fractionated into low and high melting point isomers, the latter being methohexitol (Redish et al., 1958).

**Physical properties.**

Methohexital is a white crystalline powder, readily soluble in water, the aqueous solution remaining stable for at least six weeks at 25°C. It is distributed in bottles containing 500 mg to which has been added 30 mg of anhydrous sodium carbonate.

**Pharmacology and toxicology.**

Animal experiments by Stoelting (1957) showed methohexital to be about three times as potent as thiopentone. The duration of narcosis was only half as long as with thiopentone and the drug was less likely to show cumulative effects. The electroencephalographic patterns of cerebral depression were similar for methohexitol and thiopentone. Chronic experiments demonstrated no pathological changes attributable to the drug.

**Clinical reports.**

The publications of Stoelting (1957), Reddish et al. (1958), Wyant and Chang (1959) and Taylor and Stoelting (1960) all confirmed the greater potency of methohexital as compared with thiopentone. The drug has been used in a 0.1–0.2 per cent continuous infusion and by intermittent dosage in one and two per cent solutions. In over 3,000 administrations Taylor and Stoelting found no thrombophlebitis during the postoperative period following the use of solutions not exceeding one per cent strength. The authors cannot confirm this finding when a two per cent solution has been employed but inadvertent subcutaneous injection of up to 100 mg produced no sequelae. Weyl et al. (1958) also noted this lack of local irritation following extravascular injection.

In the largest published series of cases 60 per cent of patients complained of pain at the site of injection or along the course of the vein. The intensity of the pain varied, but usually evoked a spontaneous and bitter complaint from the patient (Taylor and Stoelting, 1960). It is surprising that this complication has not been mentioned in any other publication, particularly in that of Wyant and Chang (1959) who used
methohexital as sole narcotic and whose observations were obviously made with great care. In a series of over 600 administrations by the authors and colleagues there has been no complaint of pain following the use of a two per cent solution in doses up to 950 mg.

All workers are agreed that recovery from methohexital is more rapid than after equivalent doses of thiopentone. Friedman (1959), using the drug for electroconvulsive therapy, found that treated patients could go home or return to work in about half the time noted for other barbiturates. In studies with volunteers Wyant, Dobkin and Aasheim (1957) noted the absence of "hangover" following methohexital as compared with other drugs. This was also the finding in a series of minor gynaecological procedures in which either methohexital or thiopentone was used as sole narcotic (Wyant and Chang, 1959). Using a "blind" technique and combining the barbiturate with nitrous oxide-oxygen for the operation of dilatation and curettage, Wyant and Barr (1960) have again confirmed the more rapid rate of recovery from methohexital. It has been frequently suggested that the drug would be very suitable for outpatient anaesthesia in view of this rapid recovery and absence of hangover but, up to the present, no study of this aspect of its use has been published.

Opinions vary somewhat as to the incidence and seriousness of complications following induction with methohexital. Stoelting (1957) noted only one instance of coughing and one of laryngospasm in his initial series of 285 patients. In the more recent paper, dealing with 3,340 administrations Taylor and Stoelting (1960) reported a one per cent incidence of spontaneous coughing and a slightly lower incidence of laryngospasm but about three per cent of patients had hiccoughs following induction. Compared with these low figures there was a 41 per cent incidence of hiccough reported by Wyant and Chang (1959), but it must be appreciated that these authors used the intravenous agents as the sole anaesthetic agent and that they found a 12 per cent incidence with thiopentone. In a further study, when these drugs were combined with nitrous oxide-oxygen (for the same operative procedures) hiccough did not occur in 55 patients (Wyant and Barr, 1960).

Muscle movements and tremor following induction are other complications about which reports are at variance. While not originally observed by Stoelting (1957) there was an incidence of approximately 3 per cent in the larger series reported by Taylor and Stoelting (1960). It was found that additional amounts of methohexital controlled these abnormal movements. A low incidence was also reported by Weyl et al. (1959) and Redish et al. (1958) while they did not occur at all in the series reported by Wyant and Barr (1960). However, the use of methohexital as sole narcotic for dilatation and curettage resulted in a 35 per cent incidence of minor muscle movements while 4 per cent of patients exhibited gross movements.

