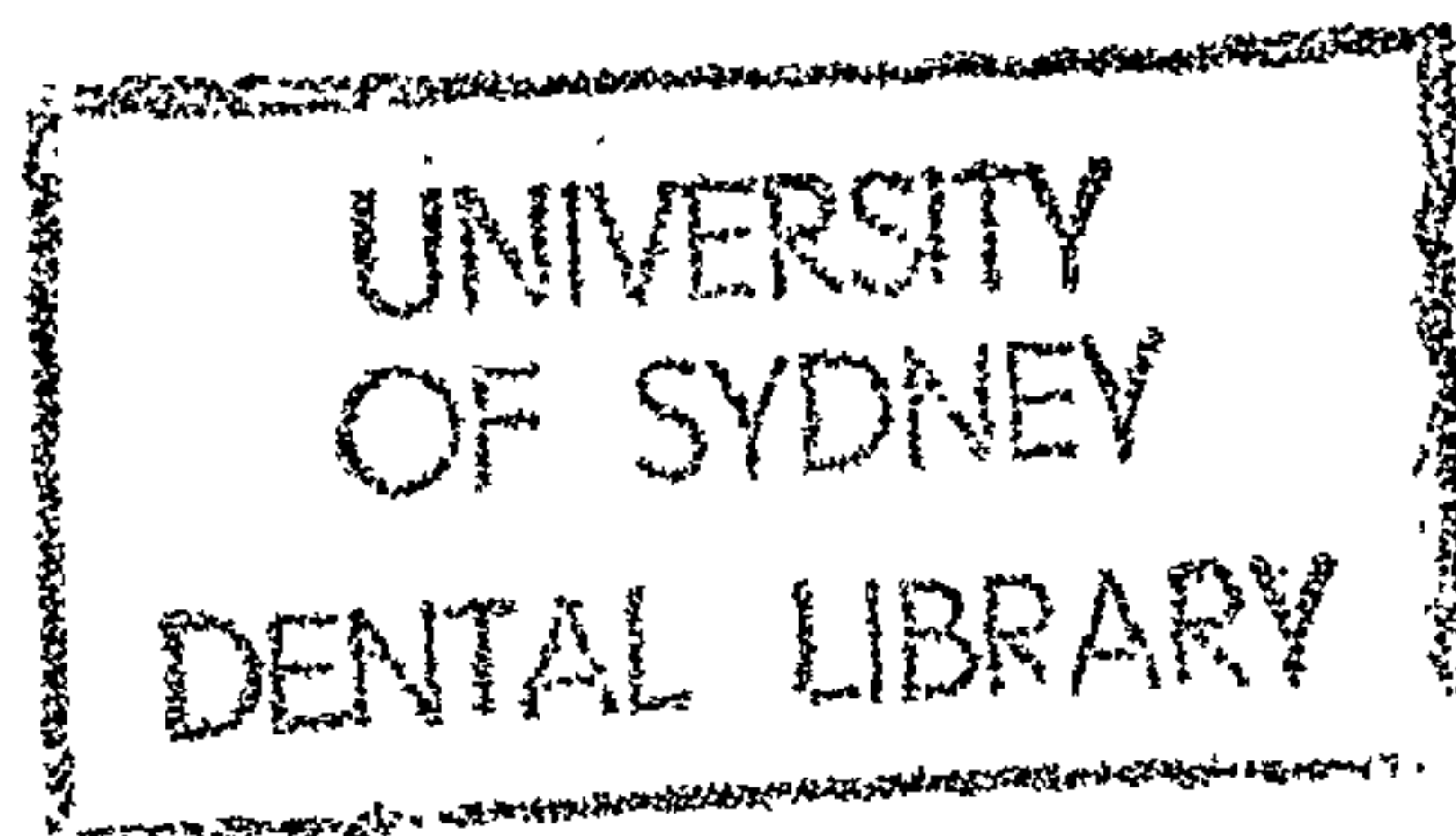


THE USE OF SODIUM METHOHEXITONE

IN GENERAL DENTAL PRACTICE

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A THESIS SUBMITTED FOR THE
DEGREE OF MASTER OF DENTAL SURGERY



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This work is dedicated to
my wife Christine
and my sons
Scott, Stuart and Robert

A B S T R A C T

The thesis, *The use of sodium methohexitone in general dental practice*, is presented in support of my candidature for the degree M.D.S.

A survey of the relevant published work on the use of sodium methohexitone in general dental practice, is presented.

The results of 4,379 administrations of sodium methohexitone by me, on 2,722 patients, is presented.

The results of a survey sent to a group of these patients is presented.

Conclusions and recommendations concerning the use of sodium methohexitone in general dental practice are made.

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PREFACE

Evidence suggests that at least half the population cannot tolerate routine dental treatment because of fear (Halikis 1966; Kleinknecht et al 1973; Drummond-Jackson 1973a; Pearson 1974; Miller et al 1975).

Foreman (1970a) analysed the records of 1,000 patients who received dental treatment whilst sedated. He found the average time since their last restorative treatment to be almost five years. He suggests that had it not been for the prospect of sedation, most would have sought emergency treatment only.

Sodium methohexitone is frequently used, particularly in Britain and the U.S.A., in a variety of sedation and anaesthesia techniques; however, a continuing controversy surrounds its use and it is easy to illustrate opposing viewpoints from the professional literature, as follows:

Of practitioners who use the drug, Blatchley (1976) states, . . . *they themselves were giving their patients a safe service, as shown by their large practices of patients who come to them repeatedly for treatment.*

Mann et al (1971) compares restorative treatment under local analgesia to treatment under methohexitone. Of their patients, there was a *considerably higher proportion who expressed 'delight' with this type of treatment as compared with patients under local analgesia.*

However, Cutler (1975) believes there has been an . . . *over enthusiastic and indiscriminate adoption of intravenous anaesthesia.*

The use of such techniques has been branded: a practice building *gimmick* (Helmore 1969a) and a *fetish* (Lynch 1973); and administrators

are supposed to *employ the hard sell* (Sara 1974).

The Australian Society for the Advancement of Anaesthesia and Sedation in Dentistry, which represents these practitioners, is seen by others to be led by a highly enthusiastic group, more concerned with money and *fashionable* dentistry than with the real quality of work (Lazar 1975).

Concern has also been expressed that the anaesthetic conditions produced by methohexitone are *prejudicial to good dentistry* (Wise et al 1969). There has been a fear that the use of water coolants has been reduced or stopped with methohexitone treatment (Galley 1969).

In undertaking this study of the use of methohexitone, my first aim was to attempt to make logical conclusions from a literature filled with a bewildering array of unsubstantiated claims. Several interesting facts emerged from my reading:

1. Australia has produced very little published material on the use of methohexitone.
2. In the international literature, dentists account for less than 50% of authorship of studies investigating the use of methohexitone in dentistry.
3. Less than half the clinical studies published relate to the use of methohexitone for conservative dentistry.
4. Few studies have been undertaken in private practice.
5. It would seem that the use of methohexitone has only once before been the subject of a Master's Degree.
6. Most studies are limited in the number of administrations. Few

have studied more than 1,000 administrations and most, less than 100.

The second aim of this thesis is to compile statistics on a large number of administrations of methohexitone for general dental treatment (presented in detail on p.344).

In order to build up a large sample with statistical significance, I had to limit my clinical research to the minimal incremental technique using methohexitone, sometimes supplemented with diazepam (usually 5mg) or local analgesia. There are many variations of this technique (some using larger doses of diazepam or other drugs), but it was not possible to include them all. By reducing the number of variables in this way, I have attempted to build a solid framework to direct my future research.

The thesis is divided into two parts - a review of the literature, and scientific results:

Part 1 - The Review

The review contains 14 sections, each dealing with a particular aspect of methohexitone. A final section in Part 1 contains my general conclusions, although conclusions are also made at the end of each individual section. In general, I have avoided discussing my scientific results in the review. Wherever possible, I have tried to avoid repetition, hence there is much cross-referencing.

Part 2 - Scientific Results

A similar format to Part 1 has been followed and at the end of each section there is a discussion of my results and, where relevant, comparisons are made with the results of others.

Finally, I have made general conclusions drawn from my clinical experience and reading.

P A R T 1

REVIEW OF LITERATURE

1-1

GENERAL HISTORY

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1-1: HISTORY OF THE DEVELOPMENT OF THE BARBITURATES

Probably the greatest advance in anesthesia for ambulatory dental patients was the introduction of the ultra-short-acting intravenous barbiturates (Recant 1960).

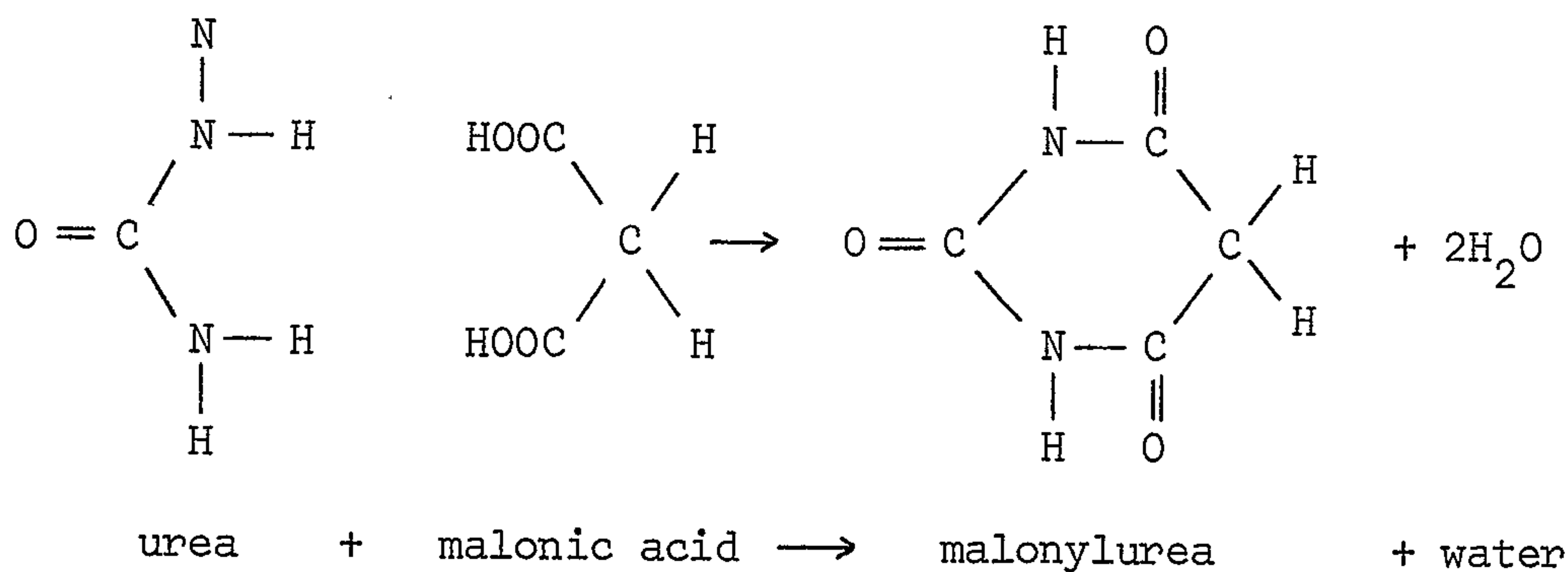
As methohexitone belongs to the barbiturate group of drugs, a brief review of the development of the group is presented.

1-1-1: DISCOVERY OF BARBITURIC ACID

The story of the development of the barbiturate group of sedative and hypnotic drugs began with the work of a young German organic research chemist, Adolf von Baeyer (Harvey 1975; Shane 1975a).

In 1864, whilst investigating derivatives of uric acid, he synthesised the compound malonylurea, a condensation product of urea and malonic acid.

DIAGRAM 1-1: CONDENSATION OF UREA & MALONIC ACID TO FORM MALONYLUREA

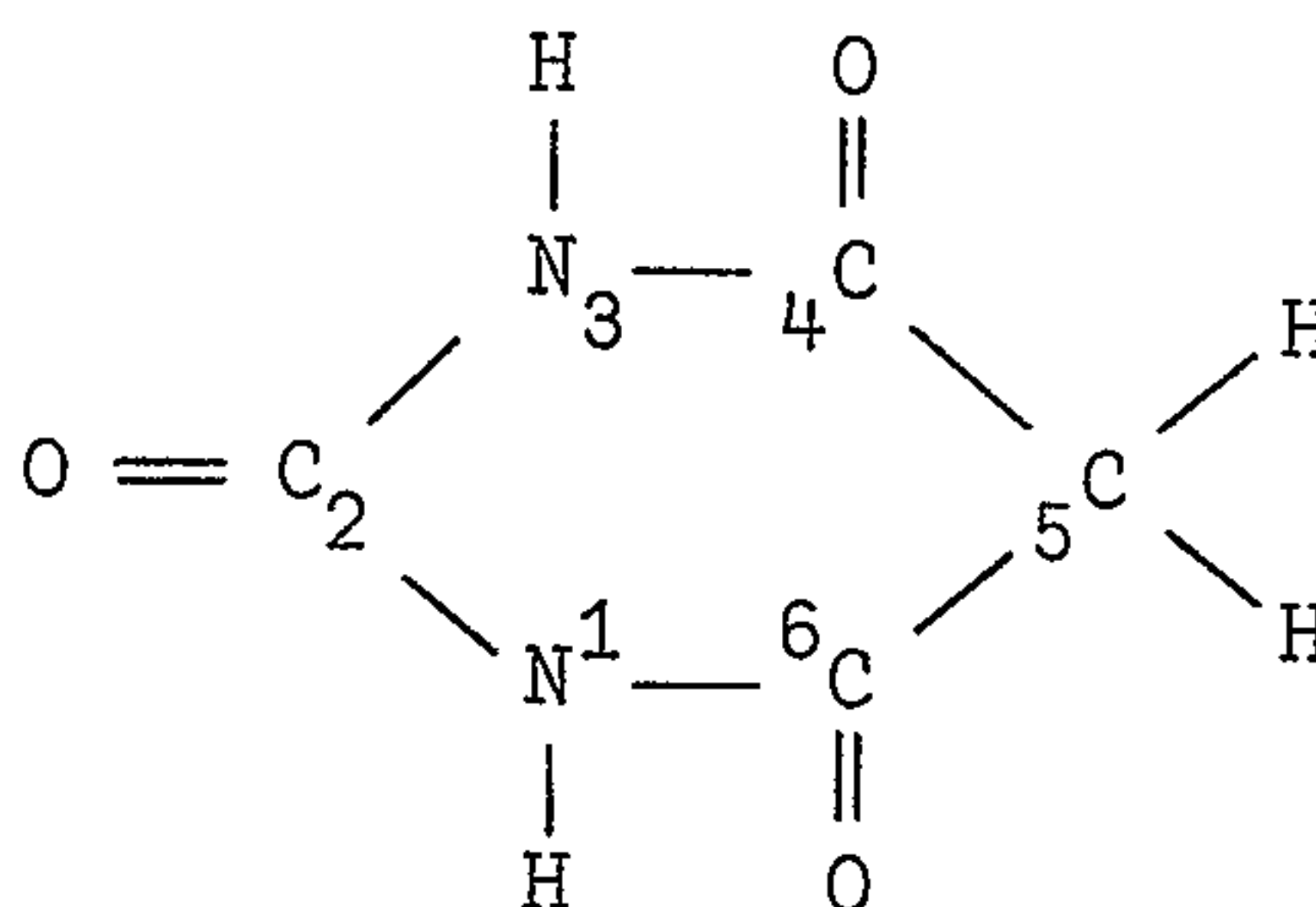


Harvey (1975) tells the story that Baeyer named his new compound after St Barbara, the patron saint of an artillery regiment.

Lloyd (1957) however, credits Conrad & Guthzeit with the synthesis of barbituric acid in 1882.

Barbituric acid is the foundation stone in the development of a group of sedatives and hypnotics that have played an important role in modern anaesthetic practice.

DIAGRAM 1-2: BARBITURIC ACID SHOWING NUMBERING USED TO IDENTIFY KEY ATOMS

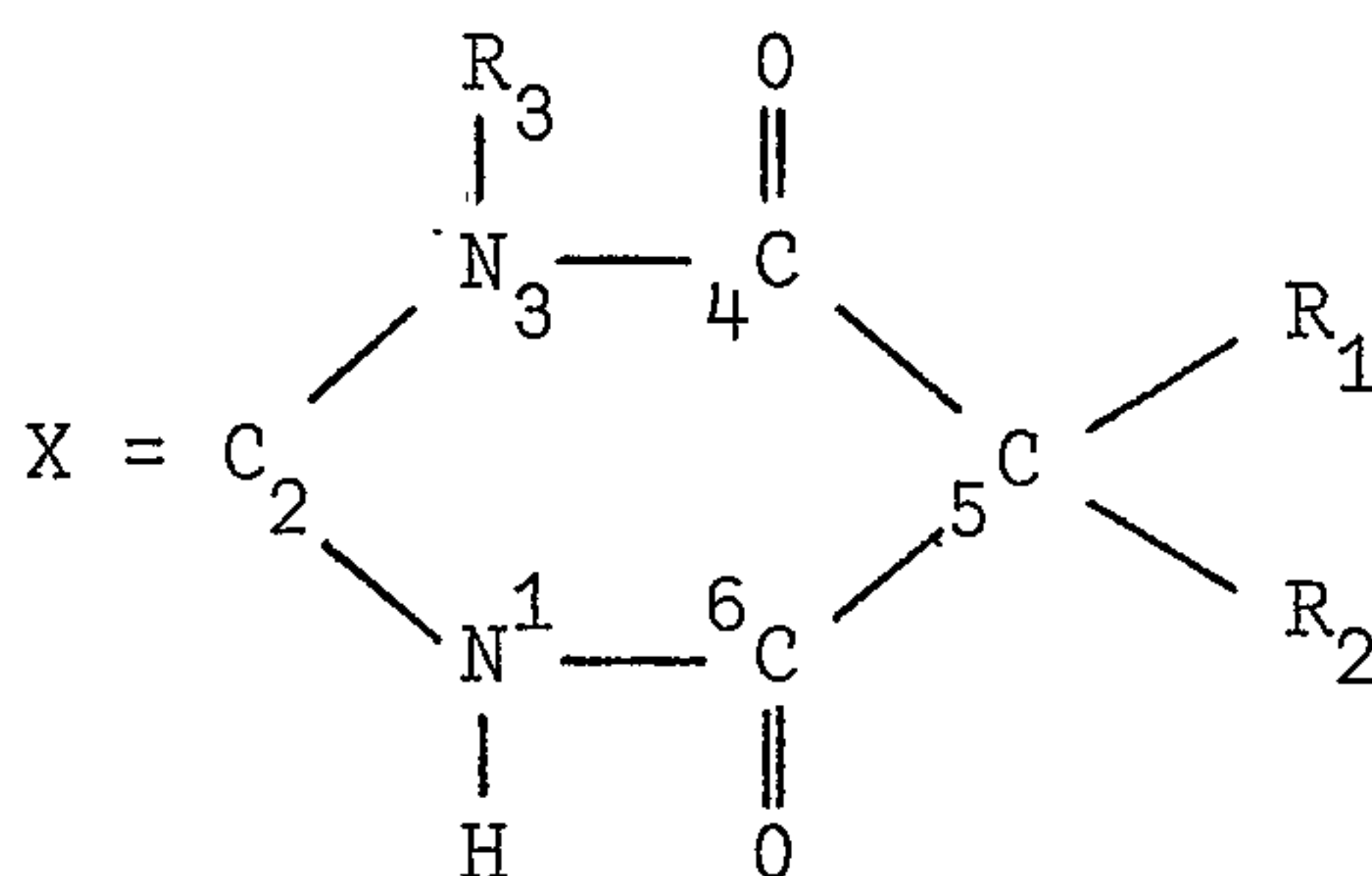


1-1-2: THE BARBITURATES

Barbituric acid has no hypnotic properties. By replacing hydrogen atoms with a number of radicals, many compounds can be produced that do exhibit hypnotic properties.

Tatum (1939) discusses possible effects produced by different radicals.

DIAGRAM 1-3: GENERAL FORMULA OF BARBITURATES



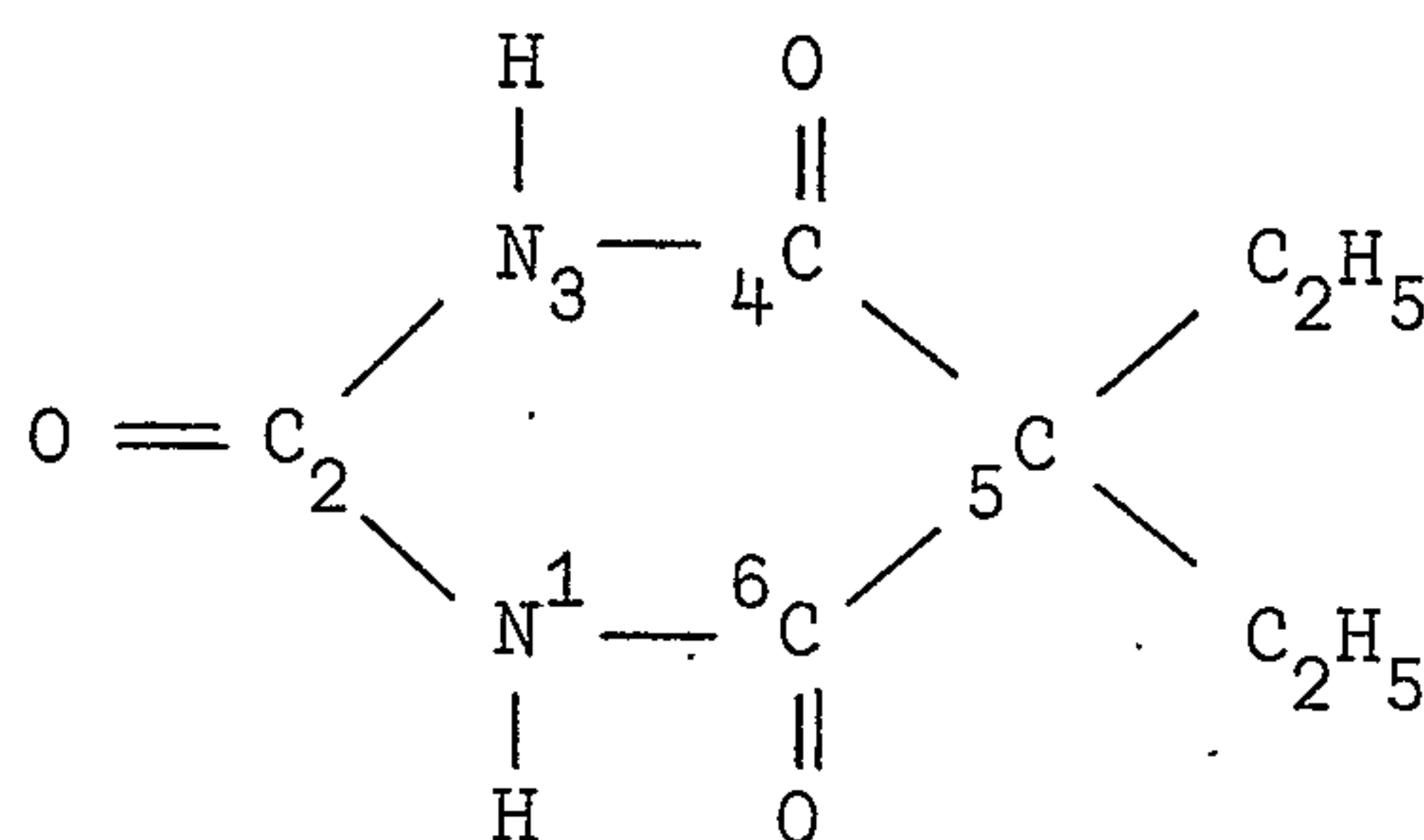
Both hydrogens at position 5 must be replaced by alkyl or aryl groups. R₃ can be a methyl group. X can be oxygen or sulphur.

True barbiturates keep the oxygen atom at the urea end of the molecule (position 2), but most hypnotic compounds derived from barbituric acid have this oxygen replaced by a sulphur atom.

Such compounds should strictly be called thiobarbiturates and, to avoid confusion, the term oxybarbiturate is often given to those compounds retaining the oxygen at this position (Harvey 1975).

The first barbiturate to be used in medical practice was barbital, introduced in 1903 by Fisher & Van Merring. For his work, Fisher received the Nobel Prize (Jorgensen & Hayden 1972c).

DIAGRAM 1-4: BARBITAL SHOWING SUBSTITUTION OF TWO HYDROGENS BY TWO ETHYL GROUPS AT POSITION 5



The early barbiturates were slow to act and recovery times were delayed, making clinical use difficult. The first rapidly acting barbiturate to be used to produce anaesthesia by the intravenous route was amobarbital (Amytal), introduced in 1929 (Office of Health Economics 1976).

But, the introduction of the ultra-short acting intravenous barbiturate, thiamylal, in the 1930's was an important breakthrough in dental anaesthesia (McCarthy 1975).

1-1-3: HEXOBARBITONE

Dundee (1961) says that the first really successful intravenous anaesthetic was hexobarbitone. This compound was introduced in Germany in 1932 and then, almost immediately, used clinically in the U.S.A. (Galley 1969).

Drummond-Jackson pioneered the use of intravenous hexobarbitone in dental practice (Jorgensen & Hayden 1972c) in the U.K. *at a time when two of the most eminent physicians of the day had on the basis of their experience of cases of suicidal overdose roundly condemned the use of barbiturates* (Obituary 1976).

1-1-4: THIOPENTONE

In the same year that hexobarbitone was synthesised, 1932, Lundy developed thionembutal at the Mayo Clinic (Dundee 1971; Jorgensen & Hayden 1972c).

This compound was introduced into clinical practice in the U.S.A. in 1934, and in the U.K. in 1935, as thiopentone (Galley 1969).

The advantage of hexobarbitone and thiopentone over their predecessors was that, provided they were given slowly, anaesthesia did not deepen after the start of unconsciousness (Galley 1969); and even more importantly, thiopentone exhibited a rapid onset of action. Because of these properties, much use was made of thiopentone with an intermittent technique (Dundee 1971).

1-1-5: PROFESSOR JORGENSEN'S WORK

In 1945, Jorgensen refined the administration of intravenous analgesics and local analgesics (Jorgensen & Hayden 1972c). He began using a technique of intravenous premedication at the Stomatology Clinic of the Medical School at the White Memorial Hospital in 1946 (Jorgensen et al 1963).

In our work, begun about seven years ago in the Stomatology Clinic of the College of Medical Evangelists School of Medicine, we

used Nembutal (pentobarbitone sodium) 'intravenously' (Jorgensen & Leffingwell 1953).

Although, Jorgensen & Hayden (1972c) give Hubbell the credit of being the first North American dentist to adopt, in his surgery, full intravenous anaesthesia, without premedication, as the sole agent for ambulatory patients.

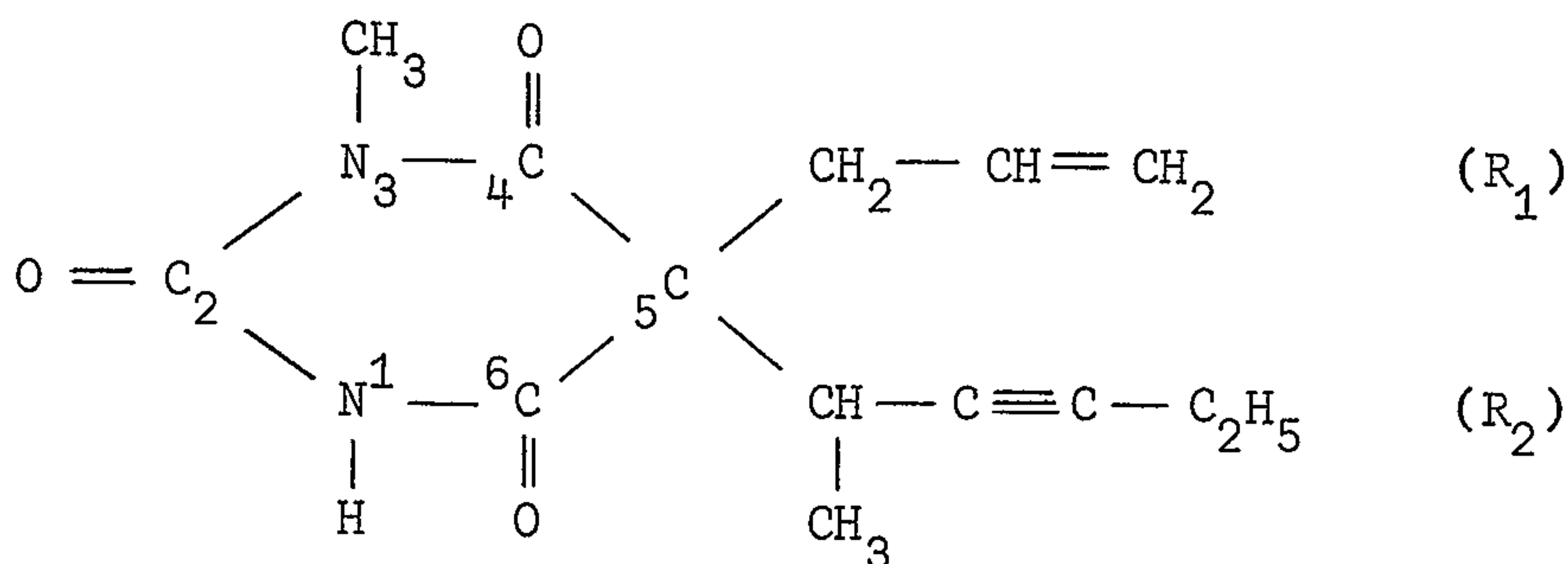
1-1-6: COMPOUND 22451

Despite the low incidence of side effects and the smooth induction of thiopentone, research continued in an attempt to find an even faster acting barbiturate.

Over 2,000 barbiturates were synthesised and tested in animals (Gruber et al 1957) and about 50 were marketed for clinical use (Harvey 1975).

In 1954, Doran synthesised a methylated oxybarbiturate called compound 22451 (Bennet 1974p).

DIAGRAM 1-5: COMPOUND 22451 SHOWING METHYL GROUP AT POSITION 3, ALLYL AT R_1 AND 1-METHYL-2-PENTYNYL AT R_2



The first trials of 22451 on patients were undertaken at the Indiana University School of Medicine, Indianapolis, under the direction of the Lilly Laboratory for Clinical Research and the University Anesthesiology Department.

The results of these trials were published by Gruber et al (1956, 1957). They observed that compound 22451 produced a high incidence of hiccoughs and skeletal muscle tremors. These were a clinical disadvantage.

Heaton (1956) conducted trials at the University of Colorado, but because of the muscle movements it produced, he could not recommend compound 22451.

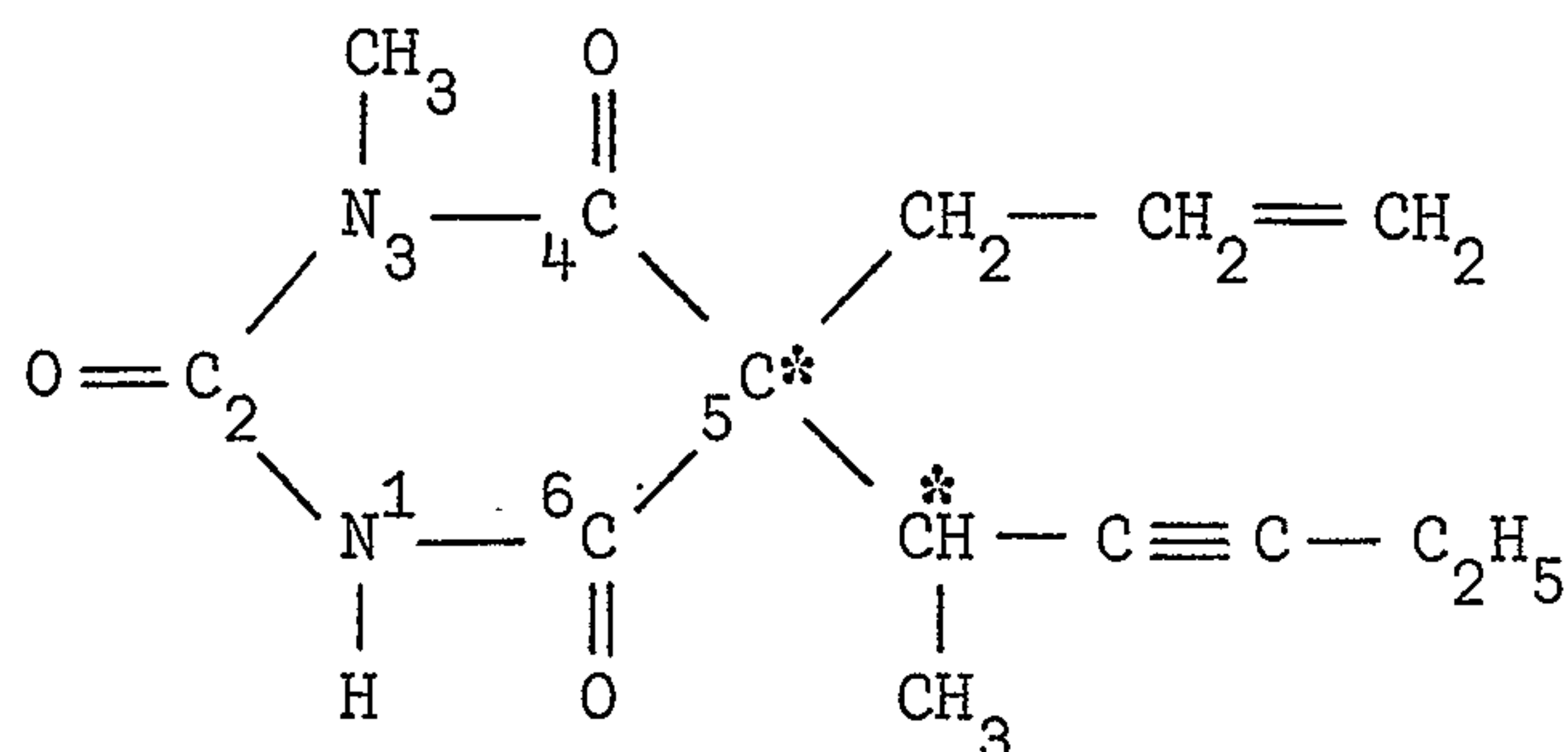
It was discovered that the molecule represented as compound 22451 exists in four stereoisomeric forms. Gibson et al (1959) investigated these differences in animals and found that each isomer exhibited significant differences in potency and incidence of side effects. This was the first barbiturate to demonstrate such differences.

Compound 22451 was a racemic mixture of two of the low melting point isomers (β -d and β -l).

1-1-7: COMPOUND 25398

A mixture of the high melting point isomers (α -d and α -b) produced desirable anaesthesia with a low incidence of side effects. This was called compound 25398.

DIAGRAM 1-6: COMPOUND 25398



* Centres of asymmetry

The different representations of the molecule are given by Gibson et al (1959) and discussed by Redish et al (1958).

Gruber et al (1957) began trials with compound 25398. Stoelting (1957) recommended it after trials on 285 patients. He did not observe undesirable muscle movements.

Following this work compound 22451 was abandoned in preference to compound 25398 which was named methohexital (Redish et al 1958) and marketed in the U.S.A. as Brevital, and in the U.K. as Brietal (Buxton 1971a).

1-1-8: METHOHEXITONE APPROVED NAME

In April 1961, the British Pharmacopoeia selected methohexitone as the approved name for methohexital (Dundee & Moore 1961b - addendum).

In the U.S.A., methohexitone is still called methohexital because there, all barbiturates end in -al. This suffix is an early misnomer alluding to the carbonyl groups present in the molecules. Throughout the British Commonwealth, the suffix -one is used (Harvey 1975).

The suffix -one will be used throughout this thesis.

1-1-9: CLARIFICATION OF NAMING OF METHOHEXITONE

I found that the different names used for methohexitone, particularly in the earlier studies, quite confusing.

To help overcome this problem, I have drawn up a table listing those studies and the names they use.

TABLE 1-1 TABLE TO CLARIFY NAMING OF METHOHEXITONE IN EARLY STUDIES			
NAME OF STUDY	ISOMER STUDIED		ISOMERS DISCUSSED
	22451	25398	
Gruber et al (1956)	+		
Heaton (1956)*	+		
Gruber et al (1957)	+		+
Stoelting (1957)		+	
Dobkin & Wyant (1957)		+	
Wyant et al (1957)		+	
Redish et al (1958)		+	+
Weyl et al (1958)		+	
Gibson et al (1959)		+	+
Wyant & Chang (1959)		+	
Egbert et al (1959)		+	
Taylor & Stoelting (1960)			+
Hubbell (1960)			+
Coleman & Green (1960)			+
Recant (1960)			+
Simpson & Rondeau (1966)			+

* Chemical name only given. (Assumed it is 22451.)

N.B. Later studies discuss only *methohexitone* which is 25398

1-1-10: CONCLUSION

- (1) The oxybarbiturate, methohexitone, was developed in the attempt to find a faster acting barbiturate with a low incidence of side effects.
- (2) I have tried to clarify the confusing nomenclature found in the literature.

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1-2-2 Effect of Molecular Structure on Properties of Methohexitone	13
1-2-3 Discrepancies in Presentation of Methohexitone Molecule	14
1-2-4 Tautomers of Methohexitone	16
1-2-5 Sodium Salt of Methohexitone	17
1-2-6 Conclusion	17

1-2-1: INTRODUCTION

Methohexitone is a white hygroscopic powder (Bennett 1974p), with a melting point of 93-94 degrees C (Sunshine et al 1966). It is prepared for use as the sodium salt, to which is added anhydrous sodium carbonate to avoid deterioration. A 500mg ampoule of methohexitone powder contains 30mg of sodium carbonate (Barron & Dundee 1961; Allen 1972a).

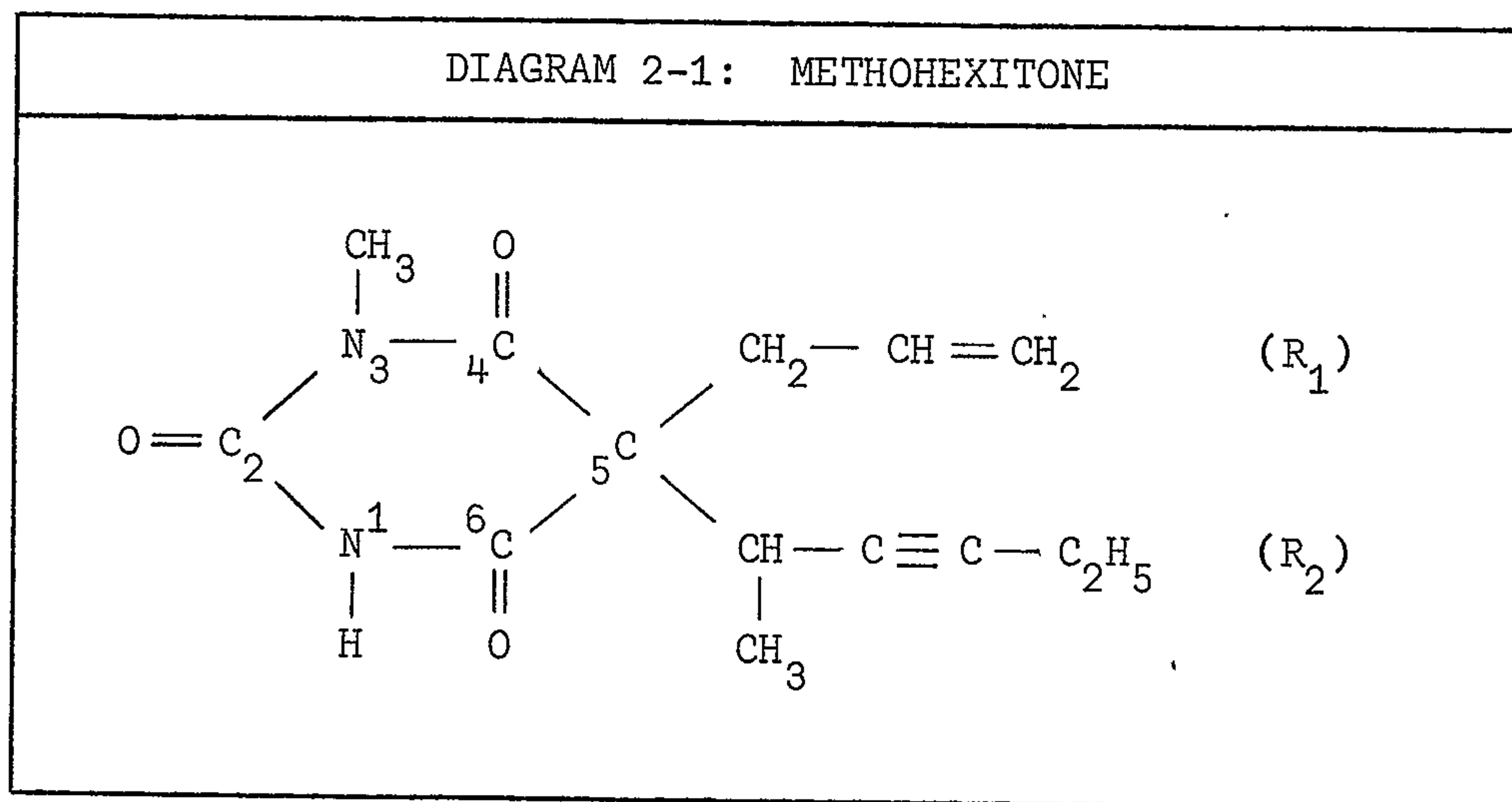
It is mixed with water for intravenous injection. The solution is strongly alkaline viz:

1.0%	-	pH 11.11	
2.5%	-	pH 10.95	
5.0%	-	pH 11.03	(Barron & Dundee 1961)

The solution is clear and colourless and will remain stable at room temperature for at least six weeks (Gibson et al 1959). Although Recant (1960) has observed a slight loss of potency on standing.

However, Redish et al (1958) say that the solution will remain stable at 25 degrees C for six months and, if refrigerated to 5 degrees C, it will remain stable for at least one year.

Hudson (1971) recommends that the solution be kept no longer than one week because research has indicated that *resistant* organisms may survive in liquids with the alkalinity of methohexitone.

1-2-2: EFFECT OF MOLECULAR STRUCTURE ON PROPERTIES OF METHOHEXITONE

The presence of the methyl radical at position 3 is thought to confer convulsive activity - manifested by tremors and involuntary muscle movements (see Diag. 2-1; see also section 1-9-4C).

There are two unsaturated side chains: an allyl radical at R_1 and a methyl pentynyl chain at R_2 . The latter chain does not appear in any other barbiturate grouping. It is thought that this side chain gives methohexitone an enhanced potency, rapid recovery and a high incidence of cough and hiccoughs during induction (Dundee & Barron 1962).

It is interesting that recent preparations of the purer high melting point isomers seem to produce a lower incidence of cough and hiccough than did the earlier samples (Haslett & Dundee 1968).

1-2-3: DISCREPANCIES IN PRESENTATION OF METHOHEXITONE MOLECULE

The methohexitone molecule has been illustrated in a number of papers. Some interesting discrepancies are apparent:

1. Despite the fact that the drug is supplied and used as the sodium salt, several papers do not show the presence of the sodium atom.
2. When the sodium atom is shown it is either attached to the oxygen atom at position 2, or it is shown attached to the nitrogen atom at position 1.
3. In three papers the methyl group at position 3 is not shown. I assume this is an oversight.
4. The triple bond in the methyl pentynyl chain has been represented by a double bond only. This is probably a printing error and occurs in two papers.

In Table 2-1, I have placed in chronological order, those papers which discuss the molecular chemistry of methohexitone. In this way I hope the discrepancies will be highlighted.

TABLE 2-1					
TABLE SHOWING PAPERS WHICH DISCUSS METHOHEXITONE CHEMISTRY					
Name of Study	Position of Na			N ₃ methyl left out	triple bond left out (R ₂)
	None	N ₁	O ₂		
Gruber et al 1957.	+				
Stoelting 1957	+				
Dobkin & Wyant 1957		+		+	
Wyant et al 1957		+		+	
Redish et al 1958			+		
Weyl et al 1958	+				
Gibson et al 1959	+				
Wyant & Chang 1959			+		
Taylor & Stoelting 1960			+		
Hubbell 1960			+		
Coleman & Green 1960			+		
Recant 1960			+		
Green & Jolly 1960			+		
Dundee & Moore 1961a		+			
Barron & Dundee 1961		+			
Dundee & Moore 1961c		+			
Miller et al 1961			+		
Lyon 1961			+		
Ogilvie 1962			+		+
Whitwam & Manners 1962		+			
Barron & Dundee 1962		+			
Dundee & Barron 1962		+			

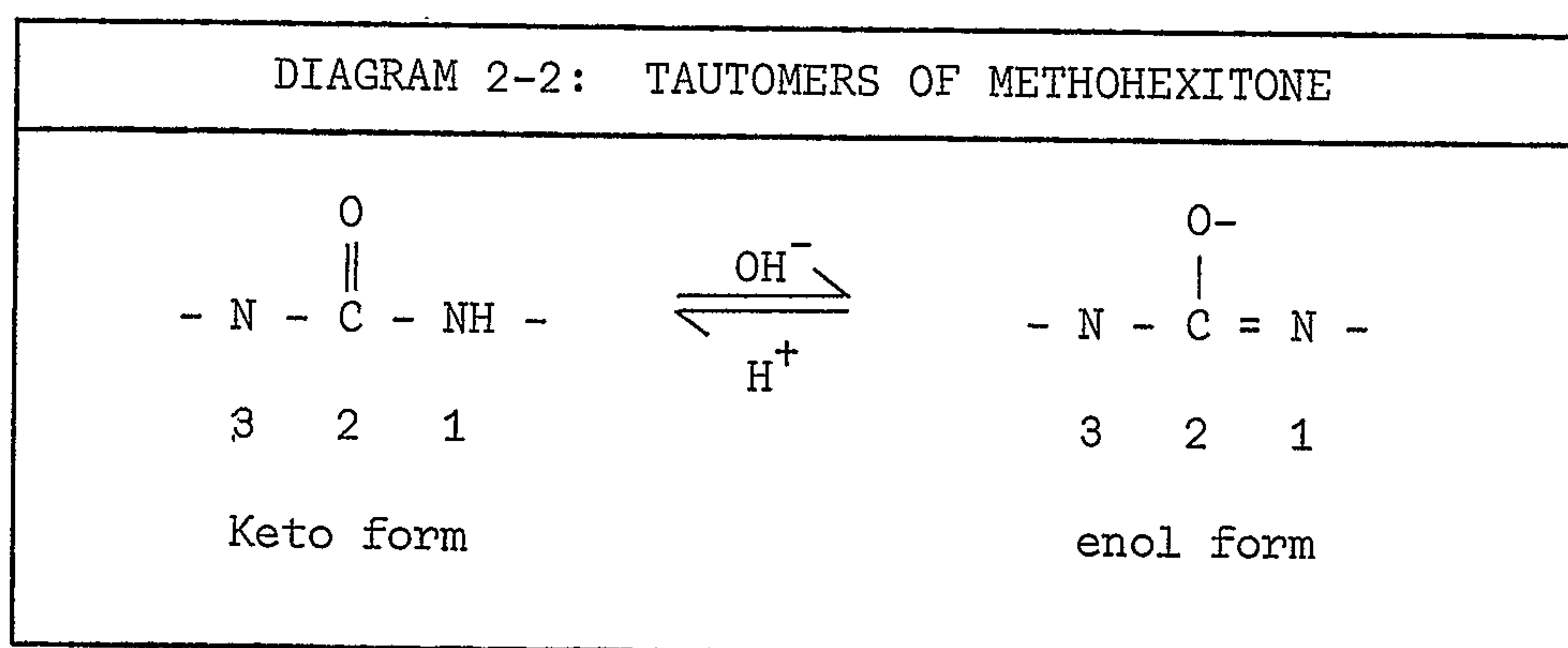
(cont)

TABLE 2-1 (continued)					
TABLE SHOWING PAPERS WHICH DISCUSS METHOHEXITONE CHEMISTRY					
Name of Study	Position of Na			N ₃ methyl left out	triple bond left out (R ₂)
	None	N ₁	O ₂		
Goldman & Harris 1963	+				
Brand 1963	+				
Marshall 1964			+		
Barron 1964		+			
Simpson & Rondeau 1966			+		
Dobkin & Su 1966			+	+	
Thornton 1970			+		+

1-2-4: TAUTOMERS OF METHOHEXITONE

Lloyd (1957) discusses the subject of tautomerism and the barbituric acid nucleus.

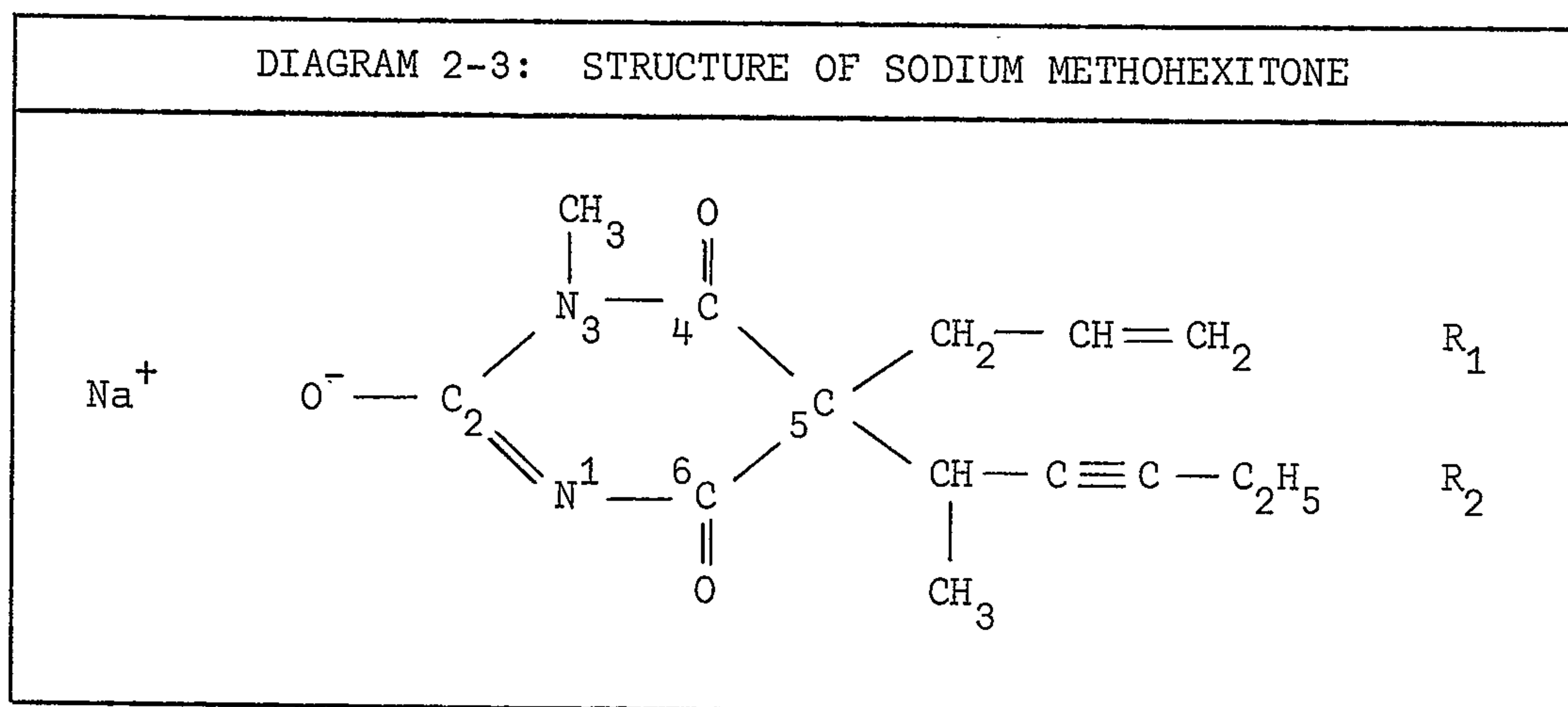
There are probably two tautomers of methohexitone. The carbonyl group at position 2 takes on acidic character because of its position between two electronegative amido nitrogens (Harvey 1975).



By changing from the keto form to the enol form, the methohexitone nucleus becomes negatively charged.

1-2-5: SODIUM SALT OF METHOHEXITONE

The sodium salt of methohexitone may be considered to have the following structure:



1-2-6: CONCLUSION

(1) In table 2-1 above it will be seen that in several papers the sodium atom is shown attached to the nitrogen atom at position 1 in the methohexitone nucleus.

However, in other papers the sodium atom is shown adjacent to the carbon 2 as in diagram 2-3 above.

In an attempt to clarify the apparent anomaly, I obtained from the manufacturers of Brietal (Lilly Industries Pty Ltd) a copy of their official structural formula of sodium methohexitone (Wooller 1977).

The sodium atom is shown adjacent to carbon 2 as in diagram 2-3.

I conclude that this is the more correct representation of the sodium salt.

(2) It is unfortunate that in the past, many inaccurate diagrams of the methohexitone atom have been published.

In table 2-1, it can be seen that there have not been any recent inaccurate representations. However, this is probably due more to the fact that there have been fewer representations than to greater accuracy of presentation.

1-3

USE IN DENTISTRY

CONTENTS

Page

1-3-1 History

19

1-3-2 Methods of Administration

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1-3-3 Conclusion

26

1-3-1: HISTORY

Stoelting (1957) first reported the use of methohexitone in dental treatment. Since then there have been more than forty other clinical studies involving methohexitone for the treatment of dental outpatients (see Table 4-1 in Section 1-4-1).

The use of methohexitone for dental treatment was the subject of a thesis by Redish for the degree of Master of Dental Science, University of Pennsylvania, based on his work at Indianapolis (Redish et al 1958).

The first report of its use in the U.K. for dental treatment was by Drummond-Jackson (1960), and in New Zealand by Wilkinson and Wilkinson (1960).

In Australia, Grainger (1970a) presented results of his experience with the drug as part of his M.D.S. thesis.

In the U.S.A., methohexitone is widely used for oral surgery at the present time (Trieger 1976).

Also see Section 1-14-2 for further comments on the popularity of methohexitone, over other barbiturates, for dental treatment.

1-3-2: METHODS OF ADMINISTRATION OF METHOHEXITONE

1-3-2a: To induce patients only

Green & Jolly (1960) stated, *Methohexital is considered to have great promise in dental anaesthesia, provided it is used solely as an induction agent and in the small dosage described.*

Coleman & Green (1960) stated: *It is essential that methohexital be used solely to induce sleep (not for narcosis) and that analgesia with another agent be established within the period allowed by the sleep dose.*

Blatchley (1961) suggested using methohexitone only for induction prior to maintenance with nitrous oxide and oxygen. Coleman & Harris (1963) described such a technique for extractions on outpatients.

1-3-2b: Continuous anaesthesia by drip

Methohexitone may be administered continuously by means of a saline or aqueous drip. Table 3-1 below, lists some studies that describe such techniques:

TABLE 3-1 METHOHEXITONE BY DRIP			
NAME OF STUDY	% METHOHEX. IN DRIP	DRIP	COMMENTS
Stoelting (1957)	0.1	water	+ Premed + intubation
Spiro et al (1975)	0.1 & 0.2	saline	For long procedures. Maintenance = 2-5mg/min
Tepfer et al (1964)	0.2	saline	+ Premed + intubation. Head & neck surgery lasting up to 8 $\frac{1}{4}$ hours
Adelson (1970)	0.2 & 0.4	?	+ Premed + intubation
Silver & Wolpert (1968)	0.5	?	+ Premed + L.A. One case only

Stoelting (1957) commented: *The drug did not have a cumulative effect when given by this method.* He gave up to 2,000mg and averaged 475mg of methohexitone.

However, Allen (1972a) warned that patients may easily be overdosed and he therefore recommended that this method should not be used on outpatients.

Shane (1966) found that dosage was difficult to control when only light amnesic levels were required.

Wangeman (1962) found that if deeper anaesthesia was suddenly needed, it was difficult to achieve quickly with this technique. (Dosage is discussed in Section 1-5.)

1-3-2c: Minimal incremental technique (M.I.T.)

1-3-2c(i): History

The most common method of administering methohexitone for dental treatment is by the minimal incremental technique (M.I.T.) which I will discuss in some detail.

The M.I.T. was invented in the U.S.A. by Green and Hubbell (Drummond-Jackson 1975c) but its development, and 'popularisation', is generally attributed to the late S.L. Drummond-Jackson of the U.K. and to Peter Foreman of New Zealand.

Foreman (1970b) gained experience in one of the first 'intravenous practices' in the U.K. between 1962 and 1965. He returned to New Zealand, refined the technique, and with Wilkinson et al (1965) reported on 6,704 administrations in general dental practice. Foreman (1965)

further refined the technique by keeping dosage as low as possible.

In Australia, Hodge (1968) claimed 14,000 administrations of methohexitone by the M.I.T. and reported that patient acceptance was very good. Unfortunately, none of his cases has been documented.

Apart from brief mentions by Grainger (1970a), Litchfield & Gerard (1971) and Litchfield (1974), there have been no Australian studies of the administration of methohexitone by the M.I.T.

Full descriptions of the M.I.T. have been given by Foreman (1967, 1970a) and Polyblank (1974).

1-3-2c(ii): Alternative names for the M.I.T.

The M.I.T. is called by a variety of names in the literature, and in Table 3-2 below are listed in alphabetical order, several common synonyms:

TABLE 3-2 COMMON SYNONYMS FOR M.I.T	
Amnesia-analgesia	Mini-anaesthesia
Ataralgia	Modified general anaesthesia
Chemnesia	Outpatient general anaesthesia
Chemical-hypnosis	Partial general anaesthesia
Deep sedation	Ultralight general anaesthesia
Intravenous hypnosis	Threshold anaesthesia
Methohexitone analgesia	Twilight sleep
For further information concerning these terms see Howells (1968) and McCarthy (1975)	

1-3-2c(iii): Objectives of the M.I.T.

The descriptive terms listed in Table 3-2 above, indicate some objectives of the M.I.T. The following authors have defined the objectives of the M.I.T:

Weinstock (1960) stated: *An intravenous anesthetic agent is effective for dental procedures because pain is not constant but intermittent and because complete relaxation of the musculature is neither necessary nor desirable. The depth of anesthesia is permitted to fluctuate between consciousness and unconsciousness, according to the severity of the pain stimuli of the operative procedure. The reflexes should be kept active during the course of the anesthesia, so that their protective mechanisms are functioning while the patient is asleep. The differences between this type of anesthesia and the types commonly used are far greater than is generally realised.*

Foreman (1967) defined the M.I.T. as: *The precisely controlled administration of methohexital sodium, in intermittent dosage, to produce an amnesic-analgesic state in which all normal protective reflexes are retained throughout the operative period which is unlike general anaesthesia.*

Hodge (1971) said that: *The object of the technique is to produce pleasant light sleep in which all protective reflexes are present. The state is then maintained by the addition of small increments of the drug . . . when the patient reacts to operative stimulæ. (Reflexes are discussed in Section 1-7-2.)*

1-3-2c(iv): Examples of the use of the M.I.T.

Methohexitone is usually administered unsupplemented, and to non-intubated patients, with the M.I.T. However, Table 3-3 below

lists some examples of variations in the technique:

TABLE 3-3 VARIATIONS IN THE M.I.T	
REFERENCE	METHOD WITH THE M.I.T
Douglas (1960)	Used endotracheal tube. Children
Stoelting (1957) Dundee & Moore (1961a)	With endotracheal tube
Liscombe (1968)	For tonsillectomy. No tube. <i>I feel that this method compares satisfactorily with others in common use and is worthy of further trials</i>
Young (1970)	With diazepam and local analgesia
Campbell et al (1967)	With fentanyl, diazepam and local analgesia

The M.I.T. is discussed in Sections 1-5-7, 1-5-8, 1-5-9.

1-3-2c(v): Criticism of the M.I.T.

Cadle et al (1968) stated: *The intermittent intravenous technique of outpatient dental anaesthesia with methohexitone is, despite controversy, an established technique in the dental surgery both for extractions and conservative dentistry.*

Although in his review of current techniques, Howells (1968) stated: *It is difficult to understand the advantages of the technique over inhalation maintenance.*

The Sydney oral surgeon, Helmore (1969a), said: *Patient gratitude and operator convenience are not necessarily the best yardsticks by which to judge a technique and it would indeed be a tragedy if the excellent record of Australian Dentistry were imperilled by a procedure which can easily become merely a practice building 'gimmick'.*

For a short while, a lively correspondence over the M.I.T. was published in the Australian Dental Journal (Helmore 1969b, 1969c; Foreman 1969a, 1969c).

Australians practising in the U.K. have criticised the M.I.T. Norman et al (1969) said that the routine use of the M.I.T. *incurs risks in inexperienced hands.*

The two studies that have provoked the most correspondence are Wise et al (1969) and Mann et al (1971).

Frequent mention is made of these studies throughout the review, and their main finds are briefly summarised in Table 3-4 below:

TABLE 3-4 FINDINGS OF TWO M.I.T. STUDIES	
WISE ET AL (1969)	MANN ET AL (1971)
Bad operating conditions Cumulative effect Undetected anoxia & respiratory obstruction Protection of airway against inhalation of debris could not be guaranteed	Clinical signs advocated as indicative of correct plane of anaesthesia may be misleading Because no analgesic is used the level of anaesthesia is hard to maintain Inferior working conditions to that achieved with local analgesia alone

1-3-3: CONCLUSION

For dental treatment, methohexitone may be used to:

1. Induce anaesthesia prior to maintenance with another agent.
2. Provide continuous anaesthesia as a drip.
3. Provide intermittent anaesthesia by the M.I.T. (including single dose techniques).

Table 3-5 below summarises my conclusions regarding the three methods.

TABLE 3-5 SUMMARY OF METHODS OF ADMINISTRATION	
METHOD	COMMENT
Induction only	Traditional general anaesthesia
Drip	Fine control of dosage difficult
M.I.T.	- Claimed to be different from general anaesthesia - Reflexes supposed to be maintained (See Section 1-7-2 for further discussion) - Use opposed by some

1-4

CLINICAL DENTAL STUDIES

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1-4-1: INTRODUCTION

Despite a large number of papers, articles and correspondence concerning the use of methohexitone in dentistry, there have been relatively few controlled clinical trials.

There are 45 studies that have tested methohexitone under some form of controlled clinical situation for dental treatment.

In Table 4-1 below, I have listed the 45 studies in chronological order. I have briefly mentioned the main objectives of each study, the number of administrations, whether the authors were dentists or anaesthetists, and the country of origin.

An index of abbreviations used appears immediately below the table.

In some studies, where the use of methohexitone has been compared with that of another drug, the total number of administrations shown relates only to administrations of methohexitone.

In two studies the number of administrations has not been given because the authors have grouped dental treatment with other forms of surgery, without specifying individually.

TABLE 4-1 CLINICAL DENTAL STUDIES								
NAME OF STUDY	AUTHOR	COUNTRY	PURPOSE OF STUDY	TECHNIQUE	NO. ADMINS	TYPE WORK	MY COMMENTS	
Stoelting (1957)	A1	U.S.A.	Compares M, TH, and Thiamylal	Premed. Induced with M tube, gas	?	V	Some dental	
Redish et al (1958)	A3, D1	U.S.A.	Compares M, TH, and MT	Induct. prior gas	24	E		
Weyl et al (1958)	A3	U.S.A.	Clinical eval.	Premed. some MIT some gas	1	V	200 cases only one dental	
Coleman & Green (1960)	A2	U.K.	Clinical eval.	Premed. Induced with M prior gas	373	E		
Douglas (1960)	D1	U.S.A.	Use in children	Premed. induced with M drip tube	95	E C	Children	
Drummond-Jackson (1960)	D1	U.K.	Eval. for gene- ral dentistry	M one shot	200	E C		

TABLE 4-1 (continued)

NAME OF STUDY	AUTHOR	COUNTRY	PURPOSE OF STUDY	TECHNIQUE	NO. ADMINS	TYPE WORK	MY COMMENTS
Green & Jolly (1960)	A2	U.K.	Compares M, TH	Induced with M prior to gas	500	E	
Hubbell (1960)	D1	U.S.A.	Clinical Eval.	Some pre- med, some MIT, some induced prior to gas	2500	E	
Recant (1960)	D1	U.S.A.	Compares M, TH, MT	MIT + some gas, some L.A.	2500	E	
Taylor & Stoelting (1960)	A2	U.S.A.	Compares M, TH	Premed. induced prior to gas	?	V	Some dent
Weinstock (1960)	D1	U.S.A.	Clinical Eval.	MIT + O ₂ Some gas	50	E C	
Wilkinson & Wilkinson (1960)	D2	N.Z.	Clinical Eval.	Induction prior to gas	98	E	
Bishop & Potts (1961)	A2	U.K.	Safety eval. of G.A. and L.A.	MIT	6	E	

TABLE 4-1 (continued)

NAME OF STUDY	AUTHOR	COUNTRY	PURPOSE OF STUDY	TECHNIQUE	NO. ADMINS	TYPE WORK	MY COMMENTS
Christenson et al (1961)	A2, D1	U.S.A.	Compares M, TH, and MT	Some pre- met, MIT	127	E	on 36 patients
Lyon (1961)	D1	U.S.A.	Clinical eval.	Premed. MIT, gas	513	E	
Myers & Coltman (1961)	A2	U.K.	Clinical eval.	Premed. induced with M prior to gas. Some tubed	1500	E	
Swerdlow (1962)	A1	U.K.	Compares M, TH, and G29505	Induced with M prior to gas	200	E	Also see Swerdlow (1964)
Goldman & Harris (1963)	A2	U.K.	Compares doses	Induction prior to gas, some Hal.	675	E	Series I Series Series III
Goldman & Kennedy (1964)	A2	U.K.	Compares % of solution of M	Induction prior to gas, some Hal.	298	E	

TABLE 4-1 (continued)

NAME OF STUDY	AUTHOR	COUNTRY	PURPOSE OF STUDY	TECHNIQUE	NO. ADMINS	TYPE WORK	MY COMMENTS
Young & Whitwam (1964a) Young & Whitwam (1964b) Whitwam & Young (1964)	A2	U.K.	Clinical Eval. Recovery, B.P.	Induction prior to gas, some Hal.	2000	E	
Foreman (1965)	D1	N.Z.	Stimulate thought re future	MIT	100	E C	
Wilkinson et al (1965)	D3	N.Z.	Clinical eval.	MIT + some gas	6704	E C	
Simpson & Rondeau (1966)	A1 D1	Canada	Clinical Eval.	Single shot, or induction prior to gas, tube, Hal; some premed	4000	E	
Hellewell & Hutton (1967)	A2	U.K.	Eval. for student use	Induction prior to gas, some Hal.	122	E	
Kurland (1967)	D1	U.K.	Compares Prop. and M	MIT	270	E C	Cases with M or mixture

TABLE 4-1 (continued)

NAME OF STUDY	AUTHOR	COUNTRY	PURPOSE OF STUDY	TECHNIQUE	NO. ADMINS	TYPE WORK	MY COMMENTS
Rollaston (1967)	A1	U.K.	Compares M, Prop.	MIT	150	E	
Brown et al (1968)	A1 D2	U.K.	Compares M, Diaz.	Induction prior L.A.	68	E C	
Kurland (1968)	D1	U.K.	Compares M, Prop.	Premed. + MIT	60	E C	
Allen et al (1969)	A2 D2	U.S.A.	Cardiovascular response	MIT	18	E	
Shafto (1969)	A1	U.K.	For children	MIT	500	E	Children
Swerdlow & Moore (1969)	A1 S1	U.K.	Dose duration	MIT	80	E	4 groups of 20 females
Wise et al (1969) Robinson et al (1969b)	A3 D1	U.K.	Physiological responses	MIT	30	E C	
Ryder (1970)	A1	U.K.	E.C.G. studies	MIT induction prior to gas	41	E	2 groups 13 + 28 = 41
Young (1970)	A1	U.K.	ultra light levels	M, M + diaz, M + L.A. all MIT	56	C	Synopsis only

TABLE 4-1 (continued)

NAME OF STUDY	AUTHOR	COUNTRY	PURPOSE OF STUDY	TECHNIQUE	NO. ADMINS	TYPE WORK	MY COMMENTS
Grainger (1970a)	D1	Aust.	Part MDS thesis	M, some L.A., MIT or single shot	20	E	Not pub- lished
Litchfield & Gerard (1971)	D2	Aust.	Clinical Eval.	MIT M + diaz + LA	1125	E C	Mainly concer- ned with diaz.
Mann et al (1971) Hatt et al (1971)	A4 S1 D1	U.K.	Compares M, LA	MIT	595	C	349 patients
Andrew et al (1973)	A4	U.K.	Compares M, Alth	Induction prior to gas	68	E	Children
Elliott et al (1974)	A1 D4	U.S.A.	Use with Innovar	Premed. with Inno- var, mor- phine, extra fen- tanyl, LA, MIT	800	E C	
Foreman (1974a)	D1	N.Z.	Describes a 'useful' technique	MIT M, diaz + LA	30	C	Written in USA

TABLE 4-1 (continued)

NAME OF STUDY	AUTHOR	COUNTRY	PURPOSE OF STUDY	TECHNIQUE	NO. ADMINS	TYPE WORK	MY COMMENTS
Litchfield (1974)	D1	Aust.	For handicapped	MIT + diaz	25	E C	Children
Young (1974)	A1	U.K.	Compared M, Prop	MIT, some gas + Hal	72	E	
Levin H.A. (1975)	D1	U.S.A.	Describes a technique	Premed. MIT, M + diaz	25	C	
Campbell et al (1976)	A1 D2	U.S.A.	cardiorespira- tory changes	Fentanyl, diaz, gas LA + MIT M	10	E	
Gale (1976)	A1	U.K.	Recovery compared to other drugs	MIT	16	E	

Index to Table 4-1

A	=	anaesthetist
B.P.	=	blood pressure
C	=	conservative dentistry
D	=	dentist
Diaz	=	diazepam
E	=	extractions or oral surgery
Eval	=	evaluation
G.A.	=	general anaesthesia
Gas	=	nitrous oxide & oxygen
Hal	=	halothane
L.A.	=	local analgesia
M	=	methohexitone
MIT	=	minimal incremental technique
MT	=	methurital
Premed	=	premedication also used
S	=	scientist
TH	=	thiopentone
V	=	type of work not specified

1-4-2: DISCUSSION OF STUDIES1-4-2a: Type of dental work

Less than half the studies (16) relate to the use of methohexitone for conservative dentistry. Only 28 studied the M.I.T., and then often in combination with other drugs (62%).

This is unfortunate because it is estimated that the M.I.T. is used three times as much for conservation than for extractions (Beesley et al, 1969).

However, these studies do represent at least 26,500 administrations of methohexitone, for specific dental operations, under some form of controlled situation.

TABLE 4-2

HISTOGRAM SHOWING FREQUENCY OF CLINICAL
DENTAL STUDIES PER YEAR

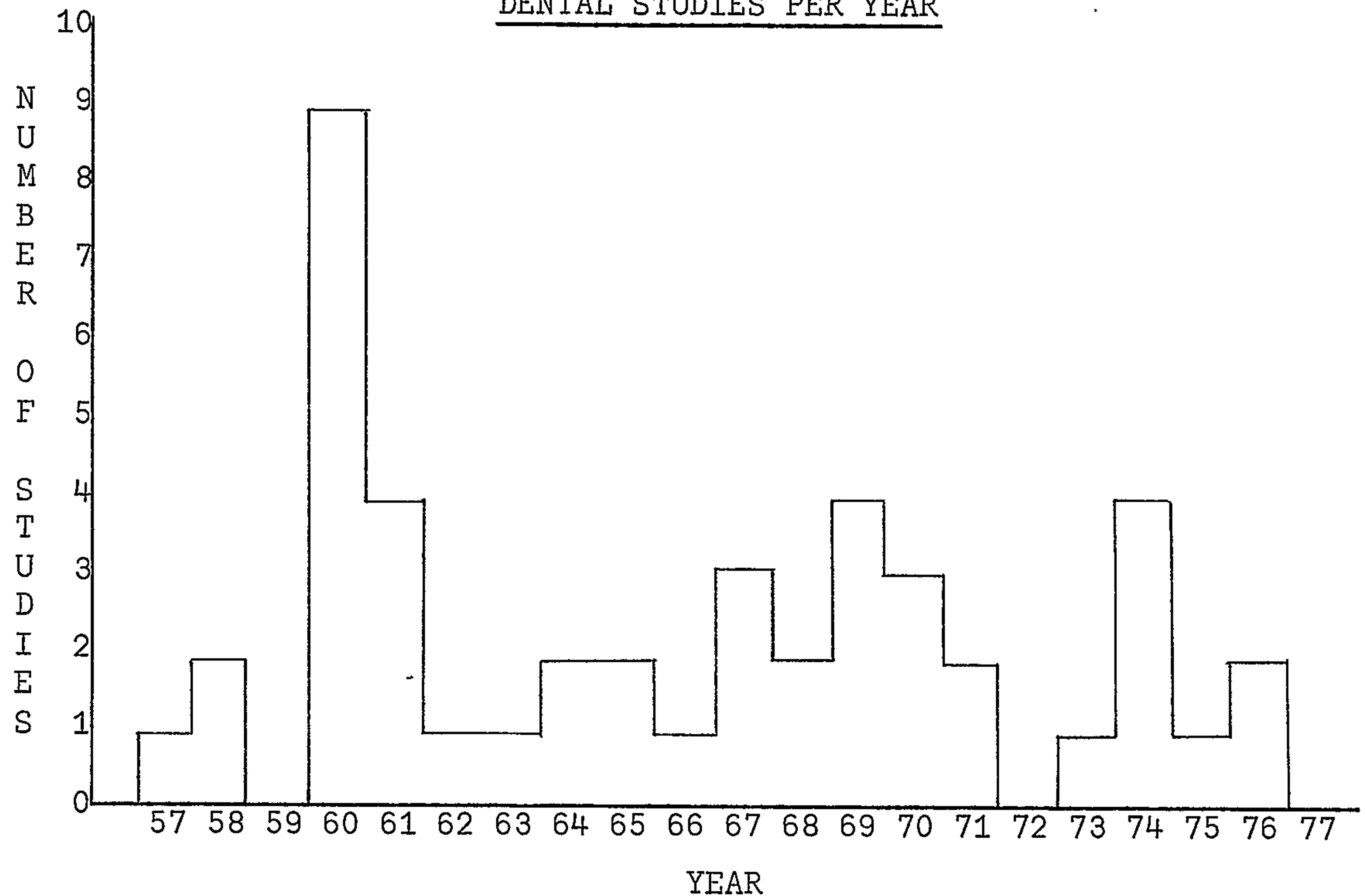


TABLE 4-3 INVOLVEMENT OF EACH COUNTRY IN CLINICAL DENTAL STUDIES	
COUNTRY	NUMBER OF STUDIES
U.K.	23
U.S.A.	14
N.Z.	4
AUSTRALIA	3
CANADA	1
TOTAL	45

1-4-2b: Frequency and type of authorship

From the histogram in Table 4-2, it can be seen that there has been steady publication of clinical dental studies for the last twenty years.