Many of the differences reported in the various publications may well be due to factors such as the strength of solution, the rate of injection, the dosage and the pre-anaesthetic medication. This latter has been studied in detail by Moore and Dundee (1961), who found that premedication with pethidine significantly reduced the incidence of muscle movements following injection while promethazine increased the incidence and severity of this complication to an alarming degree.

With a drug of the potency of methohexital, it is not surprising to find respiratory depression and apnoea mentioned as frequent complications of the induction, particularly following opiate premedication (Eckenhoff and Helrich, 1958). Dobkin and Wyant (1957) found a very high incidence with large doses, while Weyl et al. (1958) reported these complications in only 2 per cent of patients. The incidence and severity differs greatly in other publications and in the absence of dosage/incidence ratios no conclusions can be drawn.

Cardiovascular depression has not been a feature of the reports on methohexital and when hypotension has occurred it has been transient. More data is needed on this aspect of its action.

As well as the special indications which may arise from its brevity of action such as dental and outpatient procedures, Taylor and Stoelting (1960) consider methohexital to be eminently suitable for asthmatics. Weyl et al. (1958) found a slow infusion to be particularly useful for cardiac catheterization. If its lack of depressant
action on the cardiovascular system as compared with thiopentone is confirmed, it may well become the drug of choice in the elderly hypertensive subject.

**Comparison with thiopentone.**

Dundee and Moore (1961) have compared the actions of the two drugs as main narcotics for a standard operation. While agreeing with other workers that recovery from methohexital occurs more rapidly than after a comparable dose of thiopentone, they found that the course of anaesthesia was less smooth, particularly in the absence of opiate premedication. The frequency and severity of complications following induction was not such as to cause any anxiety and was more than compensated for by the minimum effects on the cardiovascular system as compared with thiopentone.

**INACTIN**

**History.**

Though originally described in the same publication as thiopentone in 1935 by Tabern and Volwiler, Inactin was not introduced into clinical practice until 1952 by Horatz and Sturtzbecher. Its pharmacology was extensively studied by Nieschultz (1953) and until the recent comparison of the action of Inactin with that of thiopentone by Dundee and Riding (1960) its clinical use in this country had not been reported.

**Physical properties.**

This drug is a yellow crystalline powder with a similar solubility and alkalinity to thiopentone.

**Pharmacology and toxicity.**

Tabern and Volwiler (1935) found that, in rabbits, the AD₃₀ was 15 mg/kg as compared with 10 mg/kg for thiopentone; the relative values for LD₅₀ being 50 mg/kg and 40 mg/kg respectively. This shows that Inactin has a slightly lower therapeutic ratio than thiopentone but the importance of this difference is doubtful in anaesthetic practice.

Block (1956) has studied the effect of single and repeated doses of Inactin on fat metabolism and hepatic function. He found no evidence of fatty infiltration of the liver during chronic Inactin intoxication and concluded that in the normal administration of Inactin to humans there is no indication that liver damage results.

**Clinical.**

With one exception, all the clinical reports on this drug have been published in the German language. These show the drug to be very similar in action and duration to thiopentone.

**Comparison with thiopentone.**

A detailed comparison of Inactin and thiopentone, involving almost 1,000 administrations of each drug, has recently been published by Dundee and Riding (1960). This confirmed the similarity between the two drugs as regards incidence of side effects and duration of action. The only difference of note was the lower potency of Inactin. The findings have been further confirmed by Dundee, Barron and King (1960) who used the drugs as main narcotic for a standard operation.

It is interesting to note that the above two publications show the effect of opiate premedication in reducing the incidence of muscle movements following thiopentone and Inactin. However, this effect is less striking than that noted by Moore and Dundee (1961) with methohexitol.