Half the studies have come from the U.K. with nearly one third from the U.S.A., and only three from Australia.

Foreman (1974b) is critical of most of the published clinical research studies, because he says they are often carried out by workers with an extensive background of medical anaesthetics, who examine only the physiology of high 'surgical' doses of methohexitone.

Whilst anaesthetists have outnumbered dentists (see Table 4-4) as authors, dentists have participated in 56% of the studies (see Table 4-5).

TABLE 4-4 INVOLVEMENT OF EACH PROFESSION IN CLINICAL DENTAL STUDIES	
PROFESSION	NUMBER*
Anaesthetists	48
Dentists	31

* Each worker counted only once,
even if appeared in more than
one study.

TABLE 4-5 COOPERATION OF THE PROFESSIONS IN PRODUCING CLINICAL DENTAL STUDIES		
AUTHORSHIP TYPE	STUDIES (NO.)	%
Anaesthetist only	20	44
Dentist only	16	36
Combination	9	20
TOTALS	45	100

1-4-2c: Wise et al (1969)

This study, critical of the use of methohexitone (see Table 3-4 above), generated a large correspondence in the journals and caused a great deal of controversy.

On the one hand it has been described as *a reasonable criticism of the original technique* (Editorial 1970) and on the other hand, a study of *gross overdosage* (Foreman 1969b).

Sykes (1969) commented, *one would like to know how many cases the authors had actually undertaken before embarking on the series in question. Demonstration is no substitute for practical experience and, as we all know, it is in the early series of cases with any technique new to us that the difficulties mainly arise.*

1-4-3: THE S.A.A.D. SURVEY

The Society for the Advancement of Anaesthesia in Dentistry conducted a survey of experienced operators using the M.I.T. The results of 445,386 administrations of methohexitone were published (Drummond-Jackson 1971d).

Although impressive numerically, it does not satisfy basic conditions for a clinical study as set out by Dundee et al (1962):

Preferably a clinical study of this nature should represent the work of one man, or a small unit, so that the conditions are uniform.

The S.A.A.D. based its figures on the results of a postal survey of a large number of administrators. For this reason, I have not included these results in the tables on clinical studies.

1-4-4: UNSUBSTANTIATED CLAIMS

The literature also contains many unsubstantiated claims concerning the use of methohexitone in dentistry. For example,

Bayne (1976) states: *I can summarise 50,000 cases, without a fatality, on patients aged 5 to 85 and state with authority that Valium, Brevital and lidocaine with epinephrine are not deleterious.* Allen (1976) has invited Bayne to do just that.

This illustrates one of the problems and controversies surrounding the use of methohexitone; often those that use it most write the least, while those that use it least write the most.

1-4-5: CONCLUSIONS

1. Because methohexitone may be used more for conservative dentistry than oral surgery in practice, it is a pity that less than half the studies are for conservative treatment (See Table 4-1).
2. The number of dentists who contributed, either solely or in collaboration with anaesthetists is low (See Table 4-5).
3. Australian authorship is low (See Table 4-3)
4. Most studies are limited in the number of administrations studied. Few have studied more than 1,000 administrations and most are on 100 or less (See Table 4-1).
5. Few studies have been undertaken in private practice. The majority have been conducted in the hospital environment which may bear little relationship to the work of the private practitioner.
6. The use of methohexitone for dentistry has only once before been the subject of a Masters Degree thesis (See Section 1-3-1).

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1-5-1: INTRODUCTION

It has been calculated that 30.96mg/Kg methohexitone would be lethal for man (Goldman & Harris 1963).

A plasma concentration of 30mg/litre of methohexitone is said to be sufficient to produce a hypnotic state (Spiro et al 1975).

In the following section I have looked at the dosages of methohexitone used in clinical practice for dental treatment.

In some cases I have also included dosages used in other surgical treatments for comparison.

Following this section I review studies on the physiological effects of methohexitone.

1-5-2: INDUCTION DOSE

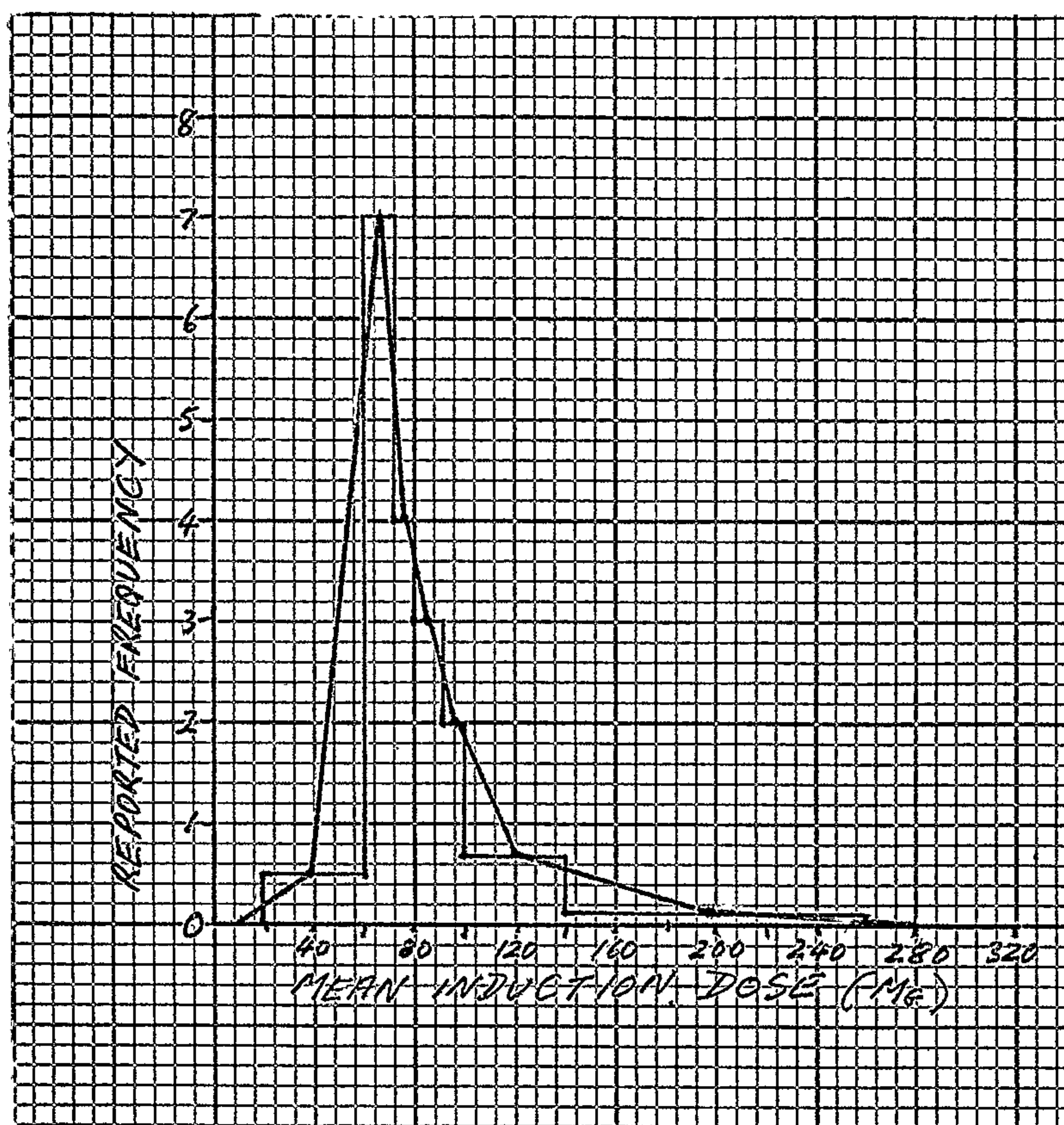
1-5-2a: Induction doses used in studies

A wide variation of the induction dosage of methohexitone has been used. In Table 5-1 below I have ranked several studies in ascending order of mean dosage. Where an author has not given a mean dosage, I have calculated an average dosage from the range given; these appear in parenthesis.

TABLE 5-1
INDUCTION DOSE

NAME OF STUDY	MEAN DOSE (mg)	RANGE (mg)	PRE- MED	COMMENTS
Lyon (1961)	(35)	20-50	+	
Redish et al (1958)	50			
Wyant & Chang (1959)	61.8	35-80	+	
Coleman & Green (1960)	70	20-100		
Recant (1960)	70	30-200		
Stoelting (1957)	70	40-220	+	
Taylor & Stoelting (1960)	70	20-250	+	
Drummond-Jackson (1971d)	(70)	60-80		Females
Young & Whitwam (1964a, 1964b)	70.4			Females
Simpson & Rondeau (1966)	75	70-80		
Foreman (1965)	(80)	60-100		
Hellewell & Hutton (1967)	80	40-100		
Mann et al (1971)	(80)	60-100		
Hubbell (1960)	84	10-150	Some	
Wilkinson et al (1965)	(90)	80-100		Females
Drummond-Jackson (1971d)	(90)	80-100		Males
Egbert et al (1959)	92	70-110		
Myers & Coltman (1961)	100	70-130	+	
Wilkinson et al (1965)	(110)	100-120		Males
Christenson et al (1961)	132		Some	
Young & Whitwam (1964a, 1964b)	136			Males
Wyant et al (1957)	240			

TABLE 5-2
 HISTOGRAM & FREQUENCY POLYGON OF
 REPORTED MEAN INDUCTION DOSE*



* Each study counts once irrespective of numbers

1-5-2b: Conclusion

The mean induction dose used in 22 instances was 84.1mg (+ 34.0mg). The median dose was 74.9mg.

Bourne (1967a) recommends that inexperienced operators should never exceed an induction dose of 100mg.

1-5-3: INDUCTION DOSE CALCULATED ON PATIENT WEIGHT

1-5-3a: Standard Dose Unsatisfactory

When he began using methohexitone, Drummond-Jackson (1960) calculated the required induction dose from the dose of thiopentone previously required by the patient. Many patients received more or less than sufficient methohexitone as a result.

The dose required to induce a particular patient has been found to vary from appointment to appointment (Drummond-Jackson 1963; Polyblank 1974) and a standard dose cannot be determined without taking several factors into consideration, such as weight and temperament (Goldman & Harris 1963).

1-5-3b: Induction dose in terms of weight

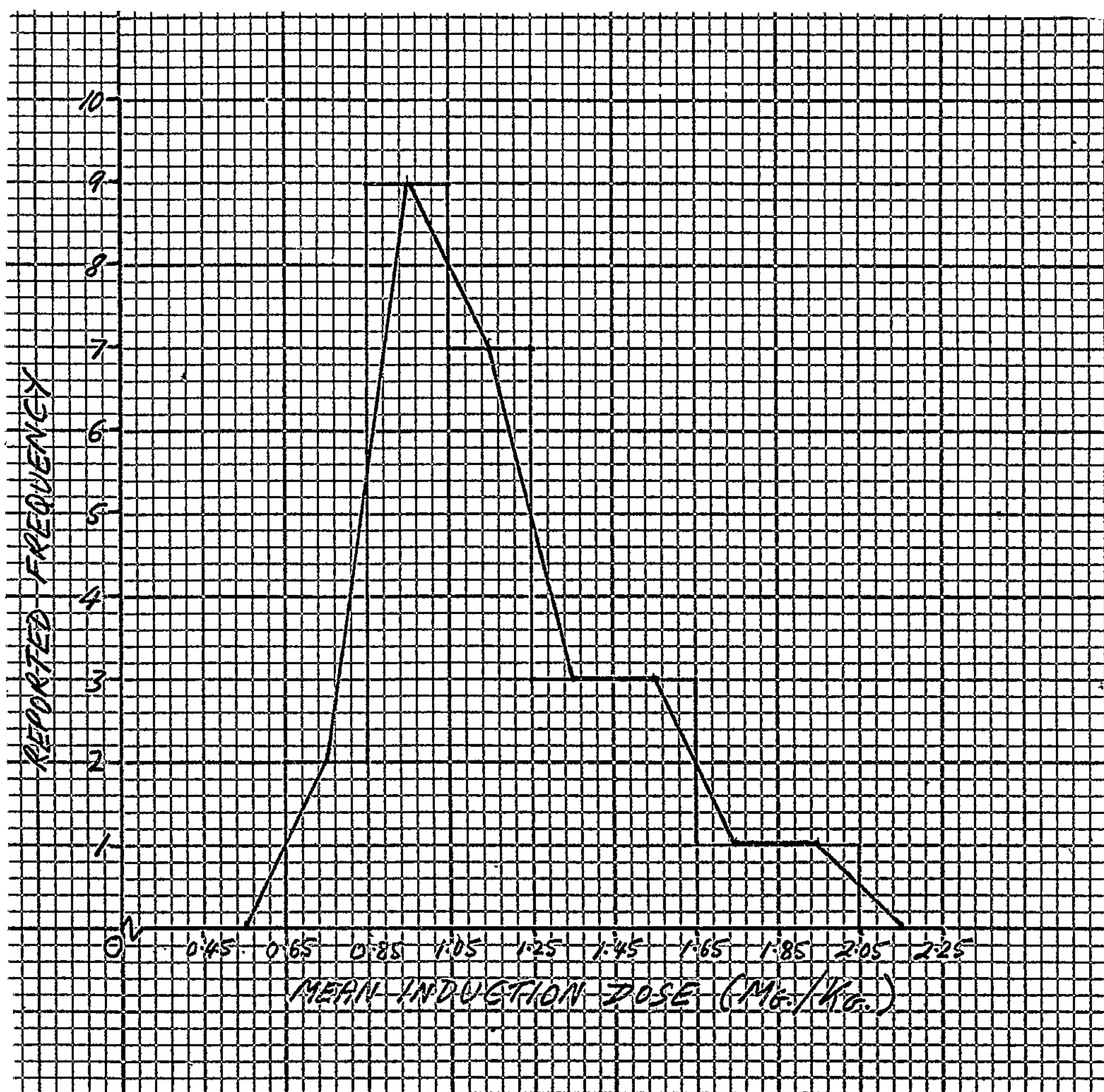
Some authors have correlated induction dose to patient weight. In Table 5-3 below I have ranked these in ascending order. Where the dosage has been given in units other than mg/Kg, I have converted these to mg/Kg. The original units appear in parenthesis.

Where an author has not given a mean dosage, I have calculated an average dosage from the range given; these appear in parenthesis.

TABLE 5-3
DOSE IN TERMS OF WEIGHT

NAME OF STUDY	MEAN DOSE mg/Kg	RANGE mg/Kg	PRE MED	COMMENTS
Green & Jolly (1960)	0.69			(5mg/stone)
Goldman & Harris (1963)	0.69			(5mg/stone)
Green et al (1963)	0.88			
Swerdlow (1962)	0.93	0.8-1.1		Adults
Swerdlow (1964)	0.93			Adults
Swerdlow (1962)	0.94	0.9-1.2		Children
Swerdlow (1964)	0.94			Children
Coleman & Green (1960)	0.97	min=0.69	+	(7mg/stone)
Allen et al (1969)	1.0			
Goldman & Harris (1963)	(1.04)	0.97-1.1		(7-8mg/stone)
Mann et al (1971)	(1.05)	0.8-1.3		
Goldman & Kennedy (1964)	1.1			(8mg/stone)
Shafto (1969)	1.1			10-15 years
Grainger (1970a)	1.1			(8mg/stone)
Young & Whitwam (1964a, 1964b)	1.18			Females
Stoelting (1957)	1.19		+	(70mg/132lb)
Hellewell & Hutton (1967)	1.2	0.3-1.7		Females
Hellewell & Hutton (1967)	1.2	0.8-1.8		Males
Ryder (1970)	1.3			Older Children
Liscombe (1968)	1.38		+	Tonsillectomy Child.(10mg/st)
Clarke (1971b)	1.38			(10mg/st) then less 20mg
Ryder (1970)	1.5			under 6 years
Shafto (1969)	1.57			1-5 years
Dundee & Moore (1961a)	1.6		+	
Young & Whitwam (1964a, 1964b)	1.7			Males
Andrew et al (1973)	2.0	1.5-2.0		Children

TABLE 5-4
 HISTOGRAM & FREQUENCY POLYGON
 REPORTED MEAN INDUCTION DOSE (MG/KG)



1-5-3c: Conclusion

The mean induction dose used in 26 instances was 1.17mg/Kg (± 0.3 mg/Kg). The median dose was 1.09mg/Kg.

1-5-4: ALTERATIONS TO CALCULATED INDUCTION DOSE

1-5-4a: Discussion

Clarke (1971a) calculated the induction dose as 10mg/6Kg then deducted 20mg. A 60Kg man would receive 80mg.

Wilkinson et al (1965), at first calculated induction dose on weight, but discontinued to because of a wide variation in depth and duration. They prefer to use a standard dose with alterations due to apparent nervousness and relevant medical history.

Coleman & Green (1960) and Green & Jolly (1960) did not weigh patients, *in order to conform with the conditions in the average dental surgery . . .*

Myers & Coltman (1961) also used a standard induction dose of 100mg, increasing or decreasing it by 20-30mg depending on anticipated difficulties or simplicity of treatment. Clarke (1971b) increases the induction dose by 10mg if the procedure will produce pain.

Simpson & Rondeau (1966) increased induction dose to an average of 150mg if the patient was to be intubated.

Recant (1960) found that less methohexitone was required for patients of an endomorphic build.

Hubbell & Royer (1963) observed that very obese patients required 30-50% less methohexitone. Bourne (1967a) suggested 25% less, if dose is calculated on weight, for obese patients.

Young & Whitwam (1964a, 1964b) were able to obtain the same effect with 1.33mg/Kg, given to a 50.9Kg man, as with 0.99mg/Kg given to a

108.2Kg man.

For patients with a muscular build, Clarke (1971b) increases his calculated dose by 10mg.

1-5-4b: Lean Body Mass

Wyant et al (1957) found that dosage was not so variable if the surface area and blood volume of the patient were considered.

On injection, methohexitone rapidly enters the tissues of lean body mass and only slowly enters fat tissue (see Section 1-6-1). Thin patients require a relatively larger dose than obese ones, and so Wulfsohn & Joshi (1974) present a formula for calculating lean body mass. If dosage is determined in this way, more correct levels will be obtained.

1-5-4c: Sex of Patient

Males require larger doses (Recant 1960; Wilkinson et al 1965; Drummond-Jackson 1971d; Young & Whitwam 1964a, 1964b; Finch & De Kornefeld 1967), although Hellewell & Hutton (1967) found that, of 122 adults induced with methohexitone, the average dose was 80mg for both men and women.

1-5-4d: Age of Patient

1-5-4d(i): Discussion

Young (1974) used the following formula to calculate induction dose:

5mg (0.5ml of 1% solution) per year of age.

Maximum = 80mg for women, 100mg for men.

However, Bourne (1967a, 1971a) reduces induction dose with age,

and he has devised a weight/age dosage table. For example, a 70Kg, twenty year old would receive 100mg whilst a 70Kg, sixty one year old would receive 55mg.

Clarke (1971b) increases the induction dose, calculated by weight, by 10mg for patients aged 12-25 years.

1-5-4d(ii): Children

Green & Jolly (1960) gave young children a *slightly* higher induction dose than that required in proportion to their weight. Swerdlow (1962, 1964) increased his mean induction dose from 0.93mg/Kg for adults, to 0.94mg/Kg for children under 15 years.

Shafto (1969) gave 1.57mg/Kg for children aged 1-5 years, compared to 1.1mg/Kg for children aged 10-15 years. Ryder (1970) gave 1.5mg/Kg to children under six years, and 1.3mg/Kg for older children.

Liscombe (1968) induced children, aged 3-10 years, with 1.57mg/Kg methohexitone. Andrew et al (1973) gave 2mg/Kg as the average induction dose to children aged 18 months to 14 years.

Hubbell (1960) gave children 75% nitrous oxide prior to methohexitone induction and found that 10-30mg was then sufficient. (Nitrous oxide is discussed in Section 1-11-3.)

Although larger doses were necessary for teenagers, Recant (1960) used 30mg methohexitone for young children and older patients.

1-5-4d(iii): Older patients (60-70 years)

Hubbell (1960) used 50% nitrous oxide, prior to methohexitone induction, in older patients. He found that 10-50mg were sufficient for induction. Similarly, Hubbell & Royer (1963) used only 20-30mg methohexitone.

Berns (1963) gave older patients an induction dose equal to one quarter to one third that of young adults.

Coleman & Green (1960) used 100mg as a standard induction dose in the first 1,000 adults of their study. They comment that although overdosage was considerable at the extremes of age, the safety margin of the drug was demonstrated. Subsequently, they reduced dosage for extremes of age.

1-5-4e: Health of Patient

Patients in poor health require a smaller induction dose. Bourne (1967a) gives the example of the middle aged diabetic where there may be associated cardiovascular degenerative changes. (Diabetes is discussed in Section 1-9-5.) Bourne (1971a) reduces induction dose if patients are taking C.N.S. depressant drugs or B.P. reducing drugs. (These drugs are discussed in Section 1-9-7.)

Weinstock (1960) observed that additional methohexitone may be required where there is a higher blood pressure, because of increased metabolic rate, and where there is an increased pulse rate due to increased *irritability* (see Section 1-9-6).

Drummond-Jackson (1971b) discusses dosage with respect to metabolic level and sensitivity to pain. A patient with a high metabolic rate, coupled with a low pain threshold, required more methohexitone.

Clarke (1971b) increases induction dose by 10mg if his patients have an elevated temperature, consume more alcohol than average, or if the patient is pregnant. (Pregnancy is discussed in Section 1-9-9.)

Recant (1960) has given a total dose of 640mg to induce a resistant alcoholic. (The alcoholic is discussed in Section 1-9-7h(i).)

1-5-4f: Psychological factors

Hubbell (1960) stated: *The required dose varied more with patient nervousness than with patient size.* He found that very apprehensive patients required 25-50% more methohexitone, as did Bloomfield (1966).

Clarke (1971b) suggested increasing induction dose by 10mg for nervous patients.

Claridge (1971) reviewed the literature and concluded that anxious patients and obsessional patients require extra dosage, because they show a strong sympathetic reaction to stress.

He experimented with amylobarbitone. He recorded the amount of drug required to reach threshold sedation in 192 patients. Of these patients, 34 were normal and the rest were known neurotics.

Those patients resistant to amylobarbitone behave as though they were in a state of high C.N.S. arousal, whilst the opposite was found in patients susceptible to the drug. Weight bore little relationship to drug sensitivity.

He thought it reasonable to expect similar results with other barbiturates.

Young & Whitwam (1964a, 1964b) found that the small, nervous female often requires a higher dosage than obese, placid males.

1-5-4g: Effect of premedication

Coleman & Green (1960) noted little change in dosage requirements if patients were premedicated. Kurland (1971) reduced the dose of methohexitone by one quarter to one third when he used 30mg pentazocine

for premedication in adults.

Foreman (1974a) found that after 5-10mg diazepam, 20-50mg of methohexitone was usually sufficient for induction. (The use of premedication is discussed in Section 1-11.)

1-5-4h: Resistant Patients

Young & Whitwam (1964a, 1964b) induced 2,000 patients with methohexitone prior to receiving nitrous oxide and oxygen maintenance for extractions. Two male patients were so violent during induction that the procedure had to be abandoned.

Hubbell & Royer (1963) estimate that 0.12% of patients are completely resistive to methohexitone. Some patients have received up to 400mg and still will not allow any work to be performed on them.

Grainger (1970a) reported one patient out of 20 who was vocal or restless under methohexitone (incidence = 5%).

Forman (1969) estimates that for all children and adolescents, and 40% of the 20-35 age group, methohexitone alone is inadequate.

1-5-4i: Conclusions

Conclusions are presented in Section 1-5-13. Also compare with my results, Section 2-11-2.

1-5-5: TECHNIQUES USED TO DETERMINE INDUCTION DOSE

1-5-5a: Early Techniques

Bourne (1975c) says that the early workers arrived at their correct induction dosages by injecting methohexitone till consciousness was lost. The amount already given was noted. If the operation was expected to last five minutes, a further dose, twice the size of the

original was then given. If the operation was expected to last fifteen minutes, three times the original was given. In this way the whole operation was covered by a single injection at the start.

1-5-5b: Slow induction

Table 5-5 below shows the rates at which different workers injected methohexitone until the desired level was reached.

I have calculated the dosages in mg/one second, and listed them in ascending order.

TABLE 5-5 SLOW INDUCTION RATES		
NAME OF STUDY	mg/one sec	ACTUAL RATE USED
Redish et al (1958)	0.67	10mg every 15 seconds
Campbell et al (1976)	0.67	20mg every 30 seconds
Rollason (1971)	0.8	10mg every 10-15 secs.
Clarke (1971b)	1.54	10mg every 5-8 secs.
Egbert et al (1959)	2.0	10mg every 5 seconds
Weinstock (1960)	2.0	10mg every 5 seconds
Wilkinson (1965)	2.9	20mg every 7 seconds
Howells et al (1967)	10.0	10mg every second

Redish et al (1958) stopped injecting when they thought the patient was deep enough for surgery to begin.

Clarke (1971b) recommends this technique for frail and elderly patients.

A slow induction produces euphoria and amnesia (Weinstock 1960) and may reduce dosage, especially if hypnotic suggestion is used (Rollason 1971).

1-5-5c: Auditory unresponsiveness

Egbert et al (1959) determined the correct sleep dose as that amount required till the patient stopped talking. Campbell et al (1976) judged the induction dose to be the amount of methohexitone required to lose voice contact with the patient.

Howells et al (1967) gave methohexitone until the patient failed to continue a voluntary count-up, and failed to respond to the command, *open your eyes*, repeated every ten seconds. They defined narcosis as auditory unresponsiveness.

Foreman (1967) commences work before the patient reaches this level, and says he is able to keep dosage to the absolute minimum required for that particular appointment.

1-5-5d: Loss of eyelash and other reflexes

To gauge the correct induction dose, prior to recovery tests, Wilkinson (1965) had his subjects place their knees together. The required plane was assumed to be reached when the knees fell apart, and was further confirmed by loss of eyelid reflex and eye signs.

When initially trying methohexitone, Drummond-Jackson (1960) relied on the loss of lash reflex to mean that the anaesthetic state was reached and treatment could commence. He soon discovered that, . . . *an operable state for the momentary task could be produced without loss of the lash reflexes in some cases.*

Drummond-Jackson (1971d) says that if the surgeon is also

responsible for the anaesthetic then, . . . *he awaits recovery of the patient . . . at which the lash reflex is strongly present . . .*

Foreman (1965) was able to treat 97 patients out of 100 with eyelash reflex present. Throughout the procedures some patients would nod or react to questions. (See also Section 1-7-1h.)

1-5-5e: Loss of consciousness

Bourne (1967a) found that as little as 0.5mg/Kg methohexitone can be entirely amnesic, even though the patient may appear to react and be aware of what is happening.

Thurecht (1973) and Bennett (1974j) describe techniques using methohexitone in *conscious-sedation*. (Amnesia is discussed in Section 1-7-1g.)

1-5-6: TIME FOR INDUCTION DOSE TO BE EFFECTIVE

1-5-6a: Induction time

Wyant & Barr (1960) define induction time as, *The time from completion of the injection of the drug until surgical anaesthesia was reached.*

Weinstock (1960) states: *If the induction dose has been estimated correctly, the patient passes in rapid succession into euphoria, amnesia, and finally a light plane anesthesia, which is reached in ten to twelve seconds.*

In Table 5-6 below, a list of authors is presented. They have recorded the time for loss of consciousness to occur after the induction dose has been administered:

TABLE 5-6 TIME FOR INDUCTION DOSE TO BE EFFECTIVE		
NAME	SECONDS	COMMENTS
Wyant & Chang (1959)	10-15	61.8mg methohexitone
Green & Jolly (1960)	17-20	0.69mg/Kg
Wyant & Barr (1960)	38.6	
Scott & Virden (1972)	40.0	

1-5-6b: Duration of unconsciousness

Drummond-Jackson (1960) found that the induction dose allowed one minute of operating time.

Coleman & Green (1960) used 0.97mg/Kg (7mg/stone) and obtained 2-3 minutes sleep. Premedication did not affect this time greatly.

Myers & Coltman (1961) used 100mg as the average induction dose and obtained 3 minutes relaxed working time.

Scott & Virden (1972) observed E.E.G. changes from 1.8mg/Kg and duration of anaesthesia was observed to last over three minutes (200 seconds).

Male & Allen (1977) report on the E.E.G. effect of administering 80mg methohexitone, over 5-10 minutes, to 48 patients. They comment, *clinically, the patients did not show signs of deep anaesthesia, and were able to maintain their airway and regain consciousness within five minutes.*

1-5-6c: Working time from a single induction dose

For a simple extraction, or any treatment lasting less than five minutes, Simpson & Rondeau (1966) found that a single induction dose of 70-80mg sufficient (average adult dose).

By applying pain tests, Finch & De Kornfeld (1967) measured an average 60 seconds anaesthesia from a 75mg dose, in 19 out of 26 males, whilst women gave an average of 2 minutes and 45 seconds unconsciousness. Thornton (1970) says that because of its antanalgesic properties, these results may not be relevant in practice. (Antanalgesic properties are discussed in Section 1-7-1j.)

Green et al (1963) used 0.88mg/Kg and stated: *It must, however, be stressed that barbiturates, when used in these small doses, merely induce 'sleep' and that no operative procedure can be started until analgesia is produced with nitrous oxide, or some other agent.*

1-5-7: MAINTENANCE OF ANAESTHESIA WITH METHOHEXITONE

1-5-7a: When induction dose has been insufficient

Scott & Virden (1972) found, from E.E.G. changes, that a second dose of methohexitone produces a deeper level of anaesthesia than the induction dose. (See also Section 1-7-1e.)

Where induction dose was insufficient to produce the desired level, Myers & Coltman (1961) gave a second dose of 70-100mg, up to a total dose of 200mg.

Table 5-7 below lists suggestions for the size of the second dose in relation to the initial dose.

TABLE 5-7 SIZE OF SECOND DOSE		
NAME OF AUTHOR	SUGGESTED SECOND DOSE AS A FRACTION OF INDUCTION DOSE	AUTHOR'S COMMENTS
Ryder (1970)	1/4	
Drummond-Jackson (1971d)	1/4	Check to see that failure of induction not due to tourniquet left in place
Mann et al (1971)	1/4	If responds to cavity preparation after three mins.
Bourne (1967a)	1/3	
Hubbell (1960)	1/2	
Foreman (1970a)	1/2	
Mann et al (1971)	1/2	If responds to cavity preparation within three mins.

1-5-7b: Minimal Incremental Technique (M.I.T.)

Christenson et al (1961) used the M.I.T. in 127 dental operations. The indications they used for the necessity of a further dose of methohexitone were: gross movement of the extremities, increased tone of the tongue and buccal muscles, in response to surgical stimuli.

Such responses may be only slight at first. For example, the operator may notice a slight increase in muscle resistance to a retractor (Hubbell & Royer 1963).

These signs may be in response to the pain of cavity preparation (Mann et al 1971), or the amount of pain and infection in the area of operation, on the treatment time (Lyon 1961; Simpson & Rondeau 1966) and modified by the clinical state of the patient (Bloomfield 1966).

Trieger (1976) says that it is possible to accurately titrate dosage to provide a desired effect at a point in time in a particular patient.

In Table 5-8 below I have ranked those studies, in ascending order, which give the increment rate they used. Increments have been calculated to mg/second for comparison. One study for general surgery has been included for comparison.

TABLE 5-8 INCREMENT RATES USED			
NAME OF STUDY	RATE mg/sec	ACTUAL RATE USED	COMMENT
Bloomfield (1966)	0.08	10-30mg/3-5 minutes	
Wangeman (1962)	0.1	20-40mg/4-6 minutes	General Surgery
Wilkinson et al (1965)	0.1	30-40mg/3-10 minutes	
Wise et al (1969)	0.1	5.7mg/minute	
Young (1970)	0.19	0.16mg/Kg/min. (For 70Kg man)	
Young (1970)	0.3	0.26mg/Kg/min. (For 70Kg man) Required deeper level for some patients only	

TABLE 5-8 (cont) INCREMENT RATES USED			
NAME OF STUDY	RATE mg/sec	ACTUAL RATE USED	COMMENT
Redish et al (1958)	0.4	50mg/hour	N ₂ O too
Shafto (1969)	1.0	10mg/10 seconds	Preschoolers
Shafto (1969)	2.0	10mg/5 seconds	Older Children
Hubbell & Royer (1963)	15.0		Oral Surgery

1-5-7c: Low Dosage: A safety factor with M.I.T.

McCarthy (1975) said that there should be no need to go beyond 10mg increments.

Hubbell (1960) found that the time interval between doses varied widely and half of his patients tolerated surgical procedures after the induction dose was, *apparently spent*.

But the aim of the M.I.T. is to achieve a steady level of hypnosis. This relies very heavily on the skill of the administrator (Howells 1968).

The most important factor in the safe conduct of this technique is that the effect of a dose of methohexitone will be seen within one circulation of the drug, usually within thirty seconds (Drummond-Jackson 1971d).

1-5-7d: Operator: Best to judge depth?

While he is not in favour of the dual role of operator-anaesthetist, Howells (1968) states: *It must be admitted, however, that a really skilled operator-administrator can give a most impressive demonstration.*

Drummond-Jackson (1971b) says that: *In practice, ultra-light anaesthesia is best obtained by the surgeon asking for the smallest practicable increments . . .*

The need for further increments of methohexitone is first observed by the operator who will notice an increase in the tone of the tongue and lip musculature long before these signs can be recognised by a separate anaesthetist.

Hubbell & Royer (1972) state that treatment and anaesthesia must be in harmony and the operator is best able to judge this.

Day (1973) comments, . . . *who but the operator can judge what the minimal requirements are for a smoothly run session?*

Bell (1975d) says that dentists are better equipped to treat patients under an intermittent situation than, say, a general surgeon would be. A dentist, he explains, is used to working on conscious patients and is continually aware that what he might do may produce pain and thereby a response.

In a booklet on anaesthesia, published by the British Office of Health Economics (Office of Health Economics 1976), it is admitted that the operator-anaesthetist is probably in the best position to anticipate the anaesthesia requirements as the level of stimulation changes. But it also stated that the monitoring of the cardio-

respiratory system should be the full time job of a separate person.

1-5-7e: Summary of advantages of the M.I.T.

Bourne (1975c) states that the M.I.T. has two factors in its favour:

1. Extreme lightness of narcosis needed to cover operations on the teeth. For, unlike cutaneous pain, dental pain appears to invoke little reflex flinching. Thus the level required to carry out dental treatment falls far short of true surgical anaesthesia.

He comments, . . . *anaesthesia is, in fact, misleading, when it amounts to scarcely any more than deep sleep.*

2. Brevity of action of methohexitone. With the M.I.T. the patient is never longer than about two minutes from being virtually no more than asleep. He makes the comment that because death from asphyxia takes twice this time, *the patient would wake up before he had time to die.*

(Recovery is discussed in Section 1-12.)

1-5-8: PROBLEMS WITH THE M.I.T.

1-5-8a: Difficulty in control of depth of anaesthesia

In the report of the joint subcommittee investigating dental anaesthesia, appointed by the British Ministry of Health (Swiss 1967), it is stated: *We consider it is generally difficult to control the dosage in such a manner as to keep anaesthesia at this light level consistently or to ensure a clear airway at all times without great vigilance, necessitating the presence of a trained anaesthetist in addition to the operator.*

The report added that where the same drug is used, it is impractical to draw a distinction between anaesthesia and analgesia.

Berns (1963) described an incremental methohexitone technique for dental treatment and noted that patients could slip into light anaesthesia for 20-60 seconds. He advised that anaesthetic experience was necessary when using this drug.

Furthermore, he prefers not to use methohexitone alone because it is too short acting, too variable and gives unpredictable sedation.

Coplans (1967b) said that the inadequate inhalation anaesthetics of the past should not be replaced with *sub-anaesthetic* intravenous methods if these techniques were likely to lead to hurried or incomplete work.

Further criticisms are to be found in Section 1-3-2c(v).

1-5-8b: Restlessness

Mann et al (1971) found that some patients would halt the procedure by expelling the prop and the pack from the mouth. In others, tongue movements were excessive and interfered with operating conditions. Young patients had a higher incidence of violent involuntary movements, usually ending in abandonment of the procedure.