**BUTHALITONE**

Like Inactin, although only comparatively recently introduced into clinical practice, buthalitone has been synthesized for over 25 years (Miller et al., 1936). Helmuth Weese, who introduced the first rapidly-acting barbiturate, hexobarbitone, into anaesthesia, was also concerned with its "rediscovery" (Weese and Koss, 1954) and Nobes (1955) first described its use in this country.

**Physical properties.**

These are again similar to thiopentone, but the solution is less stable and should be freshly prepared before use.

**Pharmacology and toxicology.**

Most of the reported studies have been concerned with the duration of action of buthalitone as compared with other drugs. Weese and Koss (1954), working with dogs, found that although the duration of anaesthesia with equipotent doses of hexobarbitone and buthalitone was similar, complete recovery occurred more promptly with buthalitone. This finding was substantiated by an uncontrolled study in man.

A large number of clinical observations suggested that buthalitone was a shorter acting anaesthetic
than thiopentone but it is only recently that these claims have been examined in detail. While Henderson and Mackett (1958), Keéri-Szántó and Labarre (1957) and Murray (1957) all studied the relative potencies of the two drugs in man and concluded that thiopentone was approximately twice as potent as buthalitone, O'Mullane (1957) found that at this ratio buthalitone produced a lighter level of anaesthesia as measured by the electroencephalogram. When doses of the two drugs were given which produced comparable patterns recovery of the normal pattern was slower with buthalitone than with thiopentone. This author suggests that buthalitone may give a false impression of brevity of action because the depth of anaesthesia as measured by the electroencephalogram is not as deep as is obtained with what are considered to be equipotent doses of thiopentone.

Using the patient's ability to obey verbal commands and to rise unaided to the sitting position as the criteria for recovery, Simmons and Blanchard (1957) were unable to demonstrate any difference between thiopentone and buthalitone. In a recent study, using a more complicated technique for determining the time of complete recovery Simmons and Curwen (1960) found no statistically significant difference between buthalitone and thiopentone.

Acute and chronic toxicity studies in animals by Weese and Koss (1954) and Vollmer and Haaf (1954) failed to reveal any deleterious effects of buthalitone as compared with other intravenous barbiturates. Evidence suggests that the drug is broken down by the liver.

Clinical.

From the above it is to be expected that much of the published clinical data concerns the use of buthalitone in minor surgery. Thus we have the reports of Drummond-Jackson (1956), Young (1956) and Mostert and Durham (1957) who used the drug in dental surgery, either alone or prior to nitrous oxide. These writers were all impressed with the smoothness of anaesthesia, the rapid uncomplicated recovery and the almost complete absence of hangover. On many occasions patients were able to leave the surgery unaccompanied within 30 minutes of operation.

Following the recommendation of Weese and Koss (1956), a number of authors including Ruddell (1955), Davidson and Love (1956), Guldmann (1956), Duffield and Ginsberg, (1957), Henderson and Mackett (1958) and Thoren and Matteson (1957), have used buthalitone as the main anaesthetic for minor operations. In many instances, the subjects were ambulant outpatients. Operations included incisions of abscesses, dressings, manipulation and reduction of fractures, endoscopy, external version and dilatation and curettage. Without giving much detail as to dosage, these workers are unanimous as regards rapidity of recovery and absence of hangover following is use. However, they are not all agreed on the incidence of complications during anaesthesia. Duffield and Ginsberg (1957), encountered a 31 per cent incidence of coughing while Guldmann (1956) considered that the incidence of respiratory upset was so high that he could not recommend the drug for general clinical use.

An interesting method is the "closed-vein" technique described by Davidson and Love (1956) a dose of 50 mg per stone body weight was used (maximum 500 mg). This produced a brief period of deep anaesthesia from which recovery was fairly rapid.

Little and Reid (1957) studied the use of buthalitone in electroconvulsive therapy and claimed that recovery was more rapid than after thiopentone. They also found that the respiratory depressant action of suxamethonium was antagonized by buthalitone. This has not been reported by McCall (1955) or Murray (1957) who also used the drug for electroconvulsive therapy.