Rollaston (1967) avoids further increments of methohexitone in restless patients. Brown et al (1968) state: *Only too often light unconsciousness is accompanied by restlessness and reaction to stimulus.*

Shafto (1969) found that giving further methohexitone only increased the incidence of restlessness in the children he treated. (See also Sections 1-9-2f, 1-11-3b(iv), 1-11-6h(vii) and 2-11-2.)

1-5-9: TIME LIMITS

1-5-9a: Minimal incremental technique as taught

Hellewell & Hutton (1967) stated that: *The time factor is considered to be of importance and if an operating time of ten minutes is exceeded the chances of complications arising both during and after surgery are likely to be increased.*

After ten minutes of supplemental methohexitone, Allen et al (1969) observed cardiovascular changes due to cumulative effects. (See Section 1-7.)

This time factor is critical in the M.I.T. as taught by Drummond-Jackson (1971d). In the first ten minutes, dosage is limited to the induction dose plus one quarter. The patient is allowed to recover consciousness before further methohexitone is given. No methohexitone is given after twenty minutes from the initial induction.

By allowing the patient to emerge in this way it is possible to avoid hypoxia, and his own compensatory mechanisms (e.g. yawning) will overcome some essential basic hypoxia if present (SAAD Report 1972b).

Wise et al (1969), who criticised the M.I.T., reported a mean treatment time of 74 minutes. This treatment time greatly exceeds the recommended limits (Chambiras 1970a), and has been blamed for the complications they observed (Sykes 1969).

Apparently the technique they used bore no relationship to that taught by S.A.A.D. (Drummond-Jackson 1969a).

But Bourne (1969b) says the technique is abused in just this way in practice.

1-5-9b: Further limitations on time

Bourne (1969c) said that the longest he has ever administered methohexitone, by the incremental technique, for extractions in the dental surgery, is twelve minutes.

Bourne (1969b, 1974b) feels that the technique should be reserved for dentistry that is neither difficult nor prolonged. For extractions, he suggests a limit of ten minutes, and for conservation, a limit of twenty minutes.

However, the British Ministry of Health Report on Anaesthesia in Dentistry (Swiss 1967) concluded that short anaesthetics are not necessarily safer than longer ones.

1-5-9c: Longer treatments

If the procedure is to be longer than twenty minutes, or complicated, Foreman (1970a) prefers the patient to be intubated. (See Sections 1-7-2 and 1-10-7.)

Simpson & Rondeau (1966) treat patients in hospital if the procedure is to take longer than one hour.

1-5-10: DOSE LIMITS

1-5-10a: Maximum doses used in studies

In Table 5-9 below, I have attempted to correlate average total dose with length and type of treatment from studies of the M.I.T. In some cases I have calculated the average maximum dosage, from the information given, and these appear in parenthesis.

I have included some non-dental studies for comparison and the following abbreviations have been used for the type of treatment:

DC = conservative dentistry
 DG = general dentistry
 DO = oral surgery
 DS = simulated oral surgery
 GG = minor gynaecology
 GS = general surgery
 GT = tonsilectomy

TABLE 5-9 DOSES USED IN STUDIES OF M.I.T							
	MAX. DOSE USED (mg)	AVERAGE MAX DOSE (mg)	LOWEST DOSE (mg)	SIZE OF INCRE- MENTS (mg)	TREAT- MENT TIME (mins)	TYPE WORK	PRE- MED (?)
Shafto (1969)	?	?	?	5-20	4	DO	
Foreman (1965)	?	?	?	10-40	?	DG	
Wilkinson et al (1965)	?	?	?	30-40	90(max)	DG	
Foreman (1974a)	180	(99.5)	19	20	81	DC	+
Litchfield (1974)	200	91.2	40	10-20	45-135	DG	+
Hodge (1972)	200	(180)	160	10-20	20-30	DG	
Christenson et al (1961)	?	262	?	?	19	DO	+
Elliott et al (1974)	260	105.2	90	20	5-270	DO	+
Young (1974)	280	154	80	?	?	DO	
Goldman & Kennedy (1964)	290	?	?	20	?	DO	
Allen et al (1969)	?	310	?	20-30	?	DS	
Liscombe (1968)	390	(250)	110	10-20	12-29	GT	
Foreman (1970b)	480	160	80	?	4-45	DG	

TABLE 5-9 (cont)							
DOSES USED IN STUDIES OF M.I.T							
NAME OF STUDY	MAX. DOSE USED (mg)	AVERAGE MAX DOSE (mg)	LOWEST DOSE (mg)	SIZE OF INCRE- MENTS (mg)	TREAT- MENT TIME (mins)	TYPE WORK	PRE- MED (?)
Lyon (1961)	500	127.05	20	20-40	15.08	DO	+
Wyant. & Chang (1959)	510	324.8	140	drip	15.57	GG	+
Wise et al (1969) Robinson et al (1969)	825	460	200	5-10	74	DC	+
Levin (1975)	975	?	100	?	?	DG	+
Stoelting (1957)	1800	410	50	some:drip	?	GG	+

1-5-10b: Cumulative effects of large doses

Hubbell (1960) observed cumulative effects after three maintenance doses each equal to half the induction dose.

Swerdlow & Moore (1969) conducted a dose duration study. Increased dosage led to a linear increase in sleep and recovery time.

Wise et al (1969) found that if more than 200mg is given, a noticeable reduction in peripheral tone occurs due to cumulative effects. They criticised the use of methohexitone as a result.

In their study, they used up to 825mg and, according to Chambiras (1970a), they showed the dangers of greatly exceeding the recommended limits.

Foreman (1970a) reviewed the literature and recommended that the total dose not exceed 200mg, to avoid cumulative effects.

Thurecht (1973) suggested a maximum of 250mg, whilst Bourne (1974b) limits the total to 200mg.

Children may be particularly susceptible to cumulative effects as they require larger relative doses than adults.

Chambiras (1969) states: *It is also difficult to detect the early manifestations of toxicity*, in children.

1-5-10c: Doses used in practice

Bourne (1969c) has averaged only 150mg for extractions.

Sykes (1969) claimed that in 7,000 administrations for dental treatment, the total dose has rarely approached 410mg (the mean dose in the study of Wise et al (1969)).

Beesley et al (1969) average 120mg for cavity preparations lasting ten minutes.

Foreman (1974b) feels that this is the dose level most practitioners use.

1-5-11: INJECTION RATE

1-5-11a: Dose: A function of injection rate

Dosage is also a function of the rate at which the solution is injected (Foreman 1969d; Foreman 1970a).

Drummond-Jackson (1963) obtained a deeper induction with a faster injection rate.

Young (1974) obtained a more predictable induction with 8.9mg/second than he did with 2.2mg/second.

In Table 5-10 below, I have listed those studies that have reported on the rate of injection used. I have calculated the rates in mg/second and ranked the studies in ascending order.

TABLE 5-10 INJECTION RATES		
NAME OF STUDY	SPEED OF INDUCTION DOSE	
	mg/sec	Actual rate used
Barron (1968)	1.0	6ml/min (1%)
Lind & Roland (1969)	1.0	20mg/20secs
Wulfsohn & Joshi (1974)	1.0	15mg/15secs
Egbert et al (1959)	2.0	10mg/5 secs
Weinstock (1960)	2.0	10mg/5 secs
Lyon (1961)	2.0	10mg/5 secs
Barron (1968)	2.0	12ml/60secs (1%)
Young (1974)	2.2	0.22ml/sec (1%)
Wilkinson (1965)	2.9	20mg/7 secs
Allen et al (1969)	3.0	3mg/sec
Barron (1968)	4.0	24ml/60secs (1%)
Lind & Roland (1969)	4.0	20mg/5 secs
Mann et al (1971)	5.3	60-100mg/15secs
Recant (1960)	6.7	10mg/1.5secs
Young (1974)	8.9	0.89ml/1sec (1%)
Myers & Coltman (1961)	9.1	100mg/11secs
Christenson et al (1961)	9.4	70-100mg/8-10secs
Barron (1968)	10.0	60ml/60secs (1%)
The mean speed used of the 18 instances was 4.25mg/sec and the median speed, 2.9mg/sec.		

1-5-11b: Complications of fast injection rates

Barron (1968) used a fixed dose, but varied the speed, and found a direct relationship between injection rate and incidence of cough and hiccough. At 10mg/sec. the incidence was thrice that at 1mg/sec. (Cough and hiccough is discussed in Section 1-7-2e.)

Lind & Roland (1969) recorded a significant rise in incidence of hiccoughing when comparing 4mg/sec. to 1mg/sec. However, there were no significant differences in recovery time (see Section 1-12), or incidences of vomiting, movements, laryngeal spasm or coughing. (See respectively, Sections 1-7-14; 1-7-1j; 1-7-2d; 1-7-2e.)

Whitwam & Young (1964) found no direct correlation between speed of injection and initial falls in blood pressure (see Section 1-7-10b).

Finch & De Kornfeld (1967) injected 75mg methohexitone very quickly through a 20 gauge needle and observed apnoea or airway obstruction. (Apnoea is discussed in Section 1-7-3b.)

1-5-12: STRENGTH OF SOLUTION

1-5-12a: Strengths used in studies

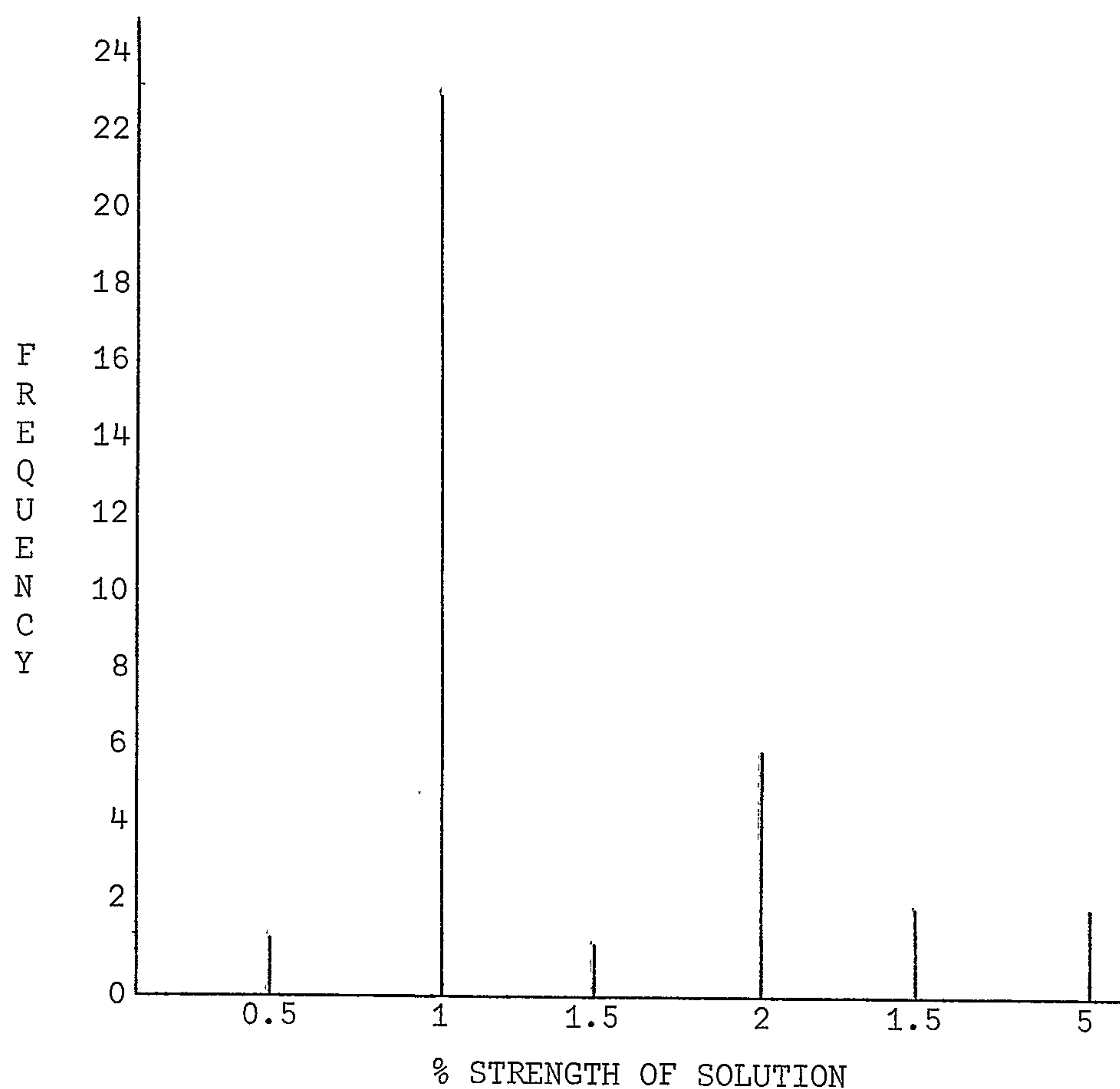
The dosage of methohexitone received by the patient must also be related to the percentage of the solution used. In Table 5-11 below I have listed the solution strengths that have been used in 35 instances.

TABLE 5-11
PERCENTAGES USED IN STUDIES

NAME OF STUDY	%AGE OF SOLUTION
Recant (1960)	0.5
Redish et al (1957)	1.0
Stoelting (1957)	1.0
Weyl et al (1958)	1.0
Egbert et al (1959)	1.0
Wyant & Chang (1959)	1.0
Douglas (1960)	1.0
Hubbell (1960)	1.0
Recant (1960)	1.0
Wyant & Barr (1960)	1.0
Christenson et al (1961)	1.0
Dundee et al (1961)	1.0
Lyon (1961)	1.0
Swerdlow (1962)	1.0
Goldman & Kennedy (1964)	1.0
Simpson & Rondeau (1966)	1.0
Hellewell & Hutton (1967)	1.0
Shafto (1969)	1.0
Ryder (1970)	1.0
Mann et al (1971)	1.0
Bourne (1974b)	1.0
Elliott et al (1974)	1.0
Litchfield (1974)	1.0
Campbell et al (1976)	1.0
Young & Whitwam (1964a)	1.6

TABLE 5-11 (cont)	
PERCENTAGES USED IN STUDIES	
NAME OF STUDY	%AGE OF SOLUTION
Recant (1960)	2.0
Dundee et al (1961)	2.0
Goldman & Kennedy (1964)	2.0
Foreman (1965)	2.0
Grainger (1970a)	2.0
Hodge (1971)	2.0
Wyant et al (1957)	2.5
Levin (1975)	2.5
Drummond-Jackson (1964)	5.0
Goldman & Kennedy (1964)	5.0

TABLE 5-12
VERTICAL BAR CHART OF % USED



It can be seen that the 1% solution is most favoured, being used in 23 instances (66%) and the 2% solution only 6 times (17%).

1-5-12b: 5% solution

Drummond-Jackson (1963) said that a 5% solution would allow 100mg of methohexitone to be given in a 2ml syringe. But the use of such a solution had not been approved at that time.

Goldman & Kennedy (1964) recorded a higher incidence of apnoea, nausea, poor operating conditions and a longer recovery with a 5% solution, compared to a 2% and a 1% solution.

Criticism of their study came from:

- (a) Drummond-Jackson (1964), who used a 5% solution in 4,848 administrations for general dentistry. He did not observe any of these side effects.
- (b) Alterman (1964), who said that they did not correlate different injection speeds used.

Hudson (1965) says that a 5% solution gives greater control over the injection speed. But the patient is more aware of the solution moving up his arm. (Pain in the vein is discussed in 1-7-13d.)

Finch & De Kornfeld (1967) evaluated the usefulness of a proposed pre-packaged unit of 1ml of 5% methohexitone (50mg); the incidence of painful injection was 20.8% for males and 23% for females.

Francis (1964) warned against the use of 5% solutions because it is an added risk if an accidental intra-arterial injection occurred. He experimented with 2% and 5% solutions, injected intra-arterially into rabbits' ears. The 5% solution caused necrosis of the ear, the 2% solution did not. (See also Section 1-7-13b.)

1-5-12c: 2.5% Solution

Wyant et al (1957) experimented with a 2.5% solution, but felt that this concentration was responsible for the incidence of restlessness they recorded.

1-5-12d: 2% Solution

Drummond-Jackson (1963) thought that a 2% solution would be more preferable to a 1% solution because large volumes could be avoided when dosage was in excess of 100mg.

Polyblank (1974) says that the 2% solution is the most commonly used in dental practice.

If injected extravascularly, a 2% solution does not cause more irritation than lower concentrations (Recant 1960; Dundee & Moore 1961a). (Extravascular effects are discussed in Section 1-7-13c.)

At a symposium on ambulant dental anaesthesia (Bourne et al 1964), Dr Goldman said he preferred a 2% solution to a 1% solution, the advantage being, *much smoother anaesthesia and much more satisfactory working conditions*, despite an increased incidence of twitching.

In a study, comparing 1%, 2% and 5% solutions, Goldman & Kennedy (1964) found that recovery from 2% solution compared favourably with that from a 1% solution.

1-5-12e: 1.6% and 1.5% Solutions

Young & Whitwam (1964a) used a 1.6% solution *for convenience in terms of bulk* . . .

Wilkinson & Wilkinson (1960) reporting their first experiences with methohexitone, found a 1.5% solution more preferable to the recommended 1%.

1-5-12f: 1% Solution

Best clinical results were with a 1% solution in a comparative study by Recant (1960). Drummond-Jackson (1963) said that the 1% solution was the most commonly used strength.

Rollason (1971) prefers a 1% solution because it aids his slow induction technique.

Because of the larger volume, a 1% solution gives more flexibility. This could be a factor in the prevention of deaths. (Death 1974a).

Hellewell & Hutton (1967) find that apnoea is reduced with a 1% solution. Although Shafto (1969) usually observed apnoea after children were induced with a 1% solution. He also recorded a 1% incidence of painful veins on injection with a 1% solution.

Swerdlow (1962) had no venous irritation with a 1% solution. Hubbell (1960) recorded 0.1% incidence of painful injections, Simpson & Rondeau (1966) had less than 1% incidence of painful injections and no thrombophlebitis or thrombosis was observed. (See Section 1-7-13d.)

1-5-12g: Discussion

Dundee et al (1961) found no statistically significant difference in incidence of complications between 1% or 2% solutions in 1,750 patients.

Hellewell & Hutton (1967) prefer to use a 1% solution when teaching the use of methohexitone to undergraduates. They find this helps to obviate any danger of accidental extravascular injections, which are more likely to occur in inexperienced hands.

Drummond-Jackson (1971d) reported that at Dundee University, a 1% solution has been dropped in favour of a 2% solution because students were injecting too slowly, and correct induction was not taking place.

1-5-12h: Nature of solvent

Water is most commonly used, however in Table 5-13 below, three alternatives are shown.

TABLE 5-13 SOLVENTS USED		
AUTHOR	SOLVENT	PURPOSE
Recant (1960)	N Saline	To avoid venous irritation
Douglas (1960) Elliott et al (1974)	5% Dextrose	To avoid hypoglycaemia
Thompson et al (1973)	Glucose	
See also Section 1-7-15 f & g		

1-5-13: CONCLUSIONS

1. A mean induction dose, calculated from the figures in Table 5-2, was 84.1mg, or from the figures in Table 5-4, was 1.17mg/Kg.
2. A dose of 100mg should be more than sufficient for a short, simple procedure lasting less than three minutes in an adult.
3. However, several factors can influence dosage. Experience is probably the most important factor in learning to judge the correct induction dose. In Table 5-14 below, I have summarised some of these factors.

TABLE 5-14 SUMMARY OF FACTORS AFFECTING DOSE	
FACTOR	ALTERATION TO CALCULATED DOSE
Increase weight	Decrease unless calculated on lean body mass
Slow induction	Decrease
Old patients	Decrease
Sick patients	Decrease
Premedication	Decrease
Males	Increase
Children	Increase (proportionately)
Increased metabolic rate	Increase
Apprehension	Increase

4. The induction dose will be effective within 40 seconds.
5. A second dose of $\frac{1}{4}$ - $\frac{1}{2}$ the induction dose may be necessary in cases where the induction dose has not given the desired effect.
6. The M.I.T. can be used with very small increments. The need for the increments is best judged by the operator because he will be first to notice the subtle changes which indicate that the patient has become too light.
7. The M.I.T. can easily be abused. Limitations on total dosage (200mg maximum) and operating time (20 minutes maximum) help to make the technique safer.

8. To avoid the complications of cough and hiccough, methohexitone should be injected slowly.

A mean injected rate calculated from Table 5-10 is 4.25mg/sec. This rate may be hard to achieve in practice, because of syringe markings.

Probably a minimum rate of 10mg/second is the best one could achieve.

9. A 1% or 2% solution should be used as stronger solutions cause numerous complications including vein damage.

In most studies, a 1% solution was used but in practice, a 2% solution is probably more common because it is less bulky.

10. Use of solvents, other than water, is uncommon - despite suggested advantages.

1-6

DISTRIBUTION, EXCRETION AND METABOLISM

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1-6-1: DISTRIBUTION

1-6-1a: Initial high plasma concentration

Following a single intravenous injection of a therapeutic dose of methohexitone there is an immediate high plasma concentration. 80% of methohexitone in blood is bound to the protein content, the remainder is in simple solution (Harvey 1975).

1-6-1b: Redistribution

Over the next thirty minutes the plasma concentration declines rapidly as the drug enters every tissue of the body. The blood-brain barrier is crossed immediately the drug reaches it (Chambiras 1970b); the placental barrier is also rapidly crossed, offering no protection for the foetus (Keep 1973).

Further decline in plasma concentration occurs slowly and depends mainly on biotransformation of methohexitone into metabolites with no hypnotic powers (Doenicke 1965; Thornton 1970).

1-6-1c: Storage of methohexitone in fat tissues

Mark et al (1960) found that after tissue-plasma equilibrium was reached, the rate of disappearance of methohexitone from plasma was 15-19% per hour. Analysis of samples of fat tissue obtained indicated entry of the drug into fat.

It was thought that methohexitone, like all barbiturates, is highly fat soluble and would tend to be stored there. This is the reason often given for the subsequent loss of plasma concentration (Chambiras 1970b; Thurecht 1973; Woods 1974).

Although Christensen et al (1961) said that oxybarbiturates tend not to be stored in fat, as do the thiobarbiturates, but are metabolised more rapidly.

Breimer (1976) criticised some of the plasma-concentration studies because they have relied on very high initial doses of methohexitone.

He has developed a sensitive gas chromatographic method which he claims, *makes it feasible to study the pharmacokinetics after therapeutic doses in man.*

He has observed:

1. The rapid reduction in plasma concentration due to tissue redistribution.
2. A subsequent more gradual slope which reflects elimination or destruction of the drug.

He feels that fat plays a minor role in the elimination of methohexitone because he has not observed another peak in the plasma concentration curve, which he would have expected to see as the drug left the fat storage and returned to plasma. Rather, the short plasma high life is due to rapid metabolism.

1-6-2: EXCRETION

If plasma concentration is very high, barbiturates will be excreted by the kidneys, and even by the mammary glands (Tatum 1939).

Bennett (1974g) mentions renal excretion as one of the causes of termination of activity of barbiturate action. But Harvey (1975) says that the kidneys play only a minor role.

It is known that where the kidneys have been damaged, or even when a double nephrectomy has been performed, little effect is seen on the duration of activity of barbiturates (Tatum 1939).

Sunshine et al (1966) found that less than 1% of an administered dose of methohexitone was excreted unchanged in the urine or bile.

Allen (1972a) put the figure for urine excretion at 0.3% of the original dose.

1-6-3: METABOLISM

1-6-3a: Biotransformation of methohexitone

The site of metabolism of barbiturates is thought to be the liver and it is known that when liver damage has occurred, barbiturate action is prolonged (Tatum 1939).

There is very little evidence of 'detoxication' by other organs; Dundee & Wyant (1974) discuss the possible enzyme systems involved in the biotransformation of methohexitone in the liver.

1-6-3b: Metabolites of methohexitone

The two unsaturated side chains of methohexitone may make it more vulnerable to oxidation and thereby shorter-acting (Dundee & Baron 1962).

Sunshine et al (1966) found evidence of two or more metabolites excreted in the urine, but they were unable to identify them because the quantities were too small.

Doenicke (1965) reviewed the literature and reported that the major metabolite recovered from the urine was hydroxylated at the carbon atom adjacent to the terminal pentynyl side chain. (Carbon atom 5 in Diagram 2-1, Section 1-2-2.)

The main metabolite in rats and dogs is 4-hydroxymethohexitone, but the nature of the metabolites in man has not been determined (Murphy 1974).

1-6-4: CONCLUSIONS

1. The termination of the activity of methohexitone is a result of:
 - (i) Rapid redistribution.
 - (ii) Liver detoxification to inactive metabolites.
2. Very little methohexitone is excreted unchanged.
3. The nature of the metabolites in man is unknown.

1-7-1

ACTION ON CENTRAL NERVOUS SYSTEM

CONTENTSPage

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1-7-1: ACTION ON C.N.S.1-7-1a: General effect on Cerebral Function

Methohexitone exerts a general depressant action on all body tissues and it is the brain which is most sensitive (Bennett 1974e). Drummond-Jackson (1971b) presented a series of graphs depicting levels of anaesthesia, produced by methohexitone, related to Guedel planes.

According to the amount of methohexitone reaching the brain, Blatchley (1973) has listed the effects observed with increasing amounts. Table 7-1 below, summarises these effects.

	TABLE 7-1 EFFECT ON CEREBRAL FUNCTION
I N C R D E O A S S E I N G ↓	No effect
	Drowsiness
	Sleep
	Light Narcosis
	Deeper Narcosis
	Full Surgical Anaesthesia
	Respiratory & Circulatory Depression
	Respiratory & Circulatory Failure
	(after Blatchley 1973)

Furthermore, after a hypnotic dose of methohexitone: R.E.M. sleep is depressed (Graham 1975); cerebral oxygen consumption is reduced by 21%; and cerebral blood flow is reduced (Spiro et al 1975).

1-7-1b: Brain Concentration of Methohexitone

Although the adult brain represents only 2% of the total body mass, it receives 16% of the output of the left ventricle.

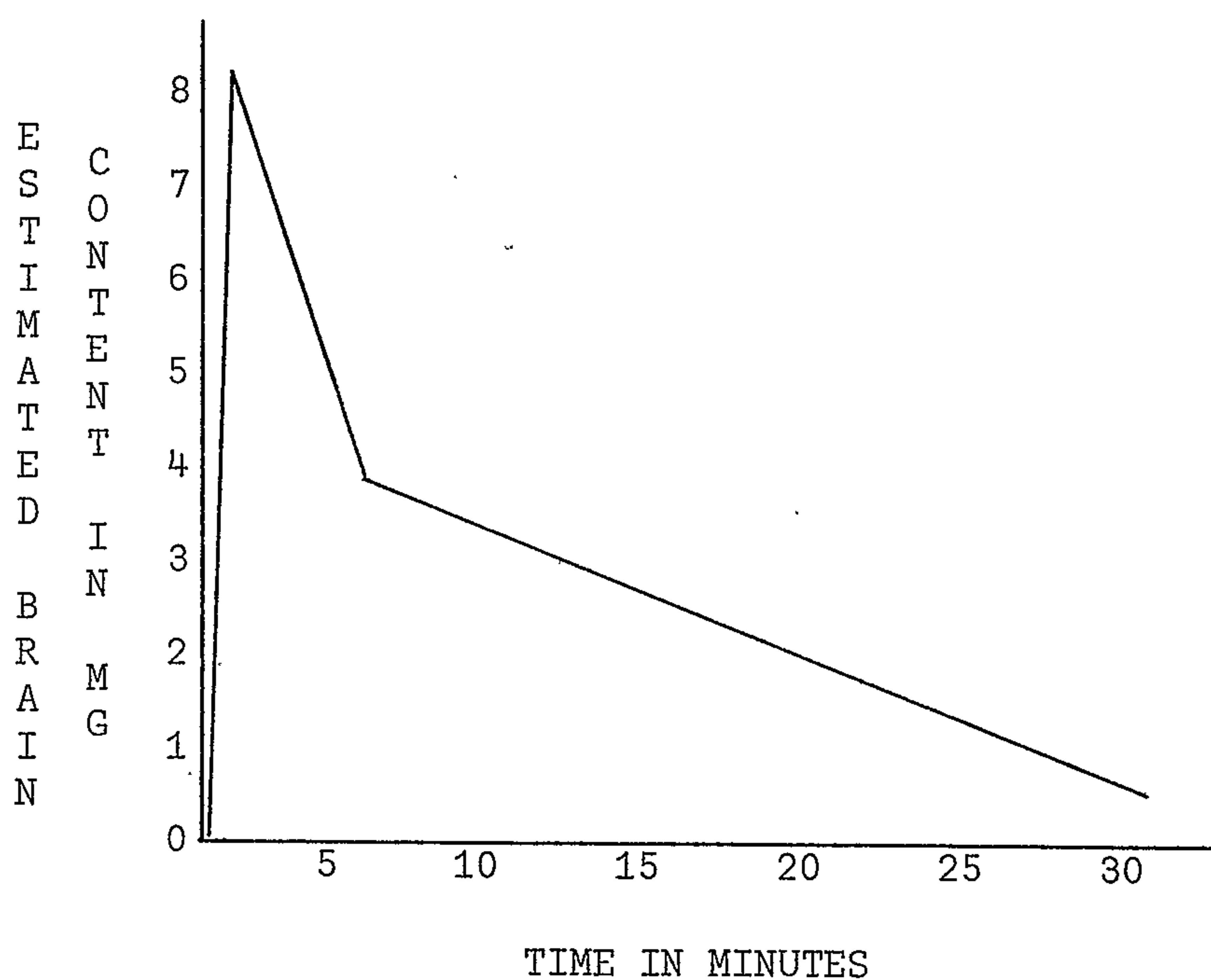
Bourne (1967m) says this means two things:

1. During the first circulation, following a single injection of methohexitone, the brain receives a proportionately higher concentration than the other body tissues.
2. The brain loses the drug proportionately more quickly with subsequent circulations.

Price (1975b) estimates that the brain receives one tenth of the injected (I.V.) dose in the first 40 seconds.

The estimated peak concentration of methohexitone in the brain one minute following injection of 80mg methohexitone is shown in Table 7-2.

TABLE 7-2
ESTIMATE BRAIN CONCENTRATION FOLLOWING SINGLE
I.V. INJECTION OF 80MG METHOHEXITONE



Five minutes later the concentration in the brain is half peak concentration, and thirty minutes after injection it is one tenth of the peak.

1-7-1c: Rapid reduction in brain concentration

The blood supply in skeletal muscle is less than that of the brain, and peak concentration occurs at about the 20 minute mark.

80% of the total dose will be found in the muscles, skin, connective tissue, skeletal tissues and the viscera, thirty minutes after injection (Chambiras 1970b).

Poorly perfused tissues such as fat do not demonstrate a peak concentration for several hours.

Thus, the concentration of methohexitone in the brain falls rapidly and recovery from the hypnotic effects is quick, even though it is some time before the drug is destroyed and its metabolites excreted.

1-7-1d: Acute tolerance

Another mechanism by which the cerebral effect and cerebral concentration could be dissociated is by the development of acute tolerance to methohexitone.

The basis for acute tolerance has not yet been established, but may be present when the anomaly of a high blood level with less cerebral depression is seen (Dundee & Wyant 1974b).

1-7-1e: Effect of larger doses of methohexitone on the brain

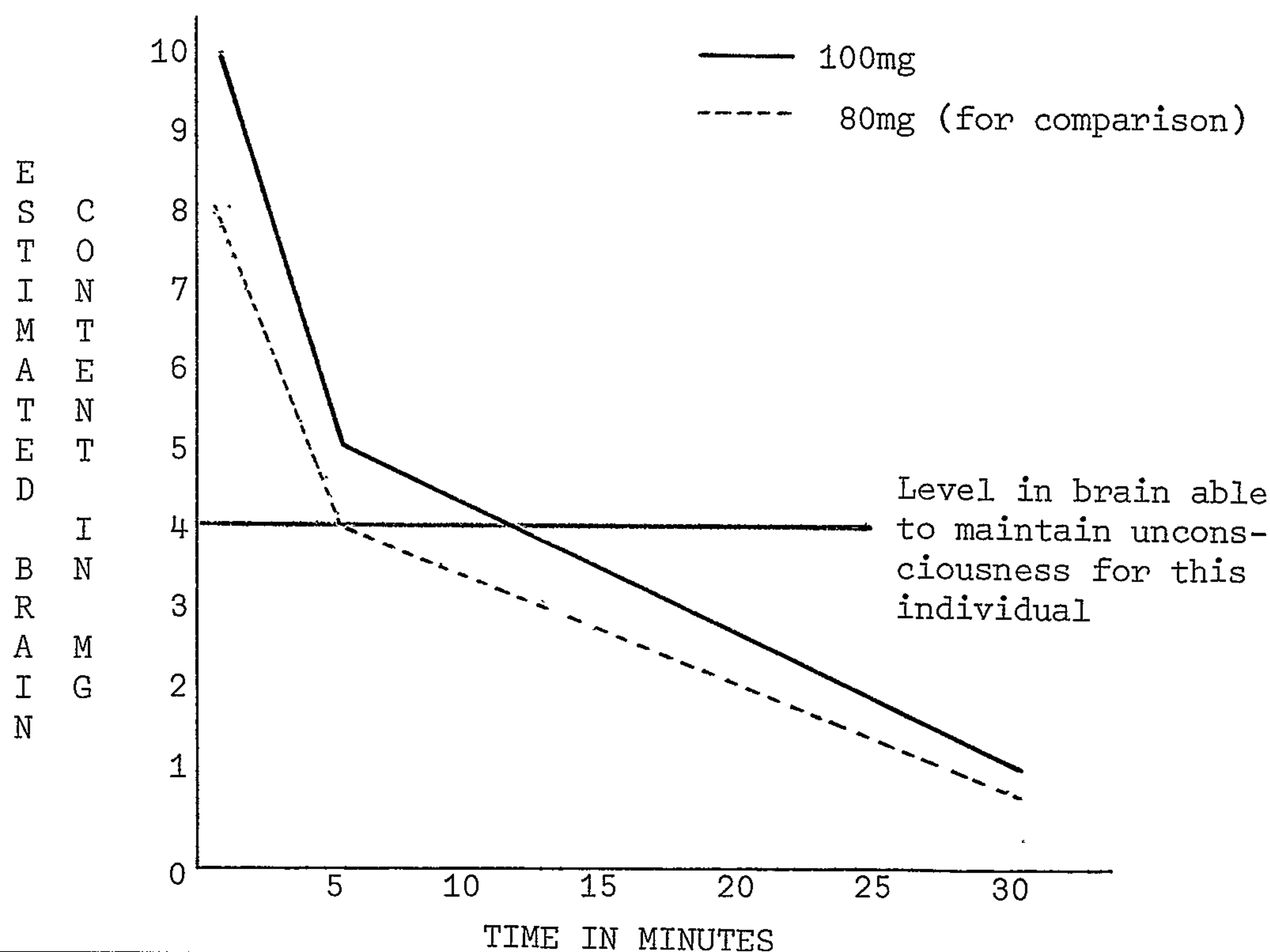
If larger doses are given, the apparent recovery will be delayed for several reasons:

1. There will be an excessive brain content.
2. There will be a reduced rate of removal from the brain due to depression of circulation.
3. Even after saturation of the extracerebral tissues there will still be a relatively high concentration of the drug in the circulation (Price 1975b).

This explains the cumulative effects that occur if excessive dosages are given by the M.I.T. (Blatchley 1973).

In Table 7-3 below I have attempted to show peak concentration in the brain just after one, five and thirty minutes following a single dose of 100mg methohexitone.

TABLE 7-3
ESTIMATED BRAIN CONCENTRATION FOLLOWING
SINGLE I.V. INJECTION OF 100mg METHOHEXITONE



If Table 7-3 is compared to Table 7-2, it can be seen that after five minutes there is more than 4mg of methohexitone remaining in the brain which may be enough to keep this particular patient unconscious (assuming that originally 80mg was the correct induction dose).

If more methohexitone is given in addition to the original dose, an additive effect on the brain content will occur and unconsciousness will continue.

1-7-1f: Cause of depressant action

The mode of action of anaesthetic drugs is controversial and I do not propose to enter this discussion except to say:

It has been postulated that barbiturates owe their depressant action to their ability to inhibit the action of lactic acid dehydrogenase; producing changes in cellular metabolism and electrical impedance of cell walls, which may explain the observed E.E.G. changes (Gruber et al 1957). In fact, depth of anaesthesia can be determined by E.E.G. changes (Scott & Virden 1972).

More recently, Graham (1975) said: *The key to their mode of action may be that a reduction in the turnover of biogenic amines is caused in the brain.*

This area seems to me to be still speculative and there is little information in the literature in relation to methohexitone.

1-7-1g: Amnesia

Lyon (1961) observed that methohexitone *exhibits the interesting property of producing amnesia in extremely light planes of anesthesia.*

Following the apparent recovery to consciousness, a period of amnesia seems to follow for up to five minutes (Foreman 1967).