None of the many clinical papers which deal with the use of buthalitone in major surgery have reported any findings of note. There is frequent reference to a rather high incidence of respiratory disturbances (coughing, hiccup, sneezing) and there are no claims that the drug is in any way superior to thiopentone.

Comparison with thiopentone.

As stated above, buthalitone is about half as potent as thiopentone as an induction agent and recovery from equipotent doses of the two drugs is similar. Judging from the fact that the drug does not seem to have displaced thiopentone to any extent in clinical use, it can be assumed that
it has not proved as satisfactory as the original drug.

**METHITURAL**

**History.**

This preparation was described by Zima, von Werder and Hotovy in 1954 and in the same year its pharmacological actions were reported by Dietmann. Reifferscheid and Dietmann (1954) first described its clinical use and all the early studies were carried out in Germany, where the drug is known as Thiogenal. In 1956 Irwin and his colleagues reported on studies carried out with the drug in America (proprietary name—Neraval) and its clinical use in the United States was first described by Boone, Munoz and Dillon (1956). The use of methitural in anaesthesia was mentioned frequently in American literature during the next three years, but Neraval is no longer commercially available. Apart from a brief report by Dundee (1956), methitural does not appear to have been used extensively in this country.

**Physical properties.**

Methitural differs from the other drugs in this review in that it contains a second sulphur atom in the alkyl side chain. Its chemical properties are similar to those of thiopentone but the aqueous solution is unstable and should be used within 24 hours of preparation.

**Pharmacology.**

Early workers considered the methyl-thioethyl radical (which is also present in the essential amino acid methionine) to be of great significance in the rapid detoxication and elimination of the drug as well as “protecting the liver” (Zima, von Werder and Hotovy, 1954). Dietmann (1954) found that in mice the total duration of narcosis with methitural was about half of that which followed doses of thiopentone producing an equal depth of anaesthesia. He also noted that it had less chronic toxicity than thiopentone. Irwin et al. (1956), however, found no significant difference in the time taken for recovery from small doses of methitural and thiopentone but with increased dosage recovery from methitural anaesthesia was significantly quicker than from thiopentone in the cat, dog and monkey. They also compared the cumulative action of equivalent doses of methitural, thiopentone and thiamylal and found that this was considerably less in the case of methitural than with the other two compounds. These workers found methitural to be about two thirds as potent as thiopentone.

The studies of Blake and Perlman (1956) showed that, like thiopentone, methitural was rapidly absorbed into body fat and that degradation occurred in the liver. No unchanged drug was found in the urine. Irwin et al. (1956) found that the affinity of the drug for fat was similar to that of thiopentone and they attributed the rapid recovery to an accelerated destruction, particularly in the liver. It is of some significance that these workers noted that methitural caused a higher incidence of tremors, abnormal muscle movements and coughing than thiopentone in animals.

On studying the effects of the drug in volunteers, Reifferscheid and Dietmann (1954) found that the potency of methitural was similar to that of hexobarbitone and appreciably less than that of thiopentone. They confirmed the animal observations reported above and concluded that recovery from methitural was more rapid than from either of the other two drugs.

**Clinical.**

Reports on the use of methitural in anaesthesia vary from the well controlled studies of Gale (1957) and Wyant, Chang and Aasheim (1958) to a large number of miscellaneous clinical observations whose sole merit is enthusiasm over the virtues of a new drug. It is proposed to discuss only the most useful of the publications.

O’Herlihy et al. (1956), using the drug for the operation of dilatation and curettage, were unable to demonstrate any shorter recovery time compared to thiopentone but they were able to demonstrate a shorter recovery time for methitural after a single hypnotic dose. Using the same operative procedure Gale (1956) could not detect any marked difference between the time for recovery between thiopentone and methitural and the study of Wyant, Chang and Aasheim (1958), carried out under almost identical conditions confirmed this finding. Similar conclusions were reached by Little, Creteur and Tovell (1959) in a study of recovery times following electroconvulsive therapy and by Egbert, Sechzer and Eckenhoff (1958) when the drugs were used for hypnosis.
Gale (1956) and Wyant, Dobkin and Asheim (1957) and Egbert, Sechzer and Eckenhoff (1958) found that methitural caused a higher incidence of coughing, hiccough and laryngospasm than thiopentone. The frequency of these complications are also commented on by Fleming and Robinson (1957) and by Smith (1957).