Retrograde amnesia, that is amnesia extending back to a point before the action of the drug, seems to occur but has not been substantiated in tests (S.A.A.D. Report 1973).

1-7-1h: Clinical applications of amnesic effect

The psychiatrists, Sergeant & Yorkston (1968), described a technique for desensitising phobic patients with methohexitone. Dosage was aimed at relaxation only. Often complete amnesia resulted, *even when they had seemed cooperative and lucid throughout the procedure.*

Methohexitone has been used in dentistry for its amnesic and sedative effects, and it is claimed that consciousness and verbal contact can be maintained (Bennett 1974e; Foreman 1974a).

In 595 administrations by the M.I.T. for conservative dentistry, Mann et al (1971) found that 94% of patients had no memory of events from the last dose given.

Day (1973) says of the M.I.T: *This is usually only a very short, or series of short sedations with an even shorter dip (or say 30 seconds or less) into a very light sub-anaesthetic type of plane - one in which the subject would cough if you tickled his throat or sneeze if you tickled the inside of his nose and yet he will have no knowledge of an extraction performed during and often extending beyond that time.*

1-7-1i: Clinical signs of light anaesthesia

Verbal contact has been used as a sign of light anaesthesia, but Mann et al (1971) found a very poor association with verbal contact and presence of eyelash reflex. Whilst they feel that verbal contact

may be more reliable than eyelash reflex as an indication of ultra-light anaesthesia, they found that 8% of patients who had respiratory obstruction could respond to verbal commands (see Section 1-7-4).

Furthermore, on nearly half of the occasions where the swallowing reflex was present, verbal contact was lost (see Section 1-7-2).

Forsyth et al (1972) studied cardiorespiratory effects and found that the loss and return of the lash reflex proved a poor and highly variable guide to depth of anaesthesia.

Carson et al (1975) investigated different recovery end points following induction with methohexitone. They found for example, that following induction with 0.75mg/Kg, eyelash reflex may remain intact, but 1.7 minutes pass until patients can talk.

Young (1970) reported on 56 cases of conservative treatment of one hour's duration with the M.I.T. alone, or in combination with either a local analgesic or diazepam.

Unfortunately no dosages are given, but he attempted to treat all patients at the ultra-light level with eyelash reflex present.

However, he found it difficult to complete any treatment with eyelash reflex present when methohexitone was used alone. His results are presented in Table 7-4 below.

TABLE 7-4				
ULTRALIGHT LEVELS WITH METHOHEXITONE				
M.I.T.	NO. CASES	NO. KEPT ULTRALIGHT SOME TIMES	NO. KEPT DEEPER AT ALL TIMES	NO. DEEPER AT SOME STAGE (NO. OF TIMES)
Alone	25	11	13	33
+ L.A.	15	13	-	6
+ diazepam	16	15	-	4
(AFTER YOUNG 1970)				
Diazepam is discussed in Section 1-11-6h(i)				
L.A. is discussed in Section 1-11-4				

Wise et al (1969) made E.E.G. recordings on thirty patients who received 200-825mg methohexitone by the M.I.T. for conservative dentistry.

They found that at some stage during treatment the E.E.G. recording was similar to that seen with advanced surgical anaesthesia, in every case.

(The eyelash reflex is also discussed in Section 1-5-5d.)

1-7-1j: Analgesia

Foreman (1965) suggests that methohexitone may have analgesic properties. He was able to treat 97 patients out of 100 whilst they were virtually awake.

However, Dundee (1964) has shown that methohexitone increases the response to pain, and is thus antanalgesic.

1-7-1k: Jactitations

Involuntary muscle movements have been observed following induction with methohexitone. These may be no more than a transient tremor of the eyelids and extremities, or may be severe and resemble clonic contractions.

Barron & Dundee (1967) conclude, from a review of their records of methohexitone administration, that it may have a *triphasic action in the brain*.

In some circumstances it can be both a stimulant and a hypnotic. More stimulation was seen with larger doses, probably because there is a release from inhibitions producing an increased sensitivity to pain.

In the S.A.A.D. Survey (Drummond-Jackson 1971d) of 445,386 administrations for general dental treatment, the following figures were recorded:

Muscle twitching	-	0.006%
Fit on venepuncture	-	one case
Violent shivering	-	three cases

In Table 7-5 below, I have ranked several clinical studies in increasing incidence of jactitations. The incidence recorded in these studies is much higher than that of the S.A.A.D. Survey.

TABLE 7-5: STUDIES REPORTING JACTITATIONS						
NAME OF STUDY	MEAN INDUCTION DOSE	MAINTENANCE	TYPE OF SURGERY	NUMBERS	INCIDENCE	
Myers & Coltman (1961)	100mg + premed	2nd Dose 70-100mg	Exo.	1500	Transient No clinical significance	
Taylor & Stoelting (1960)	70mg + premed	Gas	General Surgery	3340	2.57% marked during induction No clonic type No ill effect	
Simpson & Rondeau (1966)	70-80mg 150mg	- Gas	Exo.	4000	10%	
Hellewell & Hutton (1967)	80mg or 1.2mg/Kg	Gas, one M.I.T.	Exo.	112	11.5% during induction	
Shafto (1969)	1.1mg/Kg (young) 1.57mg/Kg (older)	M.I.T.	Exo.	500 (child)	11.6% slight 1.2% severe 1.2% inadequate jaw relaxation	
Andrew et al (1973)	2mg/Kg	Gas	Exo.	68 (child)	13.23%*	
Korttila et al (1975)	2mg/Kg	-	0	10	40%	
Wyant & Chang (1959)	61.8mg + premed	0.2% drip	D&C	66 females	56% slight 3% severe	

* includes hiccoughing

1-7-1L: Discussion of studies reporting jactitations

The high incidence recorded by Wyant & Chang (1959) could be related to the pain of the procedure (D & C), because the dental studies had a much lower incidence.

However, Taylor & Stoelting (1960) recorded a low incidence for general surgery.

Comparison is difficult because the authors' definitions of jactitations and classifications of severity, vary.

Korttila et al (1975) recorded a high incidence where no work was carried out. Probably they were able to concentrate more closely on recording such effects without the handicap of a surgical situation.

The jactitations generally caused no ill effects and were not clinically significant, nor were they convulsive.

However, Wyant & Chang (1959) describe, *one patient who required a rather large amount of methohexital to maintain anaesthesia showed repeated jactitations which were interpreted as preconvulsive movements. Anaesthesia was continued with methohexital, but no true convulsions developed. Epilepsy is discussed in Section 1-9-4.)*

1-7-1m: Prevention of Jactitations

The incidence may be related to dosage. Wyant et al (1957) observed less jactitations with a 1% solution than with 2.5%.

The incidence has been found to increase with the speed of injection (Recant 1960; Douglas 1960; Lind & Roland 1969).

Hubbell & Royer (1973) observed no jactitations when local analgesia was also used. This tends to support the view that pain may be a causative agent. By preventing the transmission of pain stimuli to the brain, the local analgesic may have prevented jactitations from occurring.

1-7-1n: Conclusions of Action on C.N.S.

1. C.N.S. recovery from methohexitone is apparently rapid and this is mainly due to rapid redistribution of the drug.
2. The amnesic effects of methohexitone are exploited for dental treatment, but patients may be deeper than clinical signs would suggest (see Sections 1-7-1g & h).
3. The traditional signs of light anaesthesia, namely verbal contact and presence of eyelash reflex, are a poor guide to depth of anaesthesia and in any case may be difficult to maintain when using methohexitone alone (see Table 7-4).
4. Methohexitone is antanalgesic.
5. Jactitations caused by methohexitone are not harmful and do not interfere with treatment.
6. The incidence of jactitations may be related to dosage (including injection speed) and pain.

1-7

ACTION ON ORGAN SYSTEMS

1-7-2

ACTION ON RESPIRATORY SYSTEM

I. LARYNGEAL REFLEXES

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1-7-2: ACTION ON LARYNGEAL REFLEX

1-7-2a: Introduction

The laryngeal reflex mechanism protects the trachea from the aspiration of foreign material (e.g. gastric material, saliva, amalgam).

Interference with the reflex may cause:

1. Aspiration of foreign material into the trachea.
2. Laryngeal spasm.
3. Coughing.
4. Hiccoughing.

1-7-2b: Effect of M.I.T. on laryngeal reflexes

In the management of all anaesthetics it must be assumed that the protective reflexes are not present (Buxton 1971a).

However, Hubbell (1960) reported 2,500 administrations of methohexitone for oral surgery and observed that, *most patients tolerated surgical procedures in very light planes of anesthesia with the swallowing, cough and gag reflexes active.*

Similar observations have been made by several other workers (Christenson et al 1961; Hubbell & Royer 1963; Wilkinson et al 1965; Baer 1971; Foreman 1974b).

Others take the view that the M.I.T. is an anaesthetic technique (Allen 1972b) and that a state of surgical anaesthesia may be induced in many patients with each increment (Bell (1975d).

Deviations from normal may occur when the patient is only light or is unconscious for brief periods (Bennett 1974b).

Trieger (1974b) advised that methohexitone should not be used in conscious sedation techniques because of these narrow limits.

Wilson, D.S. (1970) says that the problem of airway maintenance is too difficult when the M.I.T. is used for conservative dentistry.

Foreman (1967) says: *It is not advised where major surgical procedures are concerned, unless intended solely as a cover for local injections and to control psychological trauma. The technique should not be over-extended . . .*

Clarke (1971) warns that if bilateral oral surgery is to be attempted with the M.I.T., the second side should not be commenced until all bleeding has stopped on the first side. Thus a pharyngeal trickle of blood, which could cause a spasm, is avoided.

For patients requiring oral surgery, especially in the posterior regions of the mouth where pack placement can be difficult, or where bilateral blocks have been given, Litchfield (1972b) prefers not to use methohexitone at all, *to ensure full retention of all reflexes.*

1-7-2c: Aspiration

When their patients were able to respond to verbal commands, Wise et al (1969) asked them to swallow contrast media placed on the tongue. In 45% of cases the presence of the media in the bronchial tree could be detected on a radiograph.

A co-author of this study, Robinson (1970) stated: *In considering 'light anaesthesia', it should be noted that during prolonged administration of methohexitone by the 'intermittend technique', the laryngeal reflex becomes obtunded.*

According to Bourne (S.A.A.D. Report 1972d), the doses used in the above study were too high for too long, and as a result, the reflexes were diminished.

Thornton et al (1969) announced some preliminary results of their study on 595 patients receiving the M.I.T. for conservative dentistry. In 8.5% of cases there was radiographical evidence of aspiration of contrast media in the trachea.

In the main report, Mann et al (1971) explained that the dye was placed behind the pack in 201 cases. But the incidence of aspiration was given as 8% (including one patient who had inhaled a piece of amalgam, which fortunately cleared naturally).

Comparing these studies, Kurland (1969) says that Wise et al (1969) did not specify exactly where the dye was placed (e.g. near aspirator tip, or behind tongue), and this could account for the large difference in the figures.

Foreman (1969b) commented on this difference too. He wondered whether a study on conscious patients undergoing prolonged treatment under local analgesia (no sedation and usually no packing) would also show evidence of aspiration of contrast media into the bronchial tree.

He finds it difficult to accept that these results would be restricted solely to methohexitone, although of these two studies, he says it is, . . . *surprising indeed if depression of the laryngeal reflexes did not occur.*

In fact, Mann et al (1971) did test 25 patients who received only local analgesia. The dye was placed on the dorsum of the tongue,

there were no positive radiographs.

Healy & Vickers (1971) compared the efficiency of the glottic reflex in 74 patients who received diazepam, and 12 patients who received local analgesia only, for conservation.

Although positive results were obtained with diazepam, no patient who received only local analgesia had a positive result.

1-7-2d: Laryngeal spasm

1-7-2d(i): Cause

The protective reflex, designed to prevent aspiration of foreign material into the trachea, may become exaggerated under anaesthesia to form a laryngeal spasm.

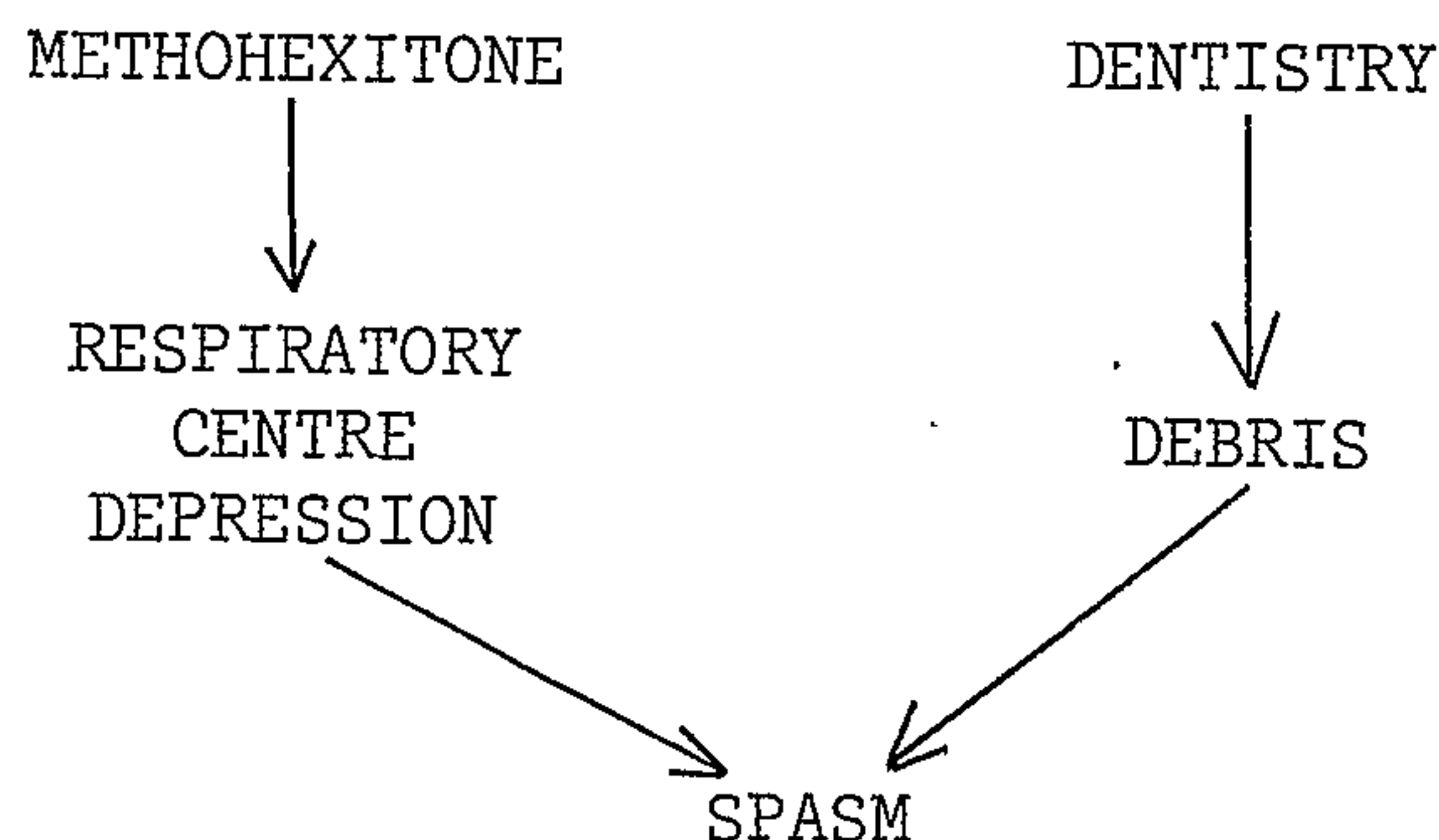
At the time Drummond-Jackson (1960) began using methohexitone, barbiturates were thought to be spasmogenic. Although Tatum (1939) had written: *It may be that this apparent stimulation is but a manifestation of release from control by higher centres or that this particular reflex is especially difficult to suppress.*

Barbiturates do not sensitise the larynx, but they do depress the respiratory centre much more intensely than they depress the laryngeal sphincter nervous mechanism.

Large doses of barbiturates will depress and arrest respiration but sphincteric function remains strongly active. Bourne (1967f) says that intense spasms are associated with large doses of barbiturate.

In diagram 1-7 below, I have summarised the role of methohexitone as a cause of laryngeal spasm.

DIAGRAM 7-1: CAUSE OF LARYNGEAL SPASM



1-7-2d(ii): Incidence

Drummond-Jackson (1960) had not recorded one laryngeal spasm in 2,000 anaesthetics since using sponge mouthpacks. He felt that the development of these packs has played a large contribution to the reduction in the incidence of laryngeal spasm. (Mouthpacking is discussed in Section 1-10-7.)

Simpson & Rondeau (1966) recorded a .1% incidence of coughing and gagging. These patients were usually smokers.

Foxeman (1967) has found that laryngeal spasm is seldom a problem at the ultra-light level used with the M.I.T. He is able to ask the patient to clear his own throat. (See also Section 1-10-6.)

Feher (1974) claims that since using a mixture of thiopentone and methohexitone, which he calls *Bri-Pent*, he has not had any laryngeal spasms or coughing spells.

In Table 7-6 below, I have listed several studies reporting an incidence of laryngeal spasm under methohexitone. The studies are

ranked in increasing order of incidence. Where a percentage incidence was not given, I have calculated it from the actual numbers. An explanation of abbreviations used in the table is as follows:

- | | | |
|----------------|---|---|
| Premed | - | Analgesic premedication used in all or some cases. Does not refer to use of atropine. |
| Technique: MIT | - | Methohexitone used in an incremental technique. |
| 1 shot | - | Single dose of methohexitone as sole anaesthetic. |
| IND | - | Induction with methohexitone prior to inhalation agents. |

TABLE 7-6: INCIDENCE OF LARYNGEAL SPASM									
NAME OF STUDY	% SPASM	NO. ADMINS	PRE MED	TECHNIQUE			COMMENTS		
				MIT	1SHOT	IND			
Wyant & Chang (1959)	0	66	+	.		+	6% incidence of coughing		
Myers & Coltman (1961)	0	1500	+		+	+			
Swerdlow (1962)	0	200			+	+			
Dundee & Lyons (1967).	0	100				+	Mixture of methohexitone and propanidid		
Lind & Roland (1969)	0	104				+	Injection rate = 20mg/20secs		
Mann et al (1971)	0	595		+					
Elliott (1974)	0	800	+	+					
Young & Whitwam (1964a)	0.05	2000				+	One case only; but severe		
Drummond-Jackson (1971d)	0.094	445386		+			S.A.A.D. Survey		
Shafto (1969)	0.2	500		+					
Hubbell (1960)	0.6	2500	+	+		+	Partial spasm = 10 cases Complete spasm = 5 cases		
Lyon (1961)	0.78	513	+	+			Nitrous oxide/oxygen too		
Hellewell & Hutton (1967)	0.8	122				+	Spasms were slight		
Taylor & Stoelting (1960)	0.82	3340	+			+	Spasms usually mild		
Coleman & Green (1960)	less 1	373	+			+			
Dundee & Lyons (1967)	1	300	+			+	Compare this to mixture		
Recant (1960)	2	2500		+			Spasms were partial		
Goldman & Kennedy (1964)	3	101				+			
Lind & Roland (1969)	3.03	99				+	Injection rate = 20mg/5secs		
Simpson & Rondeau (1966)	4	4000	+		+	+	Incidence of coughing less 1%		
Redish et al (1958)	4.2	24	+			+	Two cases of coughing		
Lind & Roland (1969)	5.1	98				+	Injection rate = 20mg/10secs		
Christenson et al (1961)	5.5	127	+	+					

1-7-1d(iii): Discussion of Table 7-6

Comparison of results is difficult because the definition of laryngeal spasm differs (Recant 1960).

Lind & Roland (1969) found that the incidence increased with the speed of injection. (Injection speeds are discussed in Section 1-5-11.)

Dundee & Lyons (1967) reduced the incidence when a mixture of propanidid and methohexitone was used (see Section 1-14-3g).

The incidence of spasm under the M.I.T. is generally low.

1-7-2d(iv): Treatment of laryngeal spasm

Coleman & Green (1960) relieved laryngeal spasm by removing the existing stimulus and giving further methohexitone.

Hubbell (1960), Lyon (1961), Hubbell & Royer (1963), Quinn et al (1973) and Spiro et al (1975) suggest that, after clearing the throat, a muscle relaxant should be administered and positive ventilation with 100% oxygen applied.

Young & Whitwam (1964a) successfully treated laryngeal spasm by clearing the airway and supplying 100% oxygen only.

Bloomfield (1966) applies pressure to the chest wall and is able to force air out of the lungs and stops the spasm.

Robinson (1970) discusses the treatment of laryngeal spasm and suggests that: *Disaster may be averted if . . . some air or oxygen forced into the lungs past the vocal cords.*

1-7-2d(v): Warnings regarding treatment of laryngeal spasm

Bourne (1967f) insists that because of the danger of aspiration, paralysing drugs should not be given nor should the lungs be forced inflated. He does not give more methohexitone, but prefers the patient to waken. He says that time should not be wasted preparing respiratory stimulants. The patient should be placed on his side, an airway established, and he should be allowed to breathe pure oxygen.

Love (1968) feels that there is no place in the dental surgery for elaborate methods of overcoming laryngeal spasm (e.g. muscle relaxants, cricothyroid puncture or tracheotomy).

1-7-2e: Cough and Hiccough

1-7-2e(i): Hiccoughing

Buxton (1971a) considers hiccoughs to be a mild form of laryngeal spasm. A patient who has fasted can still regurgitate acid gastric secretions which could irritate the cords sufficiently to cause a persistent hiccough; similarly, he has noticed that patients with hiatus hernia tend to get hiccoughs and the same patient will hiccough each time he receives treatment.

He says that atropine can sometimes prevent hiccoughs; presumably by reducing secretions that could irritate the vocal cords (see Section 1-11-5a).

Bennet (1974p) says that he has used the M.I.T. extensively and comments on hiccoughing, *they do not persist and do not seem to be significant.*

1-7-2e(ii): Coughing

Persistent coughing is due to irritation of the larynx from regurgitated gastric material or from saliva (Atkinson et al 1977).

1-7-2e(iii): Incidence of cough and hiccough

In Table 7-7 below, I have ranked in increasing order of percentage, incidence of hiccoughs, several studies reporting hiccoughs and coughs.

TABLE 7-7: INCIDENCE OF HICCOUGHS & COUGHS				
NAME OF STUDY	NUMBER	HIC- COUGH %	COUGH %	COMMENTS
Drummond- Jackson (1971d)	445386		2 cases	Reported coughing & sneezes (SAAD Survey)
Young (1970)	25		60	Incremental methohexitone only
Young (1970)	15		Less	With L.A. supplementation
Young (1970)	16		Less	With diazepam supplement
Shafto (1969)	500		Occa- sional	Incremental methohexitone
Taylor & Stoelting (1960)	3340	2.5		Induction with methohexitone prior to inhalation anaes- thesia. Premedication with morphine pethidine atropine
Hellewell & Hutton (1967)	122	3.3		Induced with methohexitone prior inhalation anaesthesia Average dose = 80mg
Young (1974)	236	3.8		Induced with methohexitone prior inhalation anaesthesia Of hiccoughs: 7 were on in- duction, 2 on recovery

TABLE 7-7 (continued)

NAME OF STUDY	NUMBER	HIC- COUGH %	COUGH %	COMMENTS
Allen et al (1969)	18	5.6		Incremental methohexitone with nitrous oxide & oxygen supplementation
Dundee & Lyons (1967)	100	9		Combined cough & hiccough. Induced with mixture of methohexitone & propanidid
Kurland (1967)	150	10		Combined cough & hiccough
Mann et al (1971)	591	11.	25	Incremental methohexitone only
Bennett (1974p)	?	10-12		No more details
Andrew et al (1973)	68	13.2		Combined cough & hiccough. Children. Induction with methohexitone prior to in- halation
Barron (1968)	50	16		Speed of 6ml/min. But other speeds of injection tested too
Lind & Roland (1969)	104	20	5.8	Injection speed = 20mg/20sec
Dundee & Lyons (1967)	300	26		Combined cough & hiccough. Induced methohexitone only
Lind & Roland (1969)	98	31.6	11.2	Injection rate = 20mg/10sec 2% solution. Induction with methohexitone prior inhala- tion
Barron (1968)	50	44		Injection rate = 60ml/min
Lind & Roland (1969)	99	50.5	7.1	Injection rate = 20mg/5sec

1-7-2e(iv): Discussion of Table 7-7

Mann et al (1971) found the incidence of coughing and hiccoughing to be *disturbingly high*, and the complication adversely affected their operating conditions for conservative work under the M.I.T.

Lind & Roland (1969) induced females, for D. & C, with 2mg/Kg methohexitone. They found a significant rise in the incidence with faster injection speeds.

The incidence is less when methohexitone is used with local analgesia, diazepam or propanidid (see Sections 1-11-4, 1-11-6h, 1-14-3g respectively).

1-7-2e(v): Prevention of hiccoughs and coughs

1. Use of M.I.T.

Foreman (1965) has found that the M.I.T. is especially valuable in heavy cigarette smokers. Rather than suffering coughing attacks under deeper anaesthesia, where it can be difficult to treat, under the incremental technique he removes the prop and asks the patient to swallow. (See also Section 1-10-6.)

Haslett & Dundee (1968) have the impression that . . . *cough and hiccup are less frequent with the more recent preparations of purer high-melting point isomers than with the earlier samples of methohexital.*

2. Propanidid-methohexitone mixtures

Kurland (1967) reduced the incidence of hiccoughing and coughing from 10% using methohexitone alone, to 1% by using a mixture of propanidid and methohexitone (see Section 1-14-3g).

Similarly, Dundee & Lyons (1967) reduced the incidence from 26% in patients induced with methohexitone alone to 9% in patients

induced with a mixture of propanidid and methohexitone.

3. Supplements

Taylor & Stoelting (1960) induced patients with methohexitone prior to general surgery. They were able to stop hiccoughing and coughing at induction by giving more methohexitone, or by the addition of inhalational anaesthetics.

Young (1970) was able to control coughing during the incremental technique either by giving more methohexitone and thus deepening anaesthesia, or by supplementing methohexitone with local analgesia or diazepam.

4. Dose

Mann et al (1971) could not establish a relationship between dosage of methohexitone and hiccoughing, because dose varied with the response of the patient.

Barron & Dundee (1967) analysed their records of 9,000 anaesthetics using various barbiturates and found that the incidence of hiccoughing and other respiratory complications increased with higher dosage.

Recant (1960) and Lyon (1961) found an increased incidence with an increased injection rate producing a too rapid induction.

Barron (1968) used a constant induction dose of 1.6mg/Kg. He varied the injection speed by using a constant rate infusion syringe. Results were recorded for 6, 12, 24 and 60ml/min. A direct relationship was found between speed and incidence of coughing and hiccoughing.

1-7-2f: Conclusions

1. With the M.I.T., there is a danger of aspiration of foreign material into the trachea because, even at light levels, the laryngeal reflexes are obtunded.
2. The danger of aspiration is worse with conservative work and surgery in the posterior area of the mouth.
3. More emphasis must be placed on the importance of safe mouth packing. This is an important preventative measure and is further discussed in Section 1-10-7.
4. The incidence of laryngeal spasm is low, and can be largely prevented.
5. Treatment of laryngeal spasm should be conservative.
6. The incidence of coughing may be higher amongst cigarette smokers because of their increased mucous saliva.
7. Patients should clear their throats by swallowing prior to induction to reduce coughing.
8. The incidence of cough and hiccough is related to dosage - particularly the speed of injection.
9. Some patients who have hiccoughed previously may have a greater tendency to hiccough on subsequent administrations.
10. See also Section 1-11-5, on the use of antisialogogues.

1-7

ACTION ON ORGAN SYSTEMS

1-7-3

ACTION ON RESPIRATORY SYSTEM

II. RESPIRATORY RATE

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1-7-3: RESPIRATORY RATE1-7-3a: Increased respiratory effort on induction

Weinstock (1960) observed that as soon as the induction dose of methohexitone takes effect there is an increased respiratory effort of 2-3 seconds duration.

Whitwam (1962) administered methohexitone for outpatient surgery and recorded respiratory movements graphically. The increased respiratory effort is clearly shown followed by a period of apnoea. Southwell (1976) observed a similar effect following increments of methohexitone.

Savege et al (1972) observed that the initial period of hyperventilation coincided with a rise in pulse rate and blood pressure. They suggest that methohexitone may exert an initial central stimulant effect.

The increased respiratory effort is not always noticed: Myers & Coltman (1961) did not find any increase in depth of respiration following 1,500 administrations of methohexitone.

1-7-3b: Apnoea1-7-3b(i): Introduction

A period of apnoea may follow the administration of methohexitone.

The initial apnoea is a result of direct depression of the medullary and pontine respiratory centres rather than by local action (Price 1975b).

Thornton (1970) reviews this topic and comments: *this complication of intravenous anaesthesia is well known and has been reported prior to*

the introduction of methohexitone in association with other drugs.

The incidence of apnoea, associated with the administration of methohexitone, may be increased by opiate premedication (Swerdlow 1962) and may be *related to the total dose, speed of injection, type of pre-medication, individual response etc.* (Young & Whitwam 1964a).

1-7-3b(ii): Studies reporting apnoea following methohexitone

Because authors define apnoea differently, it is difficult to compare those studies reporting its incidence. Table 7-8 below gives examples.

TABLE 7-8 DIFFERENT DEFINITIONS OF APNOEA	
STUDY	DEFINITION OF APNOEA
Wyant et al (1957)	<i>Tidal volumes of less than 40ml . . . when they followed a period of cessation of respiration</i>
Goldman & Kennedy (1964)	Cessation of respiration lasting >30secs
Dundee (1963) Barron (1968)	<i>Marked respiratory depression</i>
Young & Whitwam (1964a)	Assisted ventilation required
Elliot et al (1974)	Serious respiratory depression requiring drug reversal

However, in Table 7-9 below, I have listed those studies reporting apnoea following methohexitone. The table is divided into twelve sections (A-L): Each section contains a number of studies grouped together for comparison.

Where it has been possible, I have calculated the statistical significance of the incidence of apnoea. For example, I have compared some studies having at least one common author. In these cases I have assumed that the criterion is the same (e.g. definition of apnoea).

TABLE 7-9: STUDIES REPORTING INCIDENCE OF APNOEA									
NAME OF STUDY	NO.	METHOHEXITONE MEAN INDUCTION DOSE	ANALG. PREMED	INCIDENCE OF APNOEA			AUTHORS' COMMENTS	MY COMMENTS	PART
				No.	%	Mean Duration (Secs)			
Finch & De Kornfeld (1967)	50	75mg M = 0.95mg/Kg F = 1.36mg/Kg	0	15	30	30	No Surg.	Dose increase- ases ↓ Inci- dence incre- ases ↓	A No Premed. No Surgery
Korttila et al (1975)	10	2mg/Kg	0	4	40	30	No Surg.		
Wyant & Chang (1959)	66	61mg 1.05mg/Kg	+	34	56	63.5	All F. Apnoea ≤ 18 min. surgery	Less dose gives significant drop in incidence $\chi^2 = 9.228$ $0.01 > p > 0.001$	B Common Author/s
Dobkin & Wyant (1957)	7	273mg (2 x sleep)	0	7	100	82	No surg.		
Wyant et al (1957)	5*	480mg	0	4*	100*	87	*Records incomplete in 1 case. No surg.		

TABLE 7-9 (continued)

NAME OF STUDY	NO.	METHOHEXITONE MEAN INDUCTION DOSE	ANALG. PREMED	INCIDENCE OF APNOEA			AUTHORS' COMMENTS	MY COMMENTS	PART
				No.	%	Mean Duration (Secs)			
Green & Jolly (1960)	500	0.69mg/Kg	0	0	0	0	Dose < Wyant & Chang (1959) Gives reduction in incidence	Premed had no effect on incidence Lack of detail Incidence may be related to dose	C
Coleman & Green (1960)	10142	70mg 0.96mg/Kg	+	0	0	0			Common
Jolly (1960)	35	Range = 100-260mg (1½ x sleep dose)	+	Scarce (?)	?	Brief (?)			
Wise et al (1969)	30	50mg thence 5.7mg/min	0	0	0	0	Resp. rate increased	In these studies detailed physiological monitoring was conducted. Highly significant difference (0.001 $\cong$ p χ^2 = 22.879) may be due to def. of apnoea?	D
Allen et al (1969)	18	1mg/Kg	0	0	0	0			
Mann et al (1971)	578	0.8-1.3mg/Kg	0	183	32	$\cong$ 32	With maint. doses 9% apnoeic once		

M.I.T.

TABLE 7-9 (continued)

NAME OF STUDY	NO.	METHOHEXITONE MEAN INDUCTION DOSE	ANALG. PREMED	INCIDENCE OF APNOEA			AUTHORS' COMMENTS	MY COMMENTS	PART
				No.	%	Mean Duration (Secs)			
Wilkinson et al (1965)	6704	F = 80-100mg M = 100-120mg	0	?	?	Transi-ent	Nos. not significant		E
Young & Whitwam (1964a)	2000	F = 70.4mg 1.18mg/Kg M = 136mg 1.7mg/Kg	0	5	0.25	Till extractions started	Incidence $\propto$ dose	Surgery stimulates respiration	M.I.T.
Shafto (1969)	500	1.1mg/Kg Younger 1.57mg/Kg	0	most	?	till extractions started	Children		
Liscombe (1968)	30	1.38mg/Kg	+	0	0	0	Children	Diff. due to definition of apnoea?	F M.I.T.
Douglas (1960)	95	Mode = 50mg 2.45mg/Kg	+	0	0	0	Children		
Goldman & Harris (1963)	525	0.7mg/Kg	0	7	1.3	range 1-2 min	Shows effect of increase in dose	This is a highly significant difference ($\chi^2 = 11.367$ $p < 0.001$)	G Dosage
Series I Series III	150	1mg/Kg	0	9	6.0	RANGE 1-2 min			

TABLE 7-9 (continued)

NAME OF STUDY	NO.	METHOHEXITONE MEAN INDUCTION DOSE	ANALG. PREMED	INCIDENCE OF APNOEA			AUTHORS' COMMENTS	MY COMMENTS	PART
				No.	%	Mean Duration (Secs)			
Goldman & Kennedy (1964)	101	1.1mg/Kg	0	(1.5)	1.5	30-60	Shows effect of increase in strength 1% soln	Not significant ($\chi^2 = 5.349$) $0.1 > p > 0.05$ (Nos in parenthesis calculated from %)	H Solution Strength
	169	1.1mg/Kg	0	(11.2)	6.6	30-60	2% soln		
	28	1.1mg/Kg	0	(3.08)	11.0	30-60	5% soln		
Barron (1968)	50	1.6mg/Kg	0	2	4	?	Inject. Speed 6ml/min	Strength of solution not stated No significant difference ($\chi^2 = 4.031$) $0.5 > p > 0.1$	I Inject. Speed
	35	1.6mg/Kg	0	0	0	?	12ml/min		
	30	1.6mg/Kg	0	3	10	?	24ml/min		
	50	1.6mg/Kg	0	2	4	?	60ml/min		
Young (1974) Group 3	45	2.2mg/Kg	0	0	0	0	Slower Inject. Speed 0.12-0.38 ml/sec (1%, 7.2-22.8ml/min)	No difference	J Inject. Speed
	27	1.6mg/Kg	0	0	0	0	Fast induction 0.63-1.0 ml/sec (37.8-60 ml/min) 1%		

TABLE 7-9 (continued)

NAME OF STUDY	NO.	METHOHEXITONE MEAN INDUCTION DOSE	ANALG. PREMED	INCIDENCE OF APNOEA			AUTHORS' COMMENTS	MY COMMENTS	PART
				No.	%	Mean Duration (Secs)			
Dundee (1963)	300	1.57mg/Kg	0	6	2.0	?	No premed.	Dose given in Dundee & Moore (1961) The increase in incidence is probably significant ($\chi^2 = 3.997$, $0.05 > p > 0.02$)	K Premedication
	300	1.56mg/Kg	+	15	5.0	?	Premed		
Stoelting (1957)	285	70mg 1.17mg/Kg	+	76	26.67	2-3 mins	Morphine or pethidine premed	Demonstrates the problems of premed with fentanyl	L Premedication
Taylor & Stoelting (1960)	3340	70mg	+	569	17.04	≤ 3 mins	Morphine or pethidine premed		
Elliott et al (1974)	800	0.294mg/Kg each 30 secs	Innovar ± morphine ± fentanyl	6	0.75	recover after levallorphan	Premed innovar ± morphine or fentanyl At end tidal vols 25% below av.		
							Resp. depressed for 20-30 minutes		
Campbell et al (1976)	10	20mg/ 30 secs	fentanyl diazepam	10	100.0	Resp. rate halved			

1-7-3b(iii): Discussion of Table 7-9

PART A: No Surgery or premedication

The two studies were not complicated by the use of analgesic premedication or surgery. Because there is no common author, I have not evaluated the differences by χ^2 test, however it would seem that the greatest incidence, recorded in the second study, is due to the larger mean dose used.

PART B: Common authors

Because of a common author, I performed the χ^2 test. There is a significant increase in incidence with increasing dosage.

The first study recorded the lowest incidence, despite the use of analgesic premedication. Possibly the stimulus of surgery helped to reduce the incidence of apnoea.

PART C: Common authors

There is lack of detail to make comparisons. Green & Jolly (1960) compared their results to those of Wyant & Chang (1959) and claimed that the lower incidence of apnoea was due to lower dosages used.

PART D: M.I.T. and detailed monitoring

In these studies, detailed physiological monitoring was conducted on patients undergoing dental treatment with the M.I.T.

The high incidence recorded in the third study, compared with none in the other two, may be due to differences in definitions.

PARTS E & F: M.I.T.

Young & Whitwam (1964a) and Shafto (1969) found that respiration was stimulated by the commencement of extractions.

PART G: Dosage

There is a highly significant increase in the incidence of apnoea as dosage increases. The χ^2 test is probably reliable because it is derived from the one study.

PART H: Solution strength

The χ^2 test is also probably reliable and shows that there is no significant increase in incidence of apnoea with an increase in solution strength.

PART I: Injection speed

Similarly, the χ^2 test may be reliable. There is no significant difference in incidence of apnoea with an increase in speed of injection.

PART J: Injection speed

There was no difference recorded in the incidence of apnoea with an increase in injection speed.

PART K: Premedication

The increase in incidence of apnoea observed when premedication is used is probably significant.

PART L: Premedication

The last two studies demonstrate the respiratory complications of the drug fentanyl - which is discussed further in Section 1-11-6f(v).

1-7-3c: Conclusion

1. Induction of anaesthesia with methohexitone usually results in an increased respiratory effort, which may be followed by a period of apnoea.
2. Factors affecting the incidence of apnoea are summarised in Table 7-10 below:

TABLE 7-10: FACTORS AFFECTING INCIDENCE OF APNOEA		
FACTOR INCREASED	EFFECT ON INCIDENCE APNOEA	REFER TO TABLE 7-9
Dose	+	Significant - B, G See also A,D,C,E
Premed	0 (+)	C,K
	(duration up)	L
Solution strength	0	H,I,J
Injection speed	0	H,I,J
Surgical stimulation	-	A,E,F
Children	-	F

3. Variations in the definitions of apnoea make comparisons difficult.
4. Induction dosage is the most significant factor.

1-7

ACTION ON ORGAN SYSTEMS

1-7-4

ACTION ON RESPIRATORY SYSTEM

III. RESPIRATORY OBSTRUCTION

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1-7-4: RESPIRATORY OBSTRUCTION1-7-4a: Cause

Without an endotracheal tube in place during dental anaesthesia, respiration will be impeded to some extent by relaxation of the tongue occluding the pharynx, the mouthpacking and the manipulation of the mandible (Macintosh 1976).

O'Brien (1974) discusses the diagnosis of respiratory obstruction.

With the M.I.T., Shafto (1969) found that there was less tendency for the tongue to fall back and obstruct the airway than in his experience with more relaxant anaesthetic agents.

Where intermittent methohexitone was used as sole drug for conservative dentistry, Young (1970) observed some respiratory obstruction in 20 cases out of 25. In a further 15 cases using local analgesia supplementation, he noted less cases of obstruction. In a further 16 cases supplemented with diazepam, the frequency was also less and the severity reduced.

Table 7-11 below presents the results of two further studies of the M.I.T.

TABLE 7-11: RESPIRATORY OBSTRUCTION WITH THE M.I.T							
NAME OF STUDY	NO.	DOSE (MG)		RESP. OBSTRUCTION AT SOME STAGE			COMMENT
		MEAN	RANGE	NO.	%	DURATION	
Wise et al (1969)	30	460	200-825 (total)	20	66.7	30-120 (secs)	*
Mann et al (1971)	595	N.A.	60-100 0.8-1.3mg/Kg (induction)	211	35	N.A.	**

1-7-4b: Comments on Table 7-11

* Obstruction was often undetected clinically, but was measured by simultaneous recordings of:

1. A decrease in respiratory excursion, and
2. Wide swings in central venous pressure - indicating an increased respiratory effort.

** Obstruction was often undetected clinically, but was measured on the monitors used. Obstruction caused falls in arterial oxygen saturation - reversed by supporting the chin.

The study by Wise et al (1969) has drawn the following criticisms: Buxton (1969a, 1969b) commented, *In their report the statement that respiratory obstruction occurred in two thirds of the cases is alarming. The dentist, and presumably also the nurse, were experienced in this type of work. It must be assumed that the abnormal conditions prevailing, the multiplicity of apparatus and the number of personnel present, contributed to this complication. The obstructed airway may be encountered in any anaesthetic technique and its occurrence cannot therefore be used as an argument against methohexitone.*

Foreman (1969e) considers that for Wise et al (1969) to permit respiratory obstruction to occur, in several cases for up to two minutes, is *unbelievable, and totally inexcusable in view of the elaborate monitoring used.* He feels that the recommended safety precautions must have been ignored in the study.

Sykes (1969) feels that the airway was inadequately protected, or the patients were overdosed, for Wise et al (1969) to have found it necessary to administer oxygen to three patients.

1-7-4c: Conclusions concerning Respiratory Obstruction

1. Despite criticisms of the findings of Wise et al (1969), it is disturbing to learn that respiratory obstruction may be undetected clinically. (Refer to the section on Cyanosis, 1-7-5d.)
2. See conclusions in Section 1-7-5g.

1-7

ACTION ON ORGAN SYSTEMS

1-7-5

ACTION ON RESPIRATORY SYSTEM

IV. EFFECT ON BLOOD GAS LEVELS

CONTENTS

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1-7-5: EFFECT OF M.I.T. ON BLOOD GAS LEVELS1-7-5a: Fall in Blood Oxygen

Apnoea and respiratory obstruction, following the administration of methohexitone, may cause a fall in blood oxygen levels and an increase in carbon dioxide levels.

If arterial oxygen saturation falls below 90-93%, severe arterial hypoxaemia can occur (Elliott et al 1974).

Table 7-12 represents normal physiological values.

TABLE 7-12 NORMAL PHYSIOLOGIC VALUES			
	OXYGEN TENSION (TORR)	CARBON DIOXIDE TENSION (TORR)	HAEMOGLOBIN SATURATION %
ARTERIAL BLOOD	95	40	97
VENOUS BLOOD	40	46	75

1-7-5b: Studies that have measured arterial oxygen levels

Several studies have investigated the effect of methohexitone on arterial oxygen levels during dental treatment.

In Table 7-13 below, the findings of six studies are shown. In these studies the arterial oxygen levels were measured either directly from an artery or indirectly using ear oxometry.

In most cases patients were breathing air only.

TABLE 7-13: STUDIES MEASURING ARTERIAL O₂ LEVELS UNDER M.I.T

TABLE 7-13: STUDIES MEASURING ARTERIAL O ₂ LEVELS UNDER M.I.T										
NAME OF STUDY	NO.	BREATHING?	PRE MED	HOW MEASURED	O ₂ CHANGED		O ₂ SATURATION %	O ₂ TENSION TORR	COMMENTS	
					NO.	%				
Christenson et al (1961)	30	Air (Most)	+	Direct	30	100	87 mean (70-95)	N.A.	Hypoxia usually recorded after respiratory obstruction or spasm	
Wise et al (1969)	30	Air	0	Direct	5	16.7	N.A.	< 70	Severe hypoxia in some - O ₂ given, so incidence <u>Ω</u> higher	
					1	3.4	N.A.	35		
Allen et al (1969)	18	Air then O ₂	0	Direct	18	100	N.A.	< 100 with air. > 400 O ₂ breathing	Arterial oxygen tension rises if patients breathe O ₂	
Everett & Allen (1970)	9	Air	+	Direct	9	100	N.A.	< 80 (after premed)	Levels rose during treatment	
Mann et al (1971) (L.A. only)→	376	Air	0	Ear Oxo-metry	94	25	< 93	N.A.	Oxygen falls greatest with M.I.T. Compare to L.A. only. FALLS DUE TO OBSTRUCTION **	
	36	Air	18		5*	< 85				
			36		100	≈ 95				
Elliott et al (1974)	10	Air	+	Direct	10	100	N.A.	87	After premed } Danger Hypoxia	
								70		
								89		
	10	O ₂ nose piece	+	Direct	10	100	N.A.	308	After premed } O ₂ eliminates danger	
								296		
								305		

1-7-5c: Comments on Table 7-13

- * Co-author Thornton (1971) put this figure at 15%.
- ** Apnoea, lasting up to 30 seconds, did not cause oxygen saturation drop - unless accompanied by hiccoughing or coughing (Thornton 1971).

Wise et al (1969) blame the severe arterial hypoxia observed in 5 of their patients on respiratory obstruction. They measured the lactate/pyruvate ratio and found that this increased with time, indicating the accumulation of acid metabolites in the tissues due to hypoxia.

Mann et al (1971) found that holding the chin forward usually stopped the oxygen level from falling - indicating a simple respiratory obstruction as the cause of hypoxia. (See also Sections 1-7-5d and 1-7-5f for further comments.)

1-7-5d: Cyanosis

Cyanosis is a violet or grey colour of the skin produced by abnormally large amounts of reduced haemoglobin (arterial hypoxia).

Cyanosis may be central (anoxic anoxia) or peripheral (stagnant anoxia).

Facial colourings have been listed as a diagnostic aid in collapse (Stubbings 1972; O'Brien 1974).

Bourne (1974b) states: *There is no such thing in a healthy person, even under barbiturate anaesthesia, of asphyxial anoxia developing to the point of death insidiously, unnoticed by the dental team. The signs, he says, are too obvious.*

Hellewell & Hutton (1967) noted that of 122 adults induced with methohexitone (average 80mg), 5 exhibited cyanosis and a further 6 did so during maintenance with nitrous oxide and oxygen and halothane. Although apnoea occurred in 4.1% of the cases, they felt that the cyanosis seen was not due to apnoea, but to obstruction of the airway in 4 cases and inadequate inspired oxygen in 7 cases.

However, Wise et al (1969) did not observe cyanosis, despite the presence of severe hypoxia in some patients (see Table 7-13).

Corresponding further on their results, Robinson et al (1969a) state: *The importance of our findings lies in the fact that the patients were unable to extract oxygen from the arterial blood, and in the absence of cyanosis, owing to peripheral shunting, the skin colour is nearer to that of arteriolar blood.*

Robinson (1970) suggests that if a patient has stopped breathing the pulse should be checked in case a cardiac arrest has occurred, which would cause depression of the respiratory centre by absent perfusion (whereas hypoxia should cause an increase in pulse rate (Trieger 1976)).

1-7-5e: Danger of reduced oxygen levels in blood

Whether the reduced oxygen levels seen in studies is significant or not is hard to say because there may be subtle complications occurring that we are unaware of. For example, Bourne (1957) gives five cases of delayed recovery following nitrous oxide anaesthesia. Although the patients apparently recovered later, he wondered if some damage of a permanent nature occurred but was not noticed.

He says that although the brain can withstand 4-5 minutes anoxia before irreversible brain damage occurs, two and one half minutes of

cerebral circulatory arrest could cause disturbances of consciousness lasting several hours. An interval of two minutes could be critical (see Section 1-12-11 for effect on recovery).

Blaaberg (1966) writes regarding complaints from patients who refused methohexitone because of relatives who have not been the same since they had received the drug (i.e. forgetful, etc.).

Seldin & Recant (1955) conducted a *diligent search of the literature* and conclude that such cerebral damage caused by anaesthetic produced hypoxia, after administration of an anaesthetic in the dental office, has been rare.

Serious complications could arise some time after the anaesthetic and would not even be connected with the procedure, for example: initiation of coronary thrombosis; increased risk of ischaemia of heart and brain and anoxic damage to these and other organs (Swiss 1967).

Obviously, cerebral and cardiac hypoxia will occur if:

1. Flow of blood is impaired through these organs (stagnant anoxia).
 2. Blood is not adequately oxygenated (anoxic anoxia).
 3. Oxygen carrying capacity of blood is reduced (anaemic anoxia).
- (Whitwam & Young 1964; Bourne 1967i).

1-7-5f: Benefit of oxygen supplementation

In the British Health Ministry Report on Anaesthesia (Swiss 1967) it is stated: *With intravenous anaesthesia, if apparatus for administering oxygen is not used the patient has to depend upon oxygen from the air, perhaps in the presence of partial respiratory obstruction.*

This factor is particularly important with children, whose airways are smaller and for whom the risk of adverse reaction to the anaesthetic is greater.

The figures shown in Table 7-13 above indicate the improvement seen in arterial oxygen levels if patients are given increased concentrations of oxygen to breathe.

Furthermore, Allen (1972a) recommended supplementing minimal incremental methohexitone with 100% oxygen to avoid the falls in blood oxygen levels that have been reported.

Goldman (1973) demonstrated graphically that over a thirty minute period a patient's haemoglobin oxygen saturation fell to 80% during conservation under intravenous methohexitone. As soon as the patient was allowed to breathe 50% nitrous oxide and oxygen, the haemoglobin oxygen saturation rose to over 90% within thirty minutes.

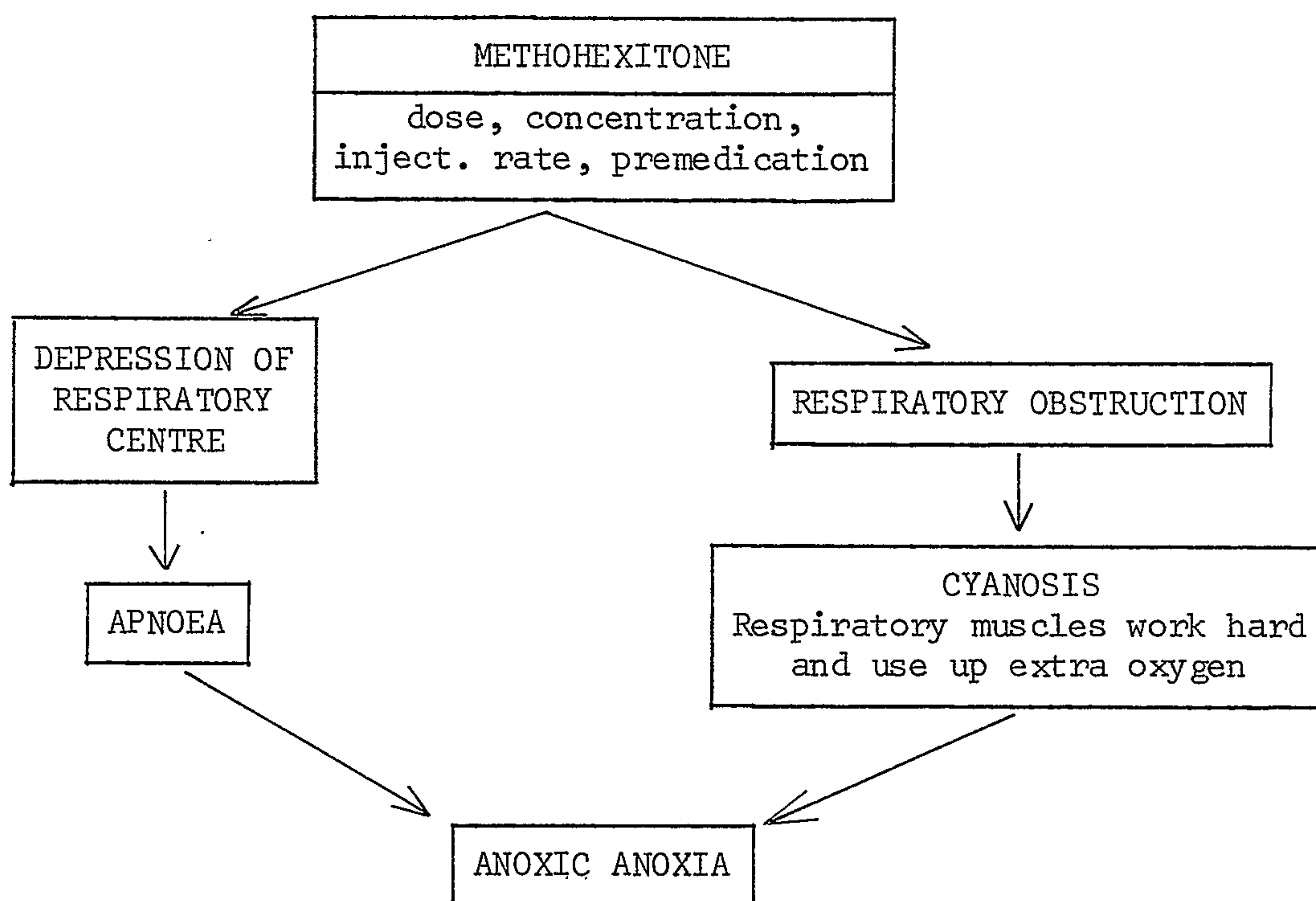
Campbell et al (1976) gave ten patients premedication with fentanyl and diazepam before methohexitone for oral surgery. Throughout the procedure, patients breathed at least 30% oxygen. Arterial oxygen levels were measured and never fell below 98.7% which was higher than the mean pre-operative saturation of 96.8%. (Oxygen supplementation is discussed further in Section 1-11-2.)

1-7-5g: Conclusions

1. The studies measuring blood oxygen levels using arterial catheterisation are few, and with limited numbers of subjects.
2. The ear oxometry method used by Mann et al (1971) allowed many more patients to be studied, but the method is not as accurate as direct sampling.

3. The studies have shown that the administration of methohexitone will produce a decrease in blood oxygen, especially following periods of respiratory obstruction.
4. Respiratory obstruction may not be noticed clinically.
5. Under methohexitone, cyanosis may not be apparent despite the presence of tissue hypoxia.
6. Allowing patients to breathe oxygen through a nosepiece, rather than to breathe air, results in improved blood oxygen levels and reduces the danger of hypoxia.
7. Diagram 7-1 below, summarises the role of methohexitone in producing anoxic anoxia.

DIAGRAM 7-2: ROLE OF METHOHEXITONE IN ANOXIC ANOXIA



Bourne (1967i) says that with simple apnoea there is a 2-5 minutes safety factor, but if respiratory obstruction is combined with it, the added effort of the respiratory muscles will reduce this safety margin.

This could account for the five cases of severe arterial hypoxia seen in the study of Wise et al (1969) where two-thirds of their patients showed obstruction from 30 to 120 seconds.

1-7

ACTION ON ORGAN SYSTEMS

1-7-6

ACTION ON CARDIOVASCULAR SYSTEM

I. HEART RATE

CONTENTS

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1-7-6: HEART RATE1-7-6a: Initial tachycardia

Methohexitone has been reported to cause bradycardia (Myers & Coltman 1961; Drummond-Jackson 1971d). However, induction of anaesthesia with methohexitone is usually reported as producing an initial tachycardia which gradually decreases (Allen et al 1969; Savege et al 1972).

Methohexitone produces a larger increase when compared to other anaesthetics (Ryder 1970), and to other sedative techniques (Southwell 1976), or to local analgesia only (Mann et al 1971).

Thornton (1971) thought that this was the most pronounced feature of his study with Mann et al (1971).

1-7-6b: Causes of Tachycardia1-7-6b(i): C.N.S. Stimulation

Savege et al (1972) postulated that methohexitone produces tachycardia by direct C.N.S. stimulation.

1-7-6b(ii): Hypoxia

Trieger (1976) suggested that the reported tachycardia could be due to hypoxia as a result of respiratory depression and obstruction.

1-7-6b(iii): Dose of methohexitone

Campbell et al (1976) stated that: *There appeared to be no relationship between total methohexital dose and the incidence of tachycardia.*

1-7-6b(iv): Pain of surgery

Reports of tachycardia due to surgical stimulation indicate that methohexitone offers no protection against the pain of extractions (Christenson et al 1961; Rollaston 1967, 1971; Shafto 1969; Ryder 1970) or the pain of cavity preparation (Mann et al 1971; Foreman 1974a; Southwell 1976).

As would be expected therefore, smaller increases in heart rate have been reported in studies investigating the supplementation of methohexitone with intravenous analgesics and/or local analgesics (Elliott et al 1974; Campbell et al 1976).

1-7-6b(v): Use of atropine

Atropine will cause tachycardia (Clarke et al 1964) and its use with methohexitone may be a contributing cause to observed increases in heart rate (Campbell et al 1976). Atropine has been shown to be safer in this respect than scopolamine (Everett & Allan 1970).

Mann et al (1971) did not blame atropine for the increases they measured. Wise et al (1969) found no difference between patients who received atropine and those who did not. (Atropine is discussed more fully in Section 1-11-5.)

1-7-6b(vi): Marijuana

Although numbers were small, Campbell et al (1976) found a relationship between marijuana smoking and tachycardia (see Section 1-9-7h(ii)).

1-7-6c: Significance of tachycardia

Shafto (1969) would not give the M.I.T. an unqualified recommendation till the significance of the observed tachycardia was evaluated.

Allen et al (1969) measured an increase in cardiac output as a result of the increased heart rate.

Ryder (1970) warned that tachycardia, produced by repeated doses of methohexitone, may lead to ultimate heart failure.

Holmes (1976) discusses these implications further.

1-7-6d: Studies reporting changes in heart rate

In Table 7-14 below, I have attempted to summarise the results of those studies reporting changes in cardiac rate following the administration of methohexitone. The Table is divided into five parts:

1. No surgery, no premedication.
2. No surgery, analgesic premedication.
3. Surgery, no premedication.
4. Surgery, atropine premedication.
5. Surgery, analgesic premedication.

TABLE 7-14: STUDIES REPORTING CHANGES IN HEART RATE									
NAME	NO.	PREMED	SURG	CARDIAC RATE		HOW MEASURED	METHOHEX DOSE	AUTHOR/S COMMENTS	MY COMMENTS
				% CHANGE FROM NORM	ACTUAL b/m				
PART 1									
Savege et al (1972)	6	0	0	14.5% ↑	$\bar{x} = 69 \rightarrow 79$	ECG	1.8mg/Kg	signif.increase compared to althesin or thiopentone	As dose increases so does %age in-crease in rate
Korttila et al (1975)	10	0	0	33% ↑		Radial Pulse	2mg/Kg		
Wyant et al (1957)	5	0	0	40% ↑		ECG	$\bar{x} = 480\text{mg}$	Rate reduces to 23% above after 90 seconds	
PART 2									
Everett & Allen (1970)	9	+	0	14% ↑ then 30% ↓		ECG	By 10mg increments	Rise & fall $\rho < 0.05$ Shane technique (+ L.A. too)	Higher dose has higher % increase
Dobkin & Wyant (1957)	7	0	0	36% ↑		ECG	$\bar{x} = 273\text{mg}$ per sq.M		

TABLE 7-14 (continued)

NAME	NO.	PREMED	SURG	CARDIAC RATE		HOW MEASU-RED	METHOHEX DOSE	AUTHOR/S COMMENTS	MY COMMENTS
				% CHANGE FROM NORM	ACTUAL b/m				
PART 3									
Allen et al (1969)	18	0	Exo	40%	↑	ECG	$\bar{x} = 310\text{mg}$	Increase $\rho < 0.001$ increase levels off (N ₂ O + O ₂ too)	High Dose Children Shows Effect of Surgery Children
Ryder (1970)	28	0	Exo	54%	↑	ECG	1.3-1.5mg/Kg induction Total = 30-160mg	Increase $\rho < 0.01$ compared to alternative techniques	
Shafto (1969)	500	0	Exo		↑	ECG (on 30 only)	1.1-1.57 mg/Kg	Constant marked tachycardia	
PART 4									
Mann et al (1971)	516	Atrop. only	Fills	36.6%	↑	ECG	0.8-1.3mg/Kg induction + increment	Increases $\rho < 0.001$ compared to L.A. only	High Doses + Atropine (?)
Wise et al (1969)	30	25 = 0 5 atrop.	Fills		↑	ECG	$\bar{x} = 460\text{mg}$	No diff.between atropine & no atropine	

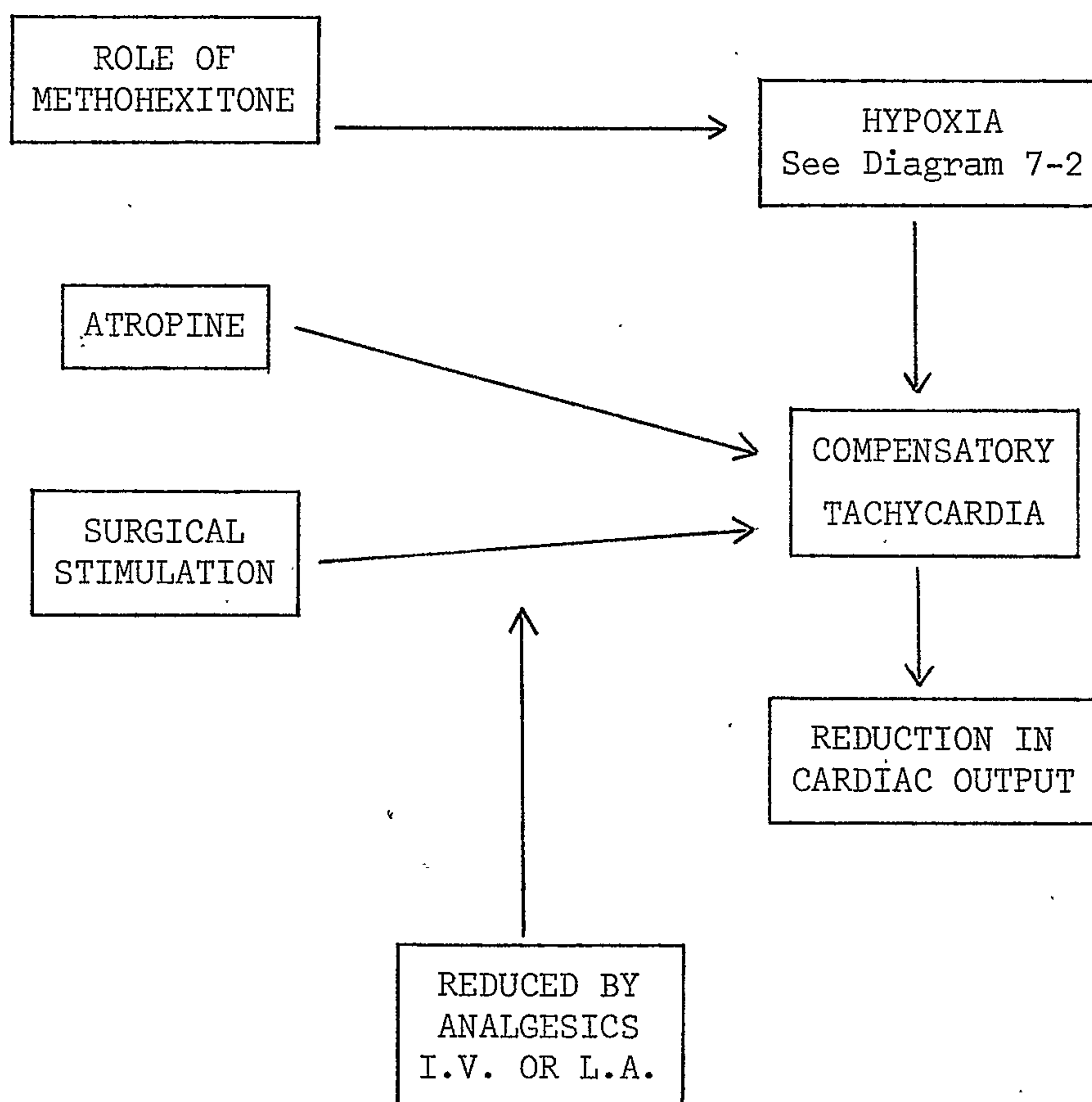
TABLE 7-14 (continued)

TABLE 7-14 (continued)

NAME	NO.	PREMED	SURG	CARDIAC RATE		HOW MEASURED	METHOHEX DOSE	AUTHOR/S COMMENTS	MY COMMENTS
				% CHANGE FROM NORM	ACTUAL b/m				
PART 5									
Myers & Coltman (1961)	1500	+	Exo	0	↓	Unchanged or reduced	$\bar{x} = 100\text{mg}$ max = 200mg	Sedation reduced rate	Premed reduces inc-rease except where metho. dose high ←High dose
Foreman (1974d)	30	+	Fills Exo		↑	Increase by $\bar{x} = 15$	$\bar{x} = 81\text{mg}$ (19-180)mg	Premed = diazepam ($\bar{x} = 19\text{mg}$) increase only temporary.	
Elliott et al (1974)	800	+	Exo		↑	≤ 120	0.294mg/Kg each 30sec	ECG not recording during procedure	
								Innovar premed + L.A.	
Christenson et al (1961)	36	some +	Exo		↑	91% > 120	$\bar{x} = 262\text{mg}$	3% preop. tachycardia due to apprehension	
Campbell et al (1976)	10	+	Exo	5-56% (range of $\bar{x}$)	↑		20mg each 30 sec	Fentanyl & diazepam premed + L.A.	

1-7-6e: Conclusions

1. Higher observed increases in heart rate are correlated with high dosage.
2. Dosage seems to be the most important factor.
3. I have summarised the findings in Diagram 7-3 below:

DIAGRAM 7-3: CAUSE AND EFFECT OF TACHYCARDIA

1-7

ACTION ON ORGAN SYSTEMS

1-7-7

ACTION ON CARDIOVASCULAR SYSTEM

II. ARRHYTHMIAS

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1-7-7: ARRHYTHMIAS

1-7-7a: Introduction

Arrhythmias may be caused by hypercarbia, hypoxia, respiratory depression, respiratory obstruction, coughing and gagging.

As methohexitone may cause one or more of these complications, it is important to investigate the incidence of arrhythmias reported from dental treatment under methohexitone.

Some agents may provoke sympathoadrenal response and an increase in circulating catecholamines leading to arrhythmias.

The clinical significance of arrhythmias during anaesthesia may have been exaggerated, although their occurrence should be noted and efforts made to correct them (Tolas et al 1967).

1-7-7b: Causes

1-7-7b(i): Increase in circulating endogenous catecholamines

1. Induction

Induction of anaesthesia releases endogenous circulating catecholamines. This may have been the cause of arrhythmias observed by Tolas et al (1967) during induction with nitrous oxide, oxygen and halothane.

2. Fear

Apprehension releases endogenous circulating catecholamines. Rollason (1967) and Magnus (1975a, 1975b) each describe a case of a nervous, but otherwise fit patient developing an arrhythmia under methohexitone.

Tomlin (1974a) describes a death (his case S20) due to adrenalin induced arrhythmia caused by apprehension and needle puncture.

3. Halothane sensitises heart to circulating catecholamines

Fisch et al (1969) observed a 42.7% incidence of arrhythmias during oral surgery under methohexitone, nitrous oxide, oxygen and halothane. They blamed halothane because it is thought to sensitise the heart to the increased action of circulating catecholamines resulting from surgery.

1-7-7b(ii): Arrhythmias caused by trigeminal nerve stimulation

Handling the trigeminal nerve, as during section of its root, will produce cardiac irregularities (Annotations 1966).

Dental extractions may produce arrhythmias because of trigeminal nerve stimulation.

Kaufmann (1965) reported on the incidence of arrhythmias in cardiac patients receiving nitrous oxide, oxygen and halothane for extractions. Arrhythmias were not observed during induction, but during extraction were . . . *so predictable that it was possible to tell when an extraction was being performed by looking at the E.C.G. monitor.*

Arrhythmias were not observed during maxillary extractions if the trigeminal nerve was first blocked by local analgesia. However, mandibular extractions continued to produce arrhythmias possibly because it is more difficult to achieve good local analgesia in the mandible.

1-7-7b(iii): Hypoxia causes arrhythmias

Arrhythmias may be secondary to hypoxia (Ryder 1970; Spiro et al 1975), and Bell (1975b) states: *Cardiac arrhythmias are fascinating,*

but are too good an excuse for side-tracking.

Bell (1975a) thought that the case described by Magnus (1975a, 1975b) could have been caused by a near terminal asphyxia.

1-7-7c: Barbiturates may offer protection against arrhythmias

Barbital stops cardiac irregularities in dogs, caused by ephedrine (Tatum 1939). Such action may be due to vagal and autonomic centre depression.

Tolas et al (1967) observed arrhythmias with gaseous induction, but not with thiopentone induction. They reviewed the literature and concluded that intravenous barbiturates reduce the incidence of arrhythmias..

1-7-7d: Incidence

Ryder (1970) compared various forms of general anaesthesia or local analgesia for dental surgery. The results are summarised in Table 7-15.

TABLE 7-15: SUMMARY OF RESULTS OF RYDER (1970)			
TYPE OF ANAESTHETIC	NO.	INCIDENCE ARRHYTHMIA	
		NO.	%
Gaseous	215	71	33.02
L.A. only	97	9	9.2
Methohexitone only	28	0	0

He commented: *The complete absence of arrhythmias with methohexitone is striking.*

I conducted a chi-squared test on these results and found them highly significant ($\chi^2 = 30.31$, $0.001 > p$) even if the L.A. only group is omitted ($\chi^2 = 13.11$, $0.001 > p$).

Mann et al (1971) compared incremental methohexitone to local analgesia for conservative dentistry. Their results are summarised in Table 7-16 below.

TABLE 7-16: RESULTS OF MANN ET AL (1971)			
TREATMENT	TOTAL	ARRHYTHMIA INCIDENCE	
		NO.	%
Methohexitone	462	10	2.2
L.A. only	88	4	4.6

Their results are not significant ($\chi^2 = 1.683$, $p > 0.1$).

Table 7-17 below lists those studies which used E.C.G. monitoring equipment and therefore were in a position to record arrhythmias.

The studies are ranked in decreasing order of methohexitone dosage.

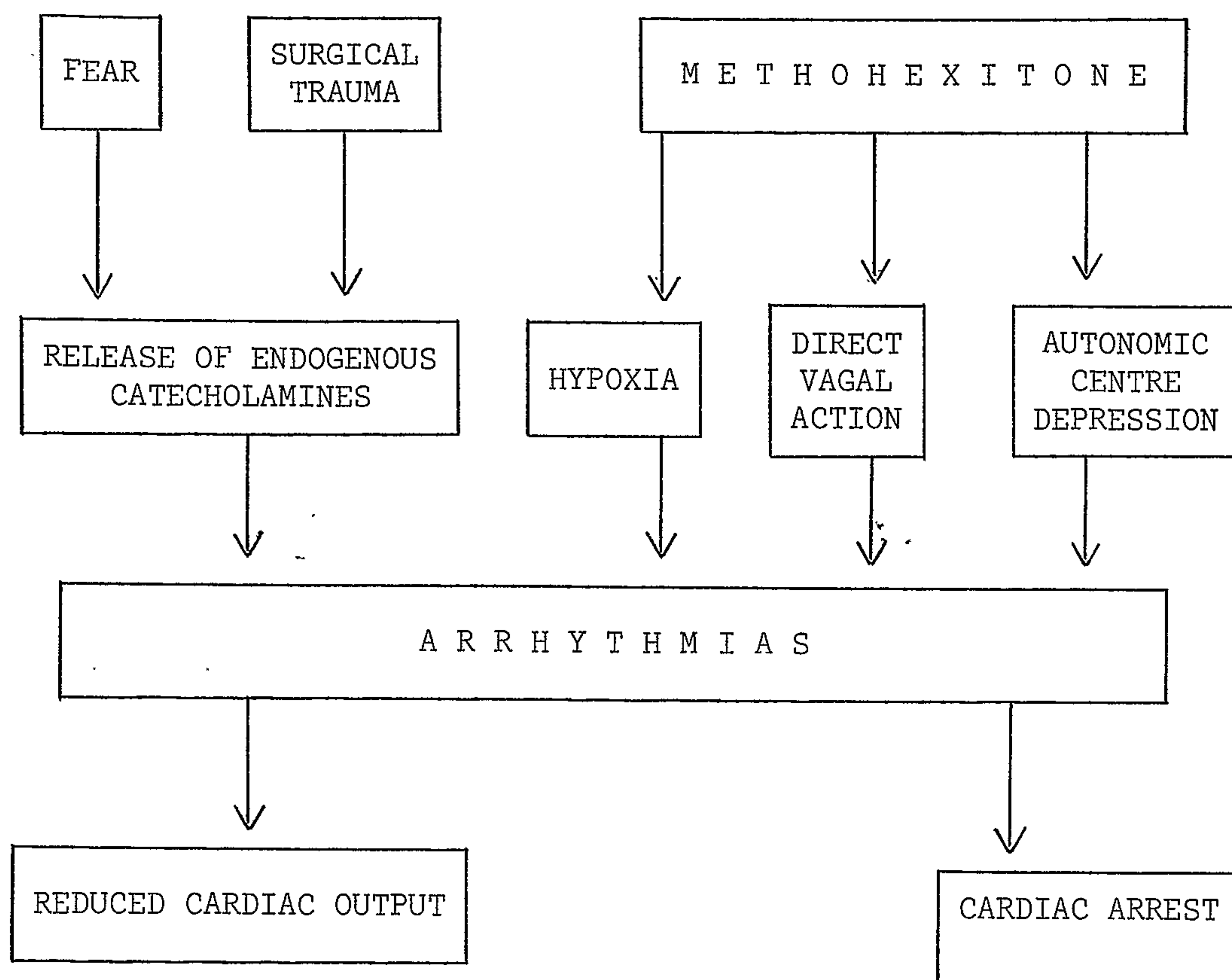
TABLE 7-17: INCIDENCE OF ARRHYTHMIAS							
NAME OF STUDY	NO.	DOSE METHO- HEXITONE	PRE MED	HALO- THANE	SURG.	INCIDENCE ARRHYTHMIA %	COMMENTS
Wyant et al (1957)	5	$\bar{x}$ = 480mg	0	0	0	0	
Wise et al (1969)	30	$\bar{x}$ = 460mg	0	0	Fills	0	
Allen et al (1969)	18	$\bar{x}$ = 310mg	0	0	0	0	
Dobkin & Wyant (1957)	7	Double sleep	0	0	0	0	
Savege et al (1972)	6	1.8mg/Kg	0	0	0	0	
Ryder (1970)	28	1.3-1.5mg/Kg Total 30-160mg by increment	0	0	Exo	0	Children
Shafto (1969)	500	1.1-1.5mg/Kg incr.	0	0	Exo	0	Children
Mann et al (1971)	462	0.8-1.3mg/Kg incr.	0	0	Fills	2.2	
Ryder (1970)	13	1.3-1.5mg/Kg	0	+	Exo	30.75	Children
Fisch et al (1969)	103	?	0	+	Exo	42.7	
Elliot et al (1974)	800	0.294mg/Kg per 30 sec	+ +LA	0	Exo	1 only	

1-7-7e: Discussion of Table 7-17

1. There is a higher incidence of arrhythmias with lower dosages of methohexitone.
2. Elliott et al (1974) recorded one patient out of 800 who had a premature ventricular contraction, otherwise there were no abnormal readings. All patients had oral surgery performed under incremental methohexitone; but all were premedicated with Innovar, extra fentanyl or morphine, and most had local analgesia.

1-7-7f: Conclusions

1. Methohexitone may offer protection against arrhythmias, but probably at the expense of myocardial depression due to high dosage.
2. Supplementation with halothane will increase the incidence.
3. By reducing the pain associated with surgery, local analgesia will help to reduce the incidence of arrhythmias.
4. Premedication, by reducing fear, may reduce the incidence.
5. In Diagram 7-4 below, I have summarised the findings.

DIAGRAM 7-4: SUMMARY OF CAUSES AND EFFECTS OF ARRHYTHMIAS

1-7

ACTION ON ORGAN SYSTEMS

1-7-8

ACTION ON CARDIOVASCULAR SYSTEM

III. CARDIAC OUTPUT

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1-7-8: EFFECT OF METHOHEXITONE ON CARDIAC OUTPUT

1-7-8a: Introduction

Cardiac output is a function of stroke volume and heart rate. Dye dilution techniques have been used to measure changes in cardiac output following the administration of methohexitone to fit young adults.

In Table 7-18 below, these studies are listed.

TABLE 7-18: EFFECTS ON CARDIAC OUTPUT

NAME	NO.	DOSE	PRE MED	WORK	HOW C.O. MEASU- RED	EFFECT ON C.O.	SIGNIFI- CANCE	EFFECT ON STROKE VOLUME	SIGNIFI- CANCE	PULSE	COMMENTS
Everett & Allen (1970)	9	10mg twice	+	0	Dye	↓ 21%	0.01 > ρ	↑ 20%	0.01 > ρ	Up then DOWN	C.O. rose after pre- med (Shane technique) then fell after 2nd methohex.
Dobkin & Wyant (1957)	7	2 x sleep dose $\bar{x} = 273$ mg/M ²	0	0	¹³¹ I	↓ 15%	Not	↓ index 34%	0.01 > ρ	Up	
Savege et al (1972)	5	1.8mg/Kg	0	0	Dye	(↑)	Not	↓ 21%	0.01 > ρ	Up	
Allen et al (1969)	18	$\bar{x} = 310$ mg (incre- ments)	0	0	Dye	↑ 16%	0.05 > ρ	↓ 20%	0.001 > ρ	Up	
Wise et al (1969)	6	$\bar{x} = 460$ mg (incre- ments)	0	Fills	Dye	↑ (index 100%)	?	?	?	Up	Basal levels only measured in three

1-7-8b: Discussion of Table 7-18

Three studies recorded significant reductions in stroke volume whilst cardiac output did not change significantly from basal measurements.

It would appear that, in the presence of a reduced stroke volume, cardiac output is maintained by an increase in heart rate.

The results of Everett & Allen (1970) are not in accord with this observation. Their results must be judged on the basis that premedication with alphaprodine, hydroxyzine and scopolamine was given, followed by only small doses of methohexitone.

The results of Wise et al (1969) were incomplete since basal measurements were made in only three cases.

Savege et al (1972) discussed the observations of Allen et al (1969) and Wise et al (1969) and concluded that the rise in cardiac output reported may have been due to hypoxia.

1-7-8c: Reasons for decreased stroke volume under methohexitone

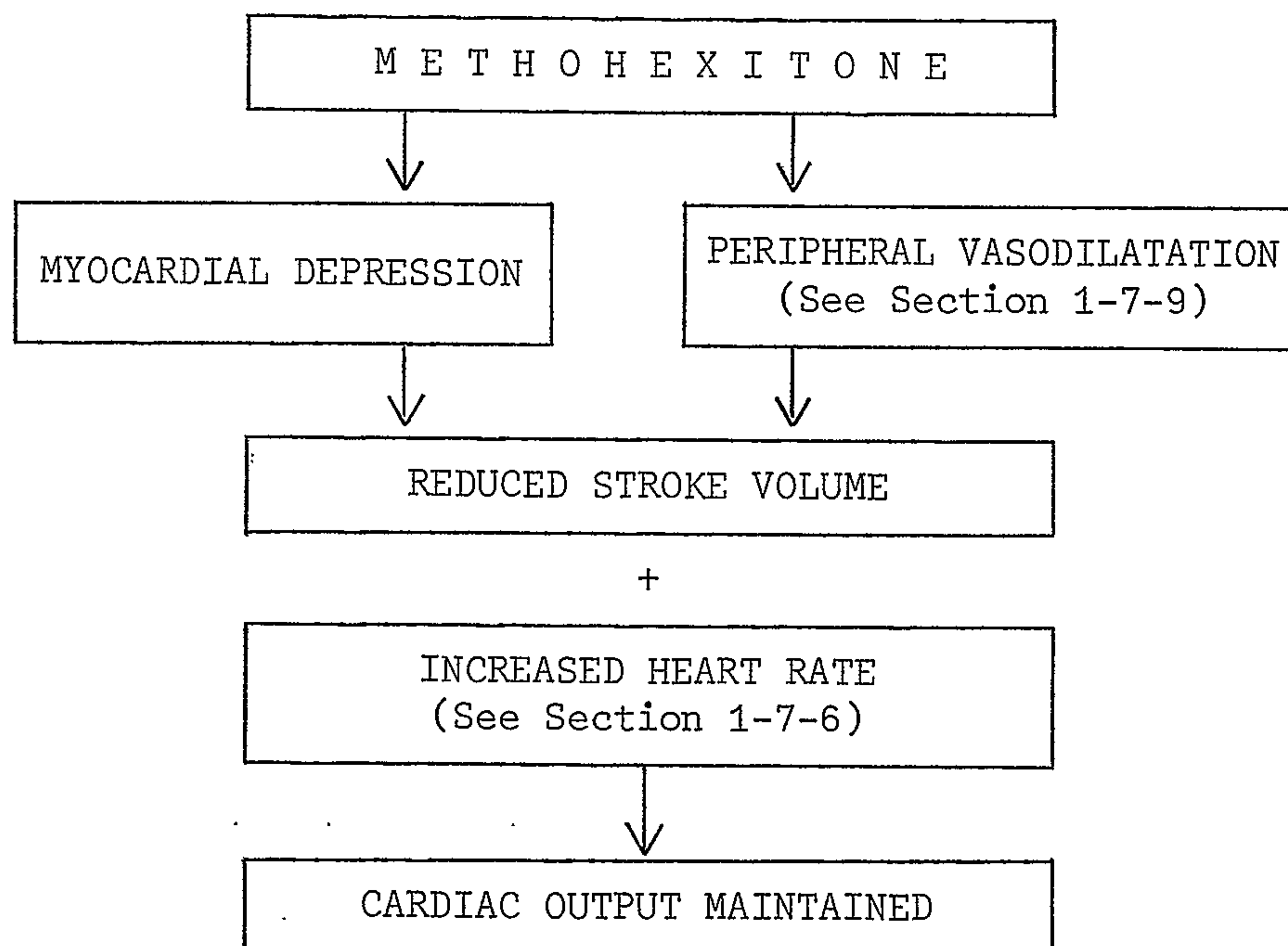
Table 7-19 below lists reasons given for observed reductions in stroke volume. The authors have come to their conclusions either by reviewing the literature or from their own work.

TABLE 7-19: CAUSES OF REDUCED STROKE VOLUME		
NAME OF STUDY	CONCLUSION DERIVED FROM	CAUSE OF REDUCED STROKE VOLUME
Dobkin & Wyant (1957) Conway & Ellis (1969)	Review Literature	Direct Myocardial Depression
Rowlands et al (1967) Dormandy & Bullough (1969) Savege et al (1972)	Own Study	
Conway & Ellis (1969) Spiro et al (1975)	Own Study	Decreased venous re- turn due to peripheral vasodilatation

1-7-8d: Conclusion

In Diagram 7-5 below, I have summarised my conclusions.

DIAGRAM 7-5: EFFECT OF METHOHEXITONE ON CARDIAC OUTPUT



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ACTION ON ORGAN SYSTEMS

1-7-9

ACTION ON CARDIOVASCULAR SYSTEM

IV. PERIPHERAL RESISTANCE

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1-7-9: EFFECT ON PERIPHERAL RESISTANCE1-7-9a: Reported changes

In Table 7-20 below, I have listed those studies that have measured changes in peripheral resistance following the administration of methohexitone.

TABLE 7-20: EFFECT ON PERIPHERAL RESISTANCE						
NAME OF STUDY	NO	DOSE	PREMED	WORK	HOW MEASURED	EFFECT ON PERIPHERAL RESISTANCE
Wise et al (1969)	30	Mean = 460mg	0	Cons.	p*	↓
Foreman (1974a)	30	?	+		p*	↓
Allen et al (1969)	18	Induct 1mg/Kg Up to 310mg	0	Exo.	Direct	↓ Significant
Dormandy & Bullough (1969)	18 No vascular disease	? sleep dose	+	Various	Direct: 89% incr. in leg blood flow	↓
Dormandy & Bullough (1969)	5 lumbar sympathectomy	sleep dose	+	Various	decreased leg blood flow	↑ 4 patients
Everett & Allen (1969)	9	2 x 10mg	+	0	Direct	↑ After initial 13% drop due to premed

* plethysmograph

1-7-9b: Discussion

The results of Dormandy & Bullough (1969) suggest that methohexitone causes peripheral vasodilatation by an action on the sympathetic system.

Chambiras (1970c) and Foreman (1974a) have suggested that pre-operative anxiety causes peripheral vasoconstriction which then becomes less under sedation.

Allen et al (1976) found that diazepam lowers peripheral resistance and stroke volume. They suggest that, *if diazepam is used in combination with methohexitone consideration should be given to the additive effects on total peripheral resistance* (see also Section 1-11-6h(ix)).

1-7-9c: Conclusion

See Section 1-7-12.

1-7

ACTION ON ORGAN SYSTEMS

1-7-10

ACTION ON CARDIOVASCULAR SYSTEM

V. BLOOD PRESSURE

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1-7-10a: Introduction

The following changes have been found:

1. On induction a sharp fall occurs which quickly rises to near basal levels.
2. During maintenance, elevations are seen, possibly due to painful stimuli.
3. Postoperative hypotension.

Each of these changes is discussed below.

1-7-10b: Initial fall in Blood Pressure

1-7-10b(i): Patient Health Status

Thornton (1970) reviewed the literature and concluded that hypertensive patients will have the most dramatic falls in blood pressure under methohexitone.

Green & Jolly (1960) reported that the largest falls in systolic pressure they observed on induction were in patients whose initial systolic was above 170 Torr.

1-7-10b(ii): Initial fall in B.P. due to anxiety

Several authors have observed that the greatest falls in B.P., on induction, occur in more anxious patients (Whitwam & Young 1964; Pollard 1969; Foreman 1974a).

However, Savage et al (1972) feel that reduction in anxiety is an unlikely cause. They were able to achieve similar results after each maintenance dose of methohexitone, when the patient is more relaxed.

1-7-10b(iii): Premedication as a cause of initial B.P. Drop

Taylor & Stoelting (1960) used morphine or pethidine prior to induction with methohexitone. Following induction they recorded falls in the systolic pressures by as much as 40 Torr. They comment: *No period of severe hypotension could be attributed to methohexital.*

Dundee (1963) compared 300 patients premedicated with pethidine to 300 who were not. Upon induction of methohexitone those who received pethidine had a greater hypotensive effect.

However, Lyon (1961) used pethidine, nitrous oxide and oxygen to supplement methohexitone and found that, *Excursions in systolic and diastolic blood pressures were well within the limits* (also see Section 1-11-6f).

1-7-10b(iv): Initial fall in B.P. due to depression of vasomotor tone

Dobkin & Wyant (1957) suggested that the initial fall in B.P., on induction, is due to a primary depression of vasomotor tone and is corrected, in part, by reflex restoration.

The results of Shovsted et al (1970) tend to support this observation. They studied inhibition sympathetic activity in cats under barbiturates. Despite depression of sympathetic activity, the barostatic reflexes remained intact (see Section on peripheral resistance, 1-7-9).

1-7-10b(v): Rapid induction as a cause of initial B.P. drop

Following from the above argument, it would seem that rapid inductions should produce the greatest falls in B.P.

Such observations have been made by Stoelting (1957) and Recant (1960).

Redish et al (1958) were able to demonstrate that a slow induction could produce a rise in blood pressure. However, Whitwam & Young (1964) could not correlate falls in blood pressure with speed of injection or dosage of methohexitone.

Nevertheless, in his review of barbiturates, Tatum (1939) warns against rapid inductions, and Thornton (1970) and Trieger (1976) discuss this topic further.

1-7-10c: Surgical stimulus causes rise in B.P.

Recant (1960) noted that whenever a pain stimulus was applied during extractions under methohexitone, marked elevations of systolic pressure occurred. He did not see these changes if local analgesia was also used.

Whitwam & Young (1964), Shafto (1969), Wise et al (1969) and Campbell et al (1976) observed similar elevations. In the latter study, these observations were made despite premedication with fentanyl and diazepam.

Christenson et al (1961) suggest that it is the very lightness of unsupplemented methohexitone which allows such elevations in blood pressure.

1-7-10d: Post operative hypotension

Despite a return to consciousness and apparent full recovery, post operative hypotension has been observed by several authors (Egbert et al 1959; Whitwam & Young 1964; Allen et al 1969; Wise et al 1969;

Everett & Allen 1970).

However, Foreman (1969b) says that it would be surprising if patients treated with any method for long periods of time in the supine position did not exhibit some degree of orthostatic hypotension on being asked to stand. He feels that the cases mentioned by Wise et al (1969) may have been due to excessive dosage of methohexitone.

1-7-10e: Studies that have measured B.P. changes

In Table 7-21, I have summarised the main findings of studies that have measured changes in blood pressure following the administration of methohexitone.

The Table is set out as follows:

PART A: No surgery, $\pm$ premedication

PART B: Surgery, no premedication

PART C: Surgery, + premedication

TABLE 7-21: BLOOD PRESSURE CHANGES										
AUTHOR	NO.	DOSE	ANAL- GESIC PREMED	TYPE OF SURG	HOW BP MEASU- RED	EFFECT ON B.P.			AUTHOR/S COMMENTS	MY COMMENTS
						After Induct	During Surg.	Reco- very		
P A R T A										
Everett & Allen (1970)	9	2. x 10mg	+	0	Direct	↓	↓	↓	Drop = progressive & significant	Sitting
Savege et al (1972)	6	1.8mg/Kg	0	0	Direct	0	↓	↓	Initial fear → sympathetic burst = higher BP readings	Supine
Egbert et al (1959)	14	Induct x̄ = 92mg Total x̄ = 186mg	0	0	Sphyg	↓ slight	0	↓	2 postop. readings = 80/60 Torr Danger of postop. hypotension	No further details Supine
Dobkin & Wyant (1957)	7	2 x sleep dose x̄ = 273mg per M ²	0	0	Direct	↓	↓	↓	Falls not significant	(?) Sitting
Korttila et al (1975)	10	2mg/Kg	0	0	Sphyg	0	0	0	Greatest decrease systolic = 13 ± 4 Torr	Supine
Wyant et al (1957)	5	x̄ = 480mg	0	0	Direct	↓	↑	?	Only diastolic ↑ Initial systolic drop > 20%	Coughing upset recordings Supine

TABLE 7-21 (continued)

AUTHOR	NO.	DOSE	ANAL- GESIC PREMED	TYPE OF SURG	HOW BP MEASU- RED	EFFECT ON B.P.			AUTHOR/S COMMENTS	MY COMMENTS
						After Induct	During Surg.	Reco- very		
P A R T B										
Goldman & Harris (1963) Series I	525	0.69 mg/Kg	0	Exo	Sphyg	0	0	0	Less than 10% fell by 20 Torr	Sitting
	150	1.04 mg/Kg	0	Exo	Sphyg	0	0	0	" " "	"
Weinstock (1960)	30	Total 50-380mg	0	Fills	Sphyg	0	0	0	Max. change by 25 Torr. Not significant	Position ?
Allen et al (1969)	18	Induct 1mg/Kg Max = 310mg	0	Exo	Direct	0	↓	0	Mean art. press. fell near end in 15% cases	Progressive fall in BP Sitting
Mann et al (1971)	457	Induct 0.8-1.3 mg/Kg	0	Fills	Digital	↓	↓	0	43.2% no change on induction. 40% no change on maintenance	Digital readings not so accurate Supine
Recant (1960)	2500	Induct x = 70mg Total max = 640mg	0	Fills	Sphyg	↓	↑	?	Elevation due to pain	Sitting,
Whitwam & Young (1964)	95	1.39- 1.91 mg/Kg	0	Exo	Sphyg	↓	↑	0	Elevation due to pain	Sitting

TABLE 7-21 (continued)

AUTHOR	NO.	DOSE	ANAL- GESIC PREMED	TYPE OF SURG	HOW BP MEASU- RED	EFFECT ON B.P.			AUTHOR/S COMMENTS	MY COMMENTS
						After Induct	During Surg.	Reco- very		
P A R T B										
Wise et al (1969)	30	200-825mg $\bar{x}$ = 460mg total	0	Fills	Direct	↓	↑	↓	25% of falls by > 20 Torr. 60% of rises by > 20 Torr	Supine
P A R T C										
Elliott et al (1974)	100	0.294 mg/sec	+	Exo	Sphyg	?	?	↓	3 had ortho- static hypotension	only took pre & post BP Semi Supine
Stoelting (1957)	285	Induct $\bar{x}$ = 70mg max = 2000mg	+	V	Sphyg	↓	0	0	4 systolic drop- ped by > 20 Torr No diastolic change	Supine
Taylor & Stoelting (1960)	3340	$\bar{x}$ = 70mg induct	+	V	Sphyg	↓	0	0	133 systolic drop by 30-40 Torr 401 by 10-20 Torr	Supine
Lyon (1961)	513	$\bar{x}$ = 127.05mg Induct	+	Fills	Sphyg	0	0	0		Supine
Levin H.A. (1975)	25	Max range 100-975mg	+	Fills	Sphyg	0	0	0	Greatest systolic change by 18 Torr	No details Semi Supine

TABLE 7-21 (continued)

AUTHOR	NO.	DOSE	ANAL- GESIC PREMED	TYPE OF SURG	HOW BP MEASU- RED	EFFECT ON B.P.			AUTHOR/S COMMENTS	MY COMMENTS
						After Induct	During Surg.	Reco- very		
P A R T C										
Southwell (1976)	< 20	Up to 200mg	+	Fills	Sphyg	0	↑	0	Elevation due to pain One up by 30 Torr	Despite L.A. Lack of detail Supine
Douglas (1960)	95	$\bar{x}$ = 130mg	+	Fills	Sphyg	↑	↑	↑ (?)	Children <i>mild rise</i>	No details Supine
Christenson et al (1961)	127	$\bar{x}$ = 132mg Induct	+	Exo	Sphyg	0	↑	0	Elevation due to pain	Sitting

Key to Abbreviations

Direct = Arterial B.P. measured directly via
arterial cannula

Sphyg = Arterial B.P. measured by sphygmomanometer

Digital = Digital blood pressure used to detect
changes in B.P.

V = General surgery

1-7-10f: Discussion of Table 7-21

1-7-10f(i): Part A - No surgery carried out

The studies are ranked in increasing dosage of methohexitone.

The general observation was that, following induction, a reduction in blood pressure occurred and lasted into the recovery period.

Everett & Allen (1970) observed the most significant falls. Whilst they used the least methohexitone, they gave analgesic premedication with alphaprodine and hydrazine.

1-7-10f(ii): Part B - Surgery carried out, no premedication

The studies are ranked in increasing dosage of methohexitone.

The general observation was that following induction, an initial drop in blood pressure occurred. In some cases, elevations in systolic pressure were observed during maintenance and were correlated with the pain of surgery.

1-7-10f(iii): Part C - Surgery carried out, premedication

The studies are ranked in increasing dosage of methohexitone.

Analgesic premedication, including the use of local analgesics, may not offer protection against the pain of surgery.

The use of premedication does not appear to have produced a trend of reduced blood pressure readings, but this may be due to a lack of detail in some of the studies.

1-7-10g: Conclusions

Because of the variation in detail and methods of measurement in the studies, I find it difficult to draw any conclusions apart from the fact that:

1. An initial drop occurs which may be lessened by slow induction.
2. Elevations due to surgical stimuli may be reduced by the use of local analgesia.
3. One must be aware of the possibility of post operative hypotension.
4. Patients should be treated supine (this is further discussed in Sections 1-7-11 and 1-10-8).

Goldman & Harris (1963) state, *dangerous falls in B.P. are unlikely to occur when intravenous induction is employed in experienced hands in the dental chair.*

Thornton (1971) says that the blood pressure changes he observed with Mann et al (1971) were of no great clinical significance for patients in the recumbent position.

5. Fainting is discussed in Section 1-7-11.

1-7

ACTION ON ORGAN SYSTEMS

1-7-11

ACTION ON CARDIOVASCULAR SYSTEM

VI. FAINTING

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1-7-11: FAINTING1-7-11a: Introduction

Bourne (1957) warned of the dangers of anaesthetising patients in the upright position. Bourne (1967i, 1967o) discusses syncope and fainting. Syncope will develop if the blood pressure drops below 50 Torr at heart level.

It is dangerous to administer any anaesthetic drug to a patient sitting upright because of the possibility of a faint occurring after the commencement of induction. The faint will be unrecognised.

If a person who faints is kept upright, he may die or his brain may be permanently damaged due to cerebral anoxia following a decrease in blood flow through the brain.

Death could occur (Mehta 1974; Brunnen 1975) and irreversible brain damage can result from as little as two and one half minutes of cerebral circulatory arrest. Such damage would be seen as a delayed recovery and a disturbance of consciousness lasting several hours.

Even in less severe cases, the brain may have received permanent neuronal damage which may not be immediately obvious to the observer, or even to a relative of the patient (see also Section 1-7-5e).

1-7-11b: Upright position considered safe

Following the report by Bourne (1957), Goldman et al (1958) took regular blood pressure readings before, during and after 100 dental extractions with nitrous oxide and oxygen in the upright position. They found no syncope and assumed that this must be so rare as not to be a cause of great alarm. They state: *This is a comforting thought*

because it confirms the safety of the practice of a hundred years' use of the sitting position, which in experienced hands does not increase the patient's risk of postoperative sequelae.

Allen et al (1969) investigated the cardiorespiratory effects of incremental methohexitone, and nitrous oxide and oxygen, in 18 healthy adults undergoing oral surgery in the 45 degree position. They commented: . . . *we feel that the hazard of sitting in the chair is less than standing up beside it giving the anesthetic.*

Wilson D.S. (1970) states: *I personally prefer the sitting up position, as any hypotension incurred in this position is due to overdosage or hypoxia rather than by the position.*

Evans (1974) has given between 400-800 dental anaesthetics annually in the upright position for thirty years; he has only once seen a faint. He does not dispute the potential added safety of the horizontal position, but by stressing its safety, the emphasis may be put in the wrong place. Patients must be protected from the stresses causing faints.

Kurer (1975) warns that the supine position alone cannot prevent all cardiovascular emergencies. The signs of deterioration of the effectiveness of heart action can be delayed until it has advanced much further than would be observed in a seated patient - but he does not recommend a return to the seated position.

The upright position is reviewed in Section 1-10-8. The role of the upright position in deaths is discussed in Section 1-13-5b.

1-7-11c: Cases of fainting under methohexitone

Young & Whitwam (1964a) reported that four patients who were sitting up, fainted on presentation of the needle or shortly after induction was commenced.

Attwood (1964) had a 28 year old man sitting upright, venepuncture was performed, but injection of methohexitone was stopped after only 20mg had been administered as a fault was noticed with the equipment. No further drug was given. The patient fainted. Had the administration continued, the faint would have been masked by the induction.

Williams (1964) gave 70mg methohexitone to a healthy 29 year old male for an extraction. The patient was sitting upright. He immediately stopped breathing and went an ashen colour. The patient quickly recovered once placed supine.

Shafto (1969) reports a case of hypotensive collapse following fainting during venepuncture. The patient was immediately placed supine. When he was sufficiently recovered he was induced again, and he collapsed once more. External cardiac massage was necessary, but recovery was uneventful. The patient said he had not eaten for 22 hours and this may have been a factor.

Litchfield & Gerard (1971) report that two patients out of 1,557 cases (involving diazepam and/or methohexitone) experienced syncope with injection.

The S.A.A.D. survey of 445,386 administrations of methohexitone by experienced operators states an incidence of fainting as 0.033% (Drummond-Jackson 1971d).

Young (1974) anaesthetised 236 patients in the upright position. There were two cases of syncope at the start and one on recovery. He says: *We now anaesthetise all dental outpatients in the supine position . . .*

1-7-11d: Repeated fainting

The tendency to faint again may last for several hours, once one attack has occurred, as in the case reported by Shafto (1969). In these cases it is best to postpone treatment (Bourne 1967o, 1974a, 1974b).

Forsyth et al (1972) describe three patients who experienced multiple fainting episodes in the sitting position under methohexitone.

Hannington-Kiff (1969) conducted a survey, over a period of three months, of patients treated in the oral surgery clinic of a large hospital.

Of the 3,000 patients treated with local analgesia and sitting up, 2% fainted; 50% of those who fainted had a previous history.

Galley (1966) anaesthetised 8 known fainters with methohexitone in the upright position. Six showed no signs of hypotension, but 2 felt faint during recovery and their blood pressures had dropped 20-25 Torr.

Pollard (1969) suggests that in known fainters, and for very anxious patients, diazepam should be given 30 minutes before treatment.

Coplans (1962) questions all patients for a history of fainting and is wary of them. He also suggests that pressure on the soft tissues over the carotid sinus may produce a fainting attack. He advised that

when supporting the jaw, the hands be placed on the mandible only

1-7-11e: Discussion

Pownall (1966) compared 2,500 anaesthetics administered in the horizontal position with previous experience of 2,500 administered in the upright position. There were no incidents in the former, but *several anxious moments* in the latter.

Forman (1971) noticed that when he changed over to seated dentistry on the supine patient, he observed at once that a smaller dosage of methohexitone was needed, yet relaxation was greater.

Jorgensen & Hayden (1972b) always used the supine or semisupine position and have never observed fainting.

Young (1974) anaesthetised 236 patients in the upright position and had to treat 11 cases of syncope. He says, . . . *we now anaesthetise all dental outpatients in the supine position . . .*

O'Brien (1974) says that the supine position does reduce the incidence and complications of fainting and more serious forms of circulatory attack.

Holmes (1976) discusses cardiac patients, and prefers the supine position because it will drastically reduce fainting.

1-7-11f: Conclusions

1. Patients with a history of fainting should be monitored carefully.
2. All patients should be treated supine. The advantage of this position is readily seen in the case histories presented above - in each case of fainting in the upright position the patient had to be placed horizontal.

1-7

ACTION ON ORGAN SYSTEMS

1-7-12 SUMMARY OF CARDIORESPIRATORY EFFECTS

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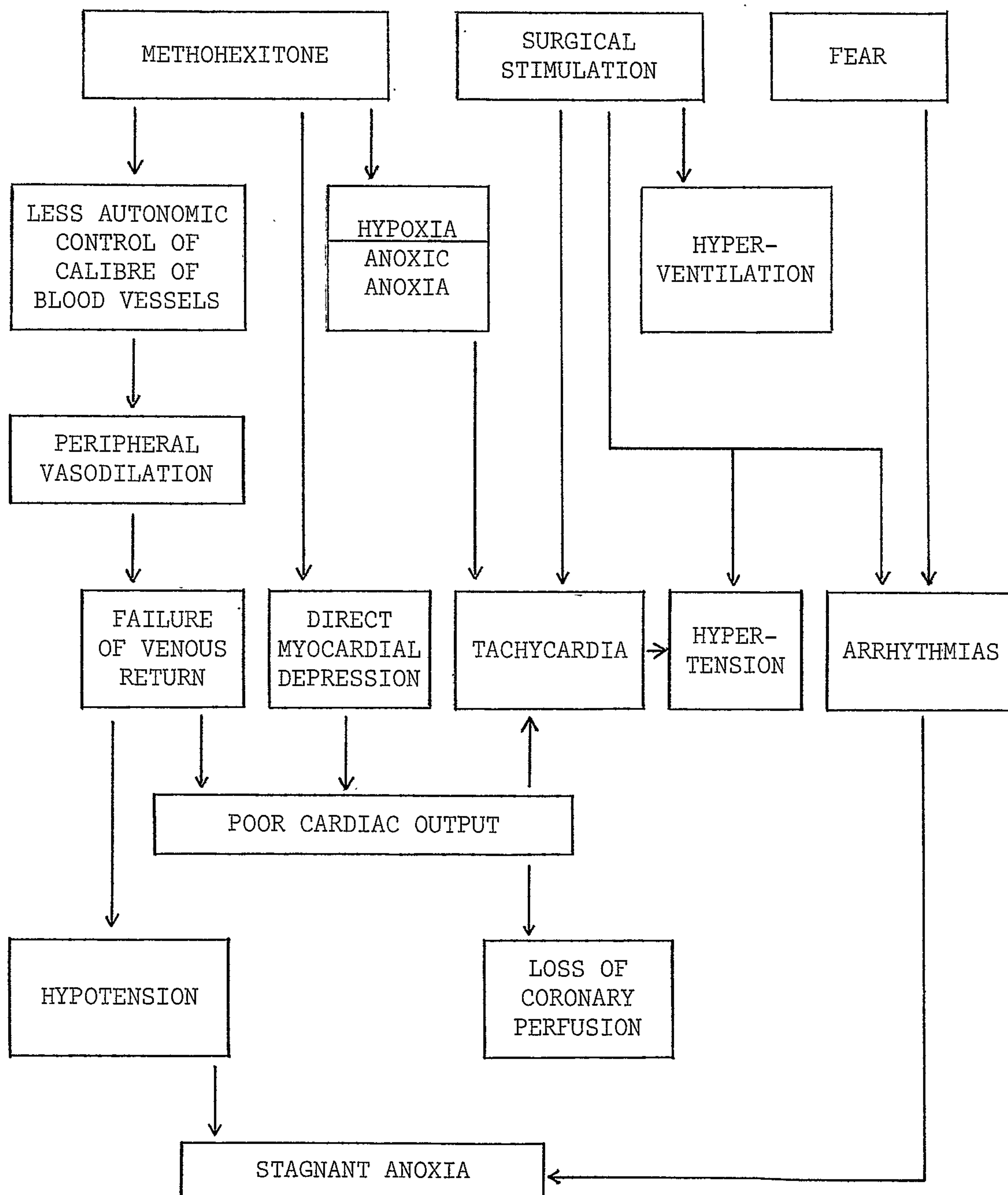
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1-7-12: SUMMARY OF CARDIORESPIRATORY EFFECTS

The effects discussed in Sections 1-7-3, 1-7-4, 1-7-5, 1-7-6, 1-7-7, 1-7-8, 1-7-9, 1-7-10 and 1-7-11 above are interdependent. In Diagram 7-6 below I have attempted to highlight the interdependence.

DIAGRAM 7-6: CAUSE & EFFECT OF CARDIORESPIRATORY OBSERVATIONS



1-7-13

LOCAL VASCULAR EFFECTS

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1-7-13: LOCAL VASCULAR EFFECTS

1-7-13a: Introduction

In this section I review the effects of:

1. Injection methohexitone into an artery.
2. Extravascular injection of methohexitone.
3. Pain caused by intravenous injection of methohexitone.

1-7-13b: Effect of intra-arterial injection of methohexitone

Chapman (1965) says that this is the most important complication of an intravenous administration.

1-7-13b(i): Animal studies

Methohexitone has been injected into arteries of calves without detrimental effect (Ogilvie 1962).

Francis (1964) injected methohexitone into the central artery of the rabbit's ear. He found that the incidence of gangrene varied with dosage, concentration and volume. He warns that a 5% solution of methohexitone is not without risk.

1-7-13b(ii): Reports of human intra-arterial injection of Methohexitone

Myers & Coltman (1961) knew of no case of intra-arterial injection of methohexitone in man. However in the S.A.A.D. Survey (Drummond-Jackson 1971d), three cases of intra-arterial injection were recorded. Fortunately there were no serious sequelae.

Miller et al (1976) reported a case in which 20mg methohexitone

were accidentally injected intra-arterially. The needle was dislodged before corrective treatment could begin. With difficulty, a needle was inserted into the brachial artery, and procaine hydrochloride was administered.

After 45 minutes the arterial spasms had reversed. The patient was admitted to hospital and warm soaks were applied to the arm. No paraesthesia was present. Ecchymosis took one week to go.

1-7-13b(iii): Cause of arterial irritation

Brown et al (1968) mixed methohexitone with blood in the proportions likely to occur in accidental intra-arterial injection. They observed the formation of crystals of methohexitone, haemolysis of erythrocytes, and platelets aggregated about the crystals.

Any of these factors could cause clotting and this could explain what happens with intra-arterial injections. There is less chance of crystals forming with the dilute solutions of methohexitone.

1-7-13b(iv): Conclusion

Methohexitone should not be injected into an artery. Such injection may cause arterial spasm and possible distal necrosis.

Fortunately, this complication has rarely been reported.

1-7-13c: Effect of extravascular injection of methohexitone

1-7-13c(i): Reports

An extravascular injection of methohexitone need not necessarily cause more than a mild, brief local tenderness, as described by Christenson et al (1961).

Hewitt et al (1966) used the largest and most obvious vein in the arm of each patient. All were examined on the 2nd or 3rd postoperative day.

They could find no correlation between the incidence of local complications and age or sex of the patients. Nor could they find any difference whether a 21 gauge or 23 gauge needle was used.

However, medium and small veins were significantly more prone to the development of local complications than large veins.

In Table 7-22 below, I have attempted to outline the findings of several studies. The studies are ranked in increasing percentage incidence.

TABLE 7-22 REPORTS OF COMPLICATIONS FOLLOWING EXTRAVASCULAR INJECTION OF METHOHEXITONE					
NAME OF STUDY	NO OF ADMINS	% SOLUTION	INCIDENCE		COMMENTS
			No	%	
Young & Whitwam (1964a)	200	1.6	0	0	All Checked postop.
Simpson & Rondeau (1966)	4000	1.0	0	0	
Drummond-Jackson (1971d)	445386	?	4.5	0.001	SAAD Survey
Shafto (1969)	500	1.0	2	0.4	Haematoma at site of injection
Christenson et al (1961)	36	1.0	several		Mild, brief local tenderness
Hubbell & Ruyer (1963)	?	1.0	2	?	Local noninfec- tious swelling for a few days
Hewitt et al (1966)	200	2.0	14	7	All checked postop.
Litchfield (1974)	25	?	2	8	Handicapped chil- dren - hard venepuncture
Mann et al (1971)	357	1	33.2	9.3	Bruising

1-7-13c(ii): Discussion of Table 7-22

Comparisons are difficult because of the variable definition of an extravascular complication.

The complication may result from difficult venepunctures, as Litchfield (1974) found. A small extravascular injection of methohexitone is fairly harmless.

1-7-13d: Vascular pain1-7-13d(i): Introduction

An intravenous injection of methohexitone may cause pain at the site of the injection or along the course of the vein.

The pain is often felt further up the arm, some distance from the injection site (Ogilvie 1962); in the upper arm (Hubbell & Royer 1963); and in the shoulder (Simpson & Rondeau 1966).

1-7-13d(ii): Incidence

Taylor & Stoelting (1960) reported a 60% incidence of pain at the site of the injection, and along the course of the vein. They comment: *The intensity of the pain varied, but usually evoked a spontaneous and bitter complaint from the patient.* In their opinion, such a high incidence detracted from the value of methohexitone.

However, often the pain is not severe enough to result in a complaint from the patient unless a direct question is asked (Barlow & Gottlich 1962). Often those who do complain at the time will forget about the sensation when questioned afterwards (Ogilvie 1962; Hubbell & Royer 1963).

Litchfield (1975) noted that the incidence is lower in children.

1-7-13d(iii): Studies reporting vascular pain

In Table 7-23 below, I have ranked in increasing order of incidence, those studies reporting venous pain. It should be noted that this complication does not refer to extravascular injections of methohexitone.

TABLE 7-23: STUDIES REPORTING VASCULAR PAIN

NAME OF STUDY	NO. ADMINS	SOLUTION		PAIN NO.	PAIN %	COMMENTS
		%	DOSE			
Coleman & Green (1960)	10,142	1	av. 70mg	0	0	But some were aware
Jolly (1960)	35	1	?	0	0	Patients premedicated
Barron & Dundee (1961)	600	2	to 950mg	0	0	
Hubbell (1960)	2,500	1	av. 84mg		0.1	
Simpson & Rondeau (1966)	4,000	1	75mg		1	
Shafto (1969)	500	1	M.I.T.	5	1	Slow injection, children
Rowlands (1969)	400	1	0.75mg/Kg	5	1.3	Lignocaine added to methohexitone
Hellewell & Hutton (1967)	122	1	?	2	1.6	
Barlow & Gottlich (1962)	220	1	?		4.	Only some questioned
Mann et al (1971)	357	1	M.I.T.		4.5	357 asked out of a total of 595 administrations
Christenson et al (1961)	36	1	M.I.T.	2	5.6	
Finch & De Kornfeld (1967)	26	5	75mg	6	7.7	Males only
Finch & De Kornfeld (1967)	25	5	50mg	2	8	Females only
Andrew et al (1973)	68	1	2mg/Kg	6	8.8	Fast injection, children
Rowlands (1969)	400	1	0.75mg/Kg	45	11.3	Plain methohexitone
Finch & De Kornfeld (1967)	24	5	50mg	5	20.8	Males only
Ogilvie (1962)	33	1	?	8	24.2	Severe in two cases
Finch & De Kornfeld (1967)	24	5	75mg	9	37.5	Females only
Taylor & Stoelting (1960)	3,340	1	av. 70mg		60	Premedicated

SEE SECTION 1-7-13e(3) FOR COMMENT

1-7-13d(iv): Discussion of Table 7-23

Although Taylor & Stoelting (1960) could find no relationship between the incidence of pain and the type of diluent used, or the speed of injection, Simpson & Rondeau (1966) found that by injecting slowly (1ml/sec. of 1%) the problem could be eliminated.

Shafto (1969) injected at the rate of 1ml/5sec. or 1ml/10sec., using a 1% solution, and still recorded some pain.

Andrew et al (1973) injected 2mg/Kg as fast as possible. They recorded a high incidence of pain.

The incidence is increased when 5% solutions are used and fast injection speeds are employed.

1-7-13d(v): Prevention

Rowlands (1969) reduced the incidence by adding 1mg/ml of lignocaine to the methohexitone solution.

Kay (1970) added 1ml of 1% lignocaine to each 10ml of methohexitone just prior to injection. He thought even less lignocaine would suffice.

Foreman et al (1968) have suggested that the temperature of the solution could be a contributing factor, and have noted that the incidence of pain increases in cold weather. Wilkinson et al (1965) suggested a solution temperature of 22 degrees C (72 degrees F).

1-7-13d(vi): Conclusion

I am intrigued as to why the venous pain is often felt far away from the injection site.

This may be due to the same effects noted by Brown et al (1968) (see Section 1-7-13b(iii)). Crystals of methohexitone are formed in the vein; this takes a few seconds and because of venous flow, is felt further away from the injection site. Or perhaps the veins in the shoulder have more pain receptors in their intima?

Unfortunately, I have been unable to find much information in the literature on this anomaly.

1-7-13e: Conclusion of local vascular effects

1. Intra-arterial injections of methohexitone are a serious complication. It has been rarely reported and its occurrence is a negligent act (see Section 1-7-13b(iv)).
2. Extravascular injection of methohexitone is harmless in small quantities.
3. Pain in the vein following intravenous injection is a complication that has been reported frequently. Its incidence varies from 0-60%. The incidence of pain may be correlated with speed of injection and concentration of solution (see Table 7-23).

1-7-14

ACTION ON GASTRO-INTESTINAL SYSTEM

VOMITING AND NAUSEA

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1-7-14: VOMITING AND NAUSEA1-7-14a: Incidence

Green & Jolly (1960) and Coleman & Green (1960) recorded an incidence of 5% vomiting on recovery from methohexitone and nitrous oxide and oxygen anaesthesia for extractions. They felt that this incidence represented the *irreducible minimum*.

However, using a similar technique, Young & Whitwam (1964a, 1964b) found the overall incidence of vomiting to be 3%. Hudson (1965) had none. Love (1968) had not observed regurgitation in over 18,000 dental anaesthetics of all types.

Using the M.I.T., Shafto (1969) had only one case of vomiting - out of 500 children. Bourne (1967e) recalls only once seeing a patient vomit after having methohexitone.

Foreman (1967) has encountered nausea and vomiting in less than 0.5% of cases where the M.I.T. was used.

Holden et al (1970) have not seen a single case of nausea or vomiting with the technique in 6,000 administrations over a period of six years.

1-7-14b: Studies reporting nausea and vomiting

There are three Tables, viz:

Table 7-24: Induction with methohexitone prior to inhalation anaesthesia.

Table 7-25: M.I.T. - (methohexitone sole drug).

Table 7-26: M.I.T. + premedication.

The studies in each table are ranked in increasing order of percentage incidence of vomiting. Not all studies were for dental treatment, but their inclusion may help to show some consistencies.

TABLE 7-24: INCIDENCE OF VOMITING - INDUCTION WITH METHOHEXITONE

NAME OF STUDY	NO.	TYPE WORK	INHALATION AGENTS	PREMED	FAST	VOMIT %	NAU-SEA %	COMMENTS
Weinstock (1960)	50	Dental	N ₂ O/O ₂	No	Yes	0	0	
Simpson & Rondeau (1966)	4000	Dental	Some: N ₂ O/O ₂ ; halothane	No	Yes	0	?	Some had pethidine which caused vomit
Andrew et al (1973)	68	Extract	N ₂ O/O ₂ Some hal.	No	Yes	0	0	
Dundee (1963)	300	Gynaec	N ₂ O/O ₂	Atropine only				(% calculated from actual no. = 9)
Young & Whitwam (1964a, 1964b)	2000	Extract	N ₂ O/O ₂ ; halothane for long cases	No	?	3		Less vomiting in longer cases
Dundee & Lyons (1967)	100	Gynaec	Induced with mix of methohex. & propanid then N ₂ O/O ₂	No	Yes	3		Mixture propanidid and methohexitone (See Section 13)
Swerdlow (1962)	121	Extract	N ₂ O/O ₂	No	Yes	3.3		Adults only
Swerdlow (1962)	79	Extract	N ₂ O/O ₂	No	Yes	3.8		Children only
Young (1974)	236	Extract	N ₂ O/O ₂ + some hal.	No	Yes	3.8		Only one vomited during treatment. (% calculated from actual figure = 9)

TABLE 7-24 (continued)

NAME OF STUDY	NO.	TYPE WORK	INHALATION AGENTS	PREMED	FAST	VOMIT %	NAU-SEA %	COMMENTS
Hellewell & Hutton (1967)	122	Extract	N ₂ O/O ₂ Some hal.	No	Yes	4.9	7.4	On recovery
Coleman & Green (1960)	373	Extract	N ₂ O/O ₂ some trichlorethylene	No	Yes	5	14	Dental outpatients part of study
Green & Jolly (1960)	500	Extract	N ₂ O/O ₂ some trichlorethylene	No	?	5		
Dundee (1963)	300	Gynaec	N ₂ O/O ₂	Pethidine Atropine	Yes	5.3		Compare to non pethidine group. (1% calculated from actual no. = 16)
Dundee & Lyons (1967)	300	Gynaec	N ₂ O/O ₂	No	Yes	9		

TABLE 7-25						
INCIDENCE OF VOMITING - INCREMENTAL TECHNIQUE, METHOHEXITONE ONLY						
NAME OF STUDY	NO.	TYPE WORK	FAST	VOMIT %	NAU-SEA %	COMMENTS
Bishop & Potts (1961)	6	Extract	Yes	0	0	
Drummond-Jackson (1971d)	445386	Dentist	?	0.103		SAAD Survey
Wilkinson et al (1965)	6740	Dental	?	0.12		(% calculated from figure given = 9)
Shafto (1969)	500	Extract	Yes	0.2		(% calculated from figure given = 1)
Mann et al (1971)	595	Dental	Yes	1.8	1.3	One vomited during induction
Lind & Roland (1969)	98	Gynaec	Yes	9.0	12.0	First part of study (some N ₂ O/O ₂)

TABLE 7-26: INCIDENCE OF VOMITING - M.I.T. + PREMEDICATION								
NAME OF STUDY	NO.	TYPE WORK	INHALA- TION FA AGENTS	PREMED	FAST	VOMIT	NAUSEA	COMMENTS
Douglas (1960)	95	dental	N ₂ O/O ₂	Promethazine Secobarb. Atropine	Yes	0	0	
Hubbell & Royer (1963)	2500	extract	Some N ₂ O/O ₂	Some Pentobarb.	?	0	0.4	
Berns (1963)	300	dental	None	Secobarb. Pethidine L.A.	No	0		
Liscombe (1968)	30	tonsils	None	Trimeprazine or Pethidine	Yes	0		Children
Elliott et al (1974)	800	extract	None	Innovar + Fentanyl	Yes	0	6	

1-7-14c: Causes of vomiting and nausea

1-7-14c(i): Hypoxia

Although Bishop & Potts (1961) looked at only six cases of methohexitone alone, their total study was of 187 adults and 70 children who received some form of anaesthetic. Of 8 adults and 11 children who vomited afterwards, 73% had shown cyanosis at some stage during the operation (see Table 7-25).

Weinstock (1960) reported that he uses 100% oxygen to avoid hypoxia, which he says can stimulate the vomiting centre. He had not experienced nausea or vomiting with patients who, because of an emergency, were treated with full stomachs (see Section 1-10-1).

1-7-14c(ii): Length of appointment

Simpson & Rondeau (1966) found vomiting to be extremely rare after any short anaesthetic, however prolonged anaesthesia, especially with inhalants, increased the incidence.

Bishop & Potts (1961) noted that patients who vomited usually had longer appointments, in contrast to Young & Whitwam (1964a, 1964b) who found the incidence to be less with longer appointments.

These studies also utilised similar techniques.

Dundee (1963) compared patients who were premedicated with pethidine to those who were not. The incidence of vomiting was almost double in the pethidine group (see Table 7-24).

1-7-14c(iv): Supplements

Wilkinson et al (1965) recorded a low incidence of vomiting and assumed this to be because no premedication or supplementation was used.

Shafto (1969) had only one case of vomiting with the incremental technique and comments: *This was in striking contrast to the author's experience using nitrous oxide and halothane.*

But Young & Whitwam (1964a, 1964b) had less vomiting in longer cases for which halothane was also used. They suggest that halothane may reduce the incidence of vomiting.

Andrew et al (1973) used nitrous oxide and halothane supplementation and recorded no nausea or vomiting.

Muir et al (1976) investigated morbidity following dental extraction with a variety of agents. They found that methohexitone is associated with a low incidence of vomiting and when used without halothane, none occurred; with halothane, the incidence was 6%. These figures are much lower than the 31.5% incidence when nitrous oxide, oxygen and halothane are used without methohexitone.

1-7-14c(v): Blood

Bourne (1967e) says that most cases of vomiting during recovery are usually due to swallowed blood.

1-7-14c(vi): Psychological factors

Young & Whitwam (1964a, 1964b) found the incidence of vomiting and nausea to be greatest in females, especially nervous females.

Foreman (1967) has seen vomiting associated with the M.I.T. and comments that these cases have *invariably been associated with pre-operative emotional stress or a disturbed psychological background.*

1-7-14d: Danger of aspiration of vomitus

If vomit has entered the trachea, an imminent complication of acid aspiration syndrome may be fatal.

The treatment is 100mg hydrocortisone and hospitalisation (Hannington-Kiff 1972; Robinson 1970). O'Brien (1974) stresses that in the patient who has inhaled gastric contents, there is often no immediate sign of any further complication. The reaction may take up to one hour, thus the need for hospitalisation.

The importance of fasting patients prior to the administration of methohexitone is discussed in Section 1-10-1.

The effect of methohexitone on the protective reflexes is discussed in Section 1-7-2.

1-7-14e: Conclusion

1. The incidence of vomiting is low when the M.I.T. is used alone and highest when nitrous oxide is used.
2. The use of pethidine increases the incidence of vomiting (see Section 1-11-6f(iii)).
3. The supplementation of oxygen may help to reduce the risk.
4. Patients must be fasted before treatment (see Section 1-10-1).
5. There is scant information in the literature of any other effects on the gastro-intestinal system.

1-7-15

ACTION ON OTHER ORGAN SYSTEMS

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1-7-15: EFFECT ON OTHER ORGAN SYSTEMS

1-7-15a: Liver function

Methohexitone exerts little effect on liver function.

Dundee & Wyant (1974c) review the literature and discuss a case of a patient who had received 16.1 grams of methohexitone over nine days with no evidence of liver dysfunction. (See Section 1-6-3a, the breakdown of methohexitone by the liver; and Section 1-9-7h(i), liver damage by alcoholism.)

1-7-15b: Renal function

I have been unable to find any relevant literature and must conclude that methohexitone has little effect.

1-7-15c: Reproductive system and foetus

Methohexitone, in doses used for dental treatment, probably has no effect on the tone of the gravid uterus (Dundee & Wyant 1974d).

The effect on the foetus is discussed in Section 1-9-9.

1-7-15d: Muscles

I have been unable to find any relevant literature.

The effect of intramuscular injections is discussed in Section 1-11-6e(iii).

The effect of methohexitone in patients with myotonic dystrophy is discussed in Section 1-9-3d.

Uncontrolled muscular movements following methohexitone is discussed in Section 1-7-1j, k, l.

1-7-15e: Blood

The solution of methohexitone is highly alkaline (see Section 1-2-1) and will cause haemolysis (see Section 1-7-13b).

1-7-15f: Metabolism

Methohexitone may impair the ability of the body to handle dextrose as does thiopentone.

The evidence for methohexitone is indirect (Dundee & Wyant 1974e).

The effect is probably of no clinical importance in short dental cases.

1-7-15g: Conclusions

1. 16.1 grams of methohexitone may not cause liver damage when given over nine days, but must have caused damage to other tissues (see Section 1-7-15a).
2. Because methohexitone may reduce the rate of metabolism of dextrose (see Section 1-7-15f), one must question the use of dextrose drips as a vehicle (see also Section 1-5-12h).
3. Hypersensitivity reactions to methohexitone are discussed in Section 1-8-2.
4. The effect of methohexitone on organs or tissues not discussed in Section 1-7 has not been reported.

1-8

UNTOWARD REACTIONS

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1-8-1: INTRODUCTION

In this section I have reviewed the literature on allergic reactions to methohexitone and the development of dependence to methohexitone.

The effect of methohexitone on patients who are suffering from any disease process is reviewed in Section 1-9.

1-8-2: ALLERGIC REACTIONS TO METHOHEXITONE

1-8-2a: Incidence

Chambiras (1971) stated: *With the increasing use of intravenously administered sedatives, tranquillizing agents and anaesthetic agents in dentistry, more severe allergic responses may be encountered.*

Stubbings (1972) said that 2% of patients may have a tendency to allergic reactions.

In the S.A.A.D. Survey (Drummond-Jackson 1971d), 0.003% of patients developed an allergic rash and 0.002% of patients developed an unspecified allergic reaction to methohexitone.

A survey of American Oral Surgeons (Driscoll 1974) revealed that in 1972 there were nine cases of anaphylactic shock associated with methohexitone, but unfortunately no further details were given.

However, Bourne (1967d) says that it is impossible to produce an anaphylactic shock with methohexitone because it is not a protein. The reactions likely to be seen are angioneurotic oedema or a severe asthmatic attack.

In the S.A.A.D. Survey (Drummond-Jackson 1971d), there was only one case of severe asthmatic attack.

Typical allergic symptoms have been described by Driggs & O'Day (1972), Stubbings (1972) and Woods (1974).

The incidence has been calculated to be 1 reaction per 7,000 administrations (Clarke et al 1975).

1-8-2b: Reported allergic reactions to methohexitone

In Table 8-1 below, I have presented a list of reported allergic reactions following the administration of methohexitone. A list of abbreviations used precedes the table.

1. Relevant medical history (RMH)

A/A	=	asthma
A/PL	=	allergic to pollens
A/PN	=	allergic to penicillin
A/S	=	allergic to sulphonamides

Otherwise all patients were healthy

2. Drugs given prior to allergic reactions (DRUGS)

A	=	atropine
Gas	=	nitrous oxide and oxygen
LA	=	local analgesia
M	=	methohexitone
OM	=	oxymorphone

3. Allergic reaction symptoms

BP	=	blood pressure fell
COLD	=	patient's skin felt cold
C/A	=	colour ashen
C/C	=	colour cyanotic
C/G	=	colour good
C/R	=	colour red
CRAMPS	=	abdominal cramps
DYS	=	dyspnoea, wheezing
OED	=	oedema
PRU	=	pruritis, itching
PUL	=	normal pulse
RHIN	=	Rhinorrhea, sneezing
SWEAT	=	sweating
URT	=	urticaria, rash

4. Treatment

V	=	vasopressor (adrenalin 1:1000)
C	=	hydrocortisone or dexamethasone
A	=	antihistamine (chlorpheniramine, diphenhydramine or mephentermine)

TABLE 8-1: REPORTED ALLERGIC REACTIONS							
NAME OF STUDY	RMH	DRUGS	DETAILS OF SYMPTOMS	TREATMENT			COMMENTS
				V	C	A	
Mason & Frew (1963)	0	M	30 secs later: C/G; DYS; PUL; RHIN	0	0	0	Recovered quickly
Blatchley & Drummond-Jackson (1971f)	0	M	At increment: C/R; OED; RHIN	0	0	+	later: +ve skin test to methohexitone
Reichert & Bassett (1972)	A/S	M	On recovery: OED; PRU	0	+	+	
Driggs & O'Day (1972) Case No. 1	A/PN	M, Gas	On recovery: BP; CRAMPS DYS; SWEAT; URT	0	+	+	Atropine too
Driggs & O'Day (1972) Case No. 2	A/PL	M, A, LA, Gas	Near end: BP; C/C; DYS; RHIN; SWEAT	0	+	+	
Driggs & O'Day (1972) Case No. 3	A/A A/PL	M, A, Gas	Near end: BP; COLD; C/A DYS; OED; RHIN	0	+	+	
Driggs & O'Day (1972) Case No. 4	0	M, A, LA	On recovery: BP; COLD; C/A; URT; SWEAT	0	+	+	
Driggs & O'Day (1972) Case No. 5	0		On recovery: BP; C/C; DYS; OED; URT	0	+	+	
Driggs & O'Day (1972) Case No. 6	A/PL	M, A, Gas	BP; C/C; OED; PRU; URT	+	+	+	

1-8-2c: Discussion of reported reactions

Glaudia et al (1975) report a case of a woman who received 180mg methohexitone and 5mg diazepam for the removal of two teeth. She was then placed on oral penicillin. Four hours later she developed acute respiratory distress, cyanosis, skin reactions and low blood pressure.

She responded to emergency treatment. The authors did not think that methohexitone or diazepam caused the reaction, . . . *because of the time element involved*, but blamed the penicillin.

The studies listed in Table 8-1 all recorded an allergic response within minutes of receiving the drugs. In all cases, recovery occurred within a few hours.

Three interesting points arise from Driggs & O'Day (1972):

1. Patients did not like lying down during treatment of the allergic reaction because of breathing difficulties.
2. They postulate that some persistent hypotensive conditions occurring after anaesthesia (but without classic allergic symptoms) may be modified allergy reactions.
3. See Section 1-8-2e, part (4).

Clarke et al (1975) comment on the low number of reports with methohexitone which they say, *may be because of its relatively infrequent use, principally confined to outpatient anaesthesia.*

1-8-2d: Treatment of allergic reactions

Foreman (1967) successfully treated two cases of allergic reactions to methohexitone. He gave an antihistamine intravenously, followed by

supportive antihistamine therapy. Unfortunately, because of lack of detail, it could not be included in the table above.

Antihistamine treatment is recommended by Blatchley & Drummond-Jackson (1971f), Bourne (1967d) and Bennett (1974m). Although Chambiras (1971) prefers not to use antihistamines, and he describes an epinephrine spray (adrenalin) he had developed for bronchodilation.

For asthma attacks, O'Brien (1974) gives aminophylline and oxygen.

Stubbings (1972) recommends adrenalin and hydrocortisone. Trieger (1976) recommends adrenalin and oxygen.

Eggleston (1975) prefers not to use intravenous adrenalin because of the danger of causing arrhythmias. He feels it is better to rely on ventilation.

Watkins et al (1975) invited all British anaesthetists to send them a blood sample of any patient who develops an allergic response shortly after induction. They hope to be able to investigate transient blood changes that may occur, and thus gain a greater understanding of the reactions.

1-8-2e: Conclusions

1. The incidence of allergy to methohexitone has been calculated by Clarke et al (1975) to be 1:7000.
2. The S.A.A.D. Survey (see 1-8-2a) reported an incidence ranging from 1:29500 to 1:50000 (approximately) - a much lower figure than (1).

3. If the 9 cases in Table 8-1 are viewed against the 26,000 administrations given in controlled studies (listed in Table 4-1, Section 1.4) then the incidence could be as high as 1:3000 (approximately).
4. One wonders why Driggs & O'Day (1972) gave two of their patients, who had already had one allergic reaction, a second administration of methohexitone. Each developed an allergic reaction with the second administration.
5. Half the patients who had an allergic reaction had a history of other allergies.

1-8-3: DEPENDENCE

1-8-3a: Discussion

The horrors of drug taking are well known. Drug dependency seems to be developing on an ever-increasing scale. Barbiturates are abused by the public and the short-acting oral hypnotics are often over-prescribed (d'Orban 1975).

So serious is the problem of drug abuse with barbiturates in the U.K. that an independent professional committee has been set up to advise physicians, dentists and pharmacists of the dangers.

The Committee is called, *Campaign on the Use and Restriction of Barbiturates* (C.U.R.B.). C.U.R.B. has circularised the professions on many occasions and has run several seminars.

It is interesting to note that C.U.R.B. is not concerned with the short acting anaesthetic agents such as methohexitone (C.U.R.B. 1976).

At a course on the use and restriction of barbiturates, organised by C.U.R.B., Thornton (1975) said: *The intravenous induction of anaesthesia by short acting barbiturates would be unlikely to cause addiction or dependency due to their pharmo-kinetic pattern.*

There are few references to the possibility of methohexitone addiction. The psychiatrists, Friedman & Silverston (1968) gave 4,000 administrations to phobic patients for desensitisation treatment. Often the same patient would receive many administrations over a short period. They did not find any dependence.

However, Sergeant & Yorkston (1968) gave similar treatment to 18 phobic or anxious patients over 200 hours of treatment. They reported one case of dependency as a result.

1-8-3b: Conclusion

This is a problem that should be kept in mind. Particularly at risk are patients who must attend for several treatments, thereby increasing their exposure to methohexitone.

1-9

PREVENTION OF COMPLICATIONS

I. PRE-OPERATIVE ASSESSMENT

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1-9-1: INTRODUCTION

In this section the pre-operative assessment of patients is discussed. This is not an exhaustive list of medical conditions because only those areas of specific concern are highlighted.

The absolute contra-indications to the use of methohexitone are discussed: acute respiratory disease, porphyria, sickle cell anaemia and myotonic dystrophy.

The condition of epilepsy is reviewed at length because a lot has been written about the possible convulsive properties of methohexitone.

General conclusions are presented in Section 1-9-12, although specific conclusions will be found at the end of some subsections.

1-9-2: METHODS OF PRE-OPERATIVE ASSESSMENT

1-9-2a: Introduction

The days have gone when we got a patient off the street, pumped him full of lignocaine and adrenaline without obtaining a history, and threw him back on the street a few minutes later (Southwell 1972).

Sara (1974) says that the concept and responsibility of total patient care is quite new to dental practice. O'Brien (1972) discusses the relevance of the patient's medical history. Bourne (1967k) presents a long list of medical conditions that may be a contraindication to the use of methohexitone.

Bennett (1974d) lists many medical conditions that may be indications for sedation.

1-9-2b: Medical History Forms

To help take a medical history, Litchfield & Gerard (1971) have suggested a simplified medical history form. The patient is requested to answer a few relevant questions and is asked to sign the form.

However, Jolly (1967) prefers not to use printed forms, and Foreman (1970a) warns that patients can give deliberately misleading information if it suits their purpose. (Also see Section 1-10-2, Consent Forms.)

1-9-2c: Medical Reports

The British Ministry of Health Report on Dental Anaesthesia (Swiss 1967) states: *Ideally the patient's fitness should be confirmed preoperatively by a report from the patient's regular medical practitioner.*

Garber (1976) recommends that patients aged forty or more be requested to show a report of a recent yearly physical examination prior to any outpatient dental anaesthetic.

Christenson et al (1961) obtained a pre-anaesthetic E.C.G., a complete blood count, a urinalysis, and a chest X-ray of every patient aged 45 years or more, or where systolic blood pressure was above 145 Torr or diastolic, above 95 Torr.

About 20% of their patients qualified for such tests.

At a symposium on ambulant anaesthesia conducted by the British Dental Association (Bourne et al 1964), Drummond-Jackson spoke against complex pre-operative tests. He stated: *The adequacy of the anaesthetist is more important than advance checking of the patient, since*

there is no method of assessing the patient's reaction as good as a test injection of the actual drug: this takes less than a minute (see Section 1-10-5, Test dose).

1-9-2d: Fitness

Goldman (1968) states: *It may be assumed that the patient who is fit to do a good day's work, or to do house work and rear children is fit for a short general anaesthetic. A child, who is allowed to play active games at school, again is fit for general anaesthesia.*

The records of the Medical Protection Societies tend to support the view, entertained by many dental surgeons, that . . . *a patient, with no obvious signs of ill health who is able to walk unaided into the surgery is a reasonable anaesthetic risk.* (Constable 1964.)

Trieger (1976) says that, *patients who are healthy and without attendant medical diseases or with well controlled medical problems are suitable for office treatment. Such patients are in category I and II of the American Society of Anesthesiologists.*

So that, even in the presence of a known cardiac disease, as long as the patient can perform his daily tasks without symptoms, he probably will tolerate a short anaesthetic (Buxton 1971a).

Berns (1963) recommends incremental methohexitone in combination with premedication for such cases, because it is important to avoid anxiety which routine dental treatment might produce.

1-9-2e: Children

The pre-operative assessment of children and the treatment of medically and physically handicapped children is discussed by Parkin et al (1970a, 1970b). Children are also discussed in Section 1-9-2f.

1-9-2f: Prevention of Restlessness

The following types of patients are likely to be restless under methohexitone (Clarke 1971b):

- Acutely apprehensive
- With an elevated temperature
- Robust physique
- Alcohol resistance
- Presence of considerable pain

Children and adolescents tend to show an exaggerated response, to even slight stimuli, under methohexitone (Foreman 1970a). In his text, *Behaviour Management in Dentistry for Children*, Wright (1975) does not mention methohexitone. Perhaps for this reason?

Jastak & Paravecchio (1975) analysed 1331 administrations of various sedatives for dental treatment. Although methohexitone was not included, their results may be helpful. They found that the incidence of unsuccessful sedations was significantly related to poor health, and that the relationship between physical illness and psychological illness may play an important part.

Gorton (1975) feels that restlessness, seen particularly in young women, is really a temper tantrum.

For further discussion, see Section 1-5-8b; conclusions, Section 1-9-12; use of nitrous oxide, Section 1-11-3b(iv); and use of diazepam, Section 1-11-6h(viii).

1-9-3: ABSOLUTE CONTRAINDICATIONS

1-9-3a: Respiratory disease

Bloomfield (1966) lists as an absolute contraindication the common cold or blocked nasal airway. Foreman (1967) has severe respiratory obstruction as the only absolute medical contraindication to methohexitone.

However, Shafto (1969) said that incremental methohexitone *proved of value in anaesthetising children with pre-operative respiratory infections and nasal obstruction.*

Buxton (1971a) prefers short procedures only when such acute respiratory disease is present. He suggests that where a chronic respiratory disease exists, the patient be asked to clear his nose first to allow enough time for a short procedure to be completed before secretions return.

1-9-3b: Porphyria

This metabolic disease occurs most commonly in South Africans of Dutch origin (Goldman 1968).

Sufferers are unable to metabolise barbiturates (Buxton 1971a). The administration of a barbiturate may cause rapid death (Price 1975b).

Patients usually know that they have the condition (Macintosh et al 1971). Buxton (1971a) recommends the use of propanidid in preference to methohexitone in such cases.

In suspected cases, the urine should be tested for the presence of porphobilinogen (Rice 1975).

1-9-3c: Sickle Cell Anaemia

Coloured patients from certain areas represent the highest incidence. A survey in Manchester, England, disclosed that 60% of negro immigrants carried the sickle cell trait (Rees-Jones 1971).

The risk factor has diluted with increased intermingling of populations and the incidence in the U.S.A. is 9% of the coloured population (Drummond-Jackson 1972b).

The administration of methohexitone to a sufferer is dangerous because any transient hypoxia, even by retching on recovery for example, may lead to sickling (Macintosh et al 1971).

Patients suffering from this disease rarely reach adulthood, but coloured children should be tested (Goldman 1968).

A simple solubility test outfit is available and gives 100% reliable readings. A positive reading is more likely to be due to the trait rather than to active anaemia and further tests will be necessary (Drummond-Jackson 1972b).

In the U.K., the National Health Service will now pay dentists a fee for carrying out the simple Sickledex test on patients in their own surgery (News 1976a).

Patients with this condition are best treated in hospital. In an emergency, where treatment must be carried out in the surgery, Buxton (1971a) recommends that procedures be kept short and that the patient breathes at least 50% oxygen.

1-9-3d: Myotonic dystrophy

Wald (1975) describes two cases and reviews the literature. The problem with such patients is that there is a multisystem involvement which may create potentially serious complications. The administration of methohexitone could produce a profound respiratory depression.

1-9-4: EPILEPSY1-9-4a: Introduction

In this section, I have reviewed the literature concerning:

1. The effect of methohexitone on patients suffering from epilepsy.
2. The role of methohexitone as a cause of epileptic-type seizures in apparently healthy subjects.

1-9-4b: Incidence

The incidence of epilepsy is estimated to be 0.5% of the population (Bennett 1974n).

1-9-4c: Methohexitone as a cause of epileptiform seizures1-9-4c(i): Positive cause

Wyant et al (1957) compared seven intravenous anaesthetic agents and found that methohexitone produced the highest incidence of spontaneous muscle movements (see also Section 1-7-1j, k, L).

Heaton (1956) compared thiopentone to methohexitone: Several patients who received methohexitone had epileptiform seizures; none who received thiopentone had epileptiform seizures.

Gruber et al (1957) noted that soon after ten control subjects received 100mg methohexitone, E.E.G. changes resembled the wave forms sometimes associated with convulsive disorders.

Redish et al (1958) took E.E.G. readings of two patients who had demonstrated jactitations under methohexitone. They report a . . . *slight deviation from normal brain wave patterns. This suggests that the administration of methohexital sodium may provoke seizures in patients with incipient epilepsy.*

The methyl group contained within the molecule is thought to be responsible (Thornton 1970). A diagram of the molecule (Diagram 2-1) is presented in Section 1-2-2.

Because it is potentially convulsant, many authors advise against giving methohexitone to epileptics (Redish et al 1958; Goldman 1966; Howells 1968; Trieger 1974a).

It may even be unwise to give methohexitone to patients who are parents or siblings of known sufferers (Thornton 1970).

1-9-4c(ii): Negative cause

Epileptiform seizures may be a withdrawal symptom in barbiturate addicts (Connell 1975).

Jacobi (1975) prefers to use barbiturates in known epileptics because seizures are prevented.

Bourne (1969a) states: *I have used methohexitone in many epileptic patients, without precipitating an attack, and question whether it is contraindicated in such patients.*

The use of methohexitone for epileptics is also advocated by Moreland et al (1969) and Kurer (1971).

Love (1970) and Kurer (1971) say that the twitching movements, sometimes observed with methohexitone, have nothing to do with epileptic seizures.

Taylor & Stoelting (1960) observed normal post-operative E.E.G. recordings from their patients who had shown marked skeletal muscle twitching (see also Section 1-7-1j, k, L).

1-9-4d: Reported cases following methohexitone

Gruber et al (1957) discuss a patient (not included in their study) with a history of organic brain disease and symptomatic epilepsy, who showed an increase in the number of typical seizures under methohexitone.

Galley (1963) describes the case of a 27 year old man who had generalised epileptiform convulsions for 20 seconds after receiving 80mg methohexitone. Previous anaesthesia with thiopentone had not produced such a reaction in this patient. As a child he had suffered from epilepsy but thought he had grown out of it.

Galley (1966) describes the case of a 37 year old female epileptic, premedicated with amylobarbitone (*Amytal*), who developed epileptiform convulsions after receiving 80mg methohexitone.

The convulsions were gradually replaced by exaggerated writhing. Further increments of methohexitone did not stop the movements.

In both these cases, a follow-up E.E.G. showed that each patient was a subclinical epileptic.

Boston & Unckles (1969) gave 100mg of methohexitone uneventfully to an 18 year old fit male epileptic who was controlled by primidone 250mg q.i.d. However, on recovery he had a major epileptic convulsion, and then another. Then his recovery was uneventful.

Goldman (1969a) reports a case of epileptic seizure in a fit male who received 100mg of methohexitone for an extraction. Afterwards, on questioning, the patient said that when he was about 5 years of age he was *said to have had epilepsy*.

Ryder (1969) gave 60mg of methohexitone to a fit 19 year old male with no history of epilepsy. Marked muscle tremors began but were disregarded. Three subsequent increments of 10mg produced tremors lasting a little longer each time. A further increment produced more violent shaking and a full epileptic attack. On questioning later, it was discovered that the patient had had epileptic fits as a child.

Shafto (1969) had one child who demonstrated severe post-operative excitement. It was discovered that his brother was an epileptic.

Mann et al (1971) gave 595 administrations of incremental methohexitone for conservative dentistry. One patient, with no previous history, developed an epileptiform attack following the first sleep dose.

Male & Allen (1977) reviewed the literature and studied E.E.G. patterns in 48 epileptic patients who received methohexitone. Two patients developed grand mal convulsions during induction; two others exhibited status epilepticus of the petit mal type, and one, of the myoclonic type, after the administration was ceased.

1-9-4e: Discussion of cases

Vickers (1963) feels that the type of movements described by Galley (1963) are not epileptic, but a reflex action at a subcortical level. He has taken E.E.G. readings during induction and has never seen epileptiform patterns.

Bourne (1969a) and Rose (1969) discuss the case described by Goldman (1969a). They feel that this attack could have been provoked by fainting and hypoxia as the patient was upright when induced.

Goldman (1969c) replied to these comments and said that the patient was breathing oxygen throughout and was at no time hypoxic, and that the blood pressure did not drop. The patient did not faint. He felt that if there is a tendency to epilepsy, methohexitone will provoke it.

Ryder (1969) agreed. In the case he described, the patient had a good pulse throughout, was never suboxygenated, and was lying down.

In the case described by Boston & Unckles (1969), the patient remarked afterwards that, *he often experienced attacks after fear or excitement.*

Apparently people with a history of epilepsy can have an attack precipitated by such factors as emotional stress (Bennett 1974d). This could be as similar a cause as fainting.

1-9-4f: Prevention of epileptiform seizures

1-9-4f(i): Use of alternative drugs

Thiopentone or propanidid have been given successfully to patients

who had experienced an attack with methohexitone (Goldman 1969a).

The 25 year old man, described by Galley (1966), had been previously induced with thiopentone without incident.

Garber (1976) has found that the incidence of muscle movements is reduced if 5-10mg diazepam is given prior to methohexitone.

Stubbings (1972) and Foreman (1974a) prefer to use diazepam (and no methohexitone) in known epileptics.

1-9-4f(ii): The well controlled epileptic

Love (1970) and Bennett (1974d) see no reason not to use methohexitone in these patients - provided they are well controlled and are treated at a time when their medication has its maximal effect.

1-9-4f(iii): Fasting as a cause of epileptic seizure

An epileptic who has fasted may be at greater risk (Male & Allen 1977; Ryder 1969).

1-9-4f(iv): Hypoxia as a cause

Dobkin & Wyant (1957) suggested that rigidity or twitching frequently suggests acute hypoxia, or toxic reactions in the nervous system.

Galley (1966) and O'Brien (1974) say that epileptic convulsions can be brought on by a cyanotic episode.

Bourne (1967, 1977) says that fainting could provoke an epileptic attack in a normal person not subject to epilepsy.

1-9-4g: Conclusions

1. The well controlled epileptic is probably not at risk, although it is probably best to use an alternative drug such as diazepam.
2. There is a danger of provoking an attack in an undiagnosed epileptic (see Section 1-9-4d).
3. Although fasting