Fitzpatrick, Clarie and Mersch (1959) noted that the injection of 10 per cent solution frequently caused pain and was often followed by venous thrombosis. This high concentration does not appear to have been used by other workers and there is no reason to suppose that a 2.5 or 5.0 per cent solution has more deleterious effects than the same concentration of thiopentone.

Comparison with thiopentone.
The dose of methitural required to produce sleep is about half as great again as that of thiopentone. The rate of recovery from equipotent doses of the two drugs is similar but methitural causes a significantly higher incidence of respiratory side effects.

B.137 AND B.82
These drugs were the most promising of a large series of N-methyl and N-ethyl substituted thio barbiturates described by Peel et al. (1959). From figure 1 it can be seen that B.137 is the N-methylated form of Inactin whilst B.82 bears a similar relationship to buthalitone.

Barron, Dundee and King (1960) found that B.137 caused a significantly higher incidence of tremor and spontaneous involuntary muscle movement than thiopentone. It was interesting to note that the incidence of this complication increased with dosage. In a further study, in which the drug was also compared with Inactin, Dundee, Barron and King (1960) confirmed these findings and also showed that the incidence of side effects was markedly reduced by opiate premedication. B.137 and Inactin appeared to be equipotent and there was no evidence to suggest that methylation of Inactin produced a compound from which recovery occurred more rapidly.

In a small series of observations with B.82, Barron and Dundee (in press) found that the incidence of tremor, muscle movements, coughing and hiccough was prohibitively high and that injection of the drug was frequently followed by a generalized erythematous rash.

It is the opinion of the authors that neither B.137 nor B.82 has any place in clinical anaesthesia.

DISCUSSION
In this review many of the newer intravenous barbiturates have been "weighed in the balance and found wanting". Buthalitone, methitural, B.137 and B.82 were all introduced and studied in the hope of finding a compound with a more rapid recovery rate than thiopentone. In no instance has this claim been substantiated and, furthermore, none of these compounds produced as good anaesthesia as thiopentone.

Apart from its lower potency, Inactin appears to be as good a compound as thiopentone, but does not seem to possess any advantages over the standard drug.

Methohexital alone appears to offer the only advance in the field of intravenous barbiturate anaesthesia. It is much more potent that thiopentone and there seems little doubt that the claims for brevity of action will stand critical analysis. It may produce a less severe degree of hypotension than thiopentone and there is a possibility that its local irritant action is less severe. Against these advantages there appears to be a higher incidence of excitatory phenomena and respiratory upset and, while this is reduced by the pre-operative use of an opiate, it is increased by phenothiazine premedication. Apart from methohexital, it may well be that further advances in intravenous anaesthesia will come from non-barbiturate drugs.

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BERNARD JOHNSON MEMORIAL

The following letter, which appeared in the last issue of the Journal, is reprinted as a reminder to our readers:

Sir,—An appeal for funds to set up a memorial to Bernard Johnson was launched last March. It was hoped at that time to raise the sum of £6,000, which would cover the cost of a memorial plaque to be placed in the Research Laboratories of the Faculty and to endow the salary of the Faculty Adviser in Postgraduate Studies. To date approximately £3,000 has been raised, which falls some way short of the minimum required for this endowment. An anonymous donor has most generously offered to match any further donations received before March 27, 1961, when the fund will be closed. Should any of your readers wish to subscribe, or to add to their previous donations, their contributions should be addressed to me at the Faculty of Anaesthetists, Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2.

GEOFFREY ORGANE,
Dean, Faculty of Anaesthetists,
Royal College of Surgeons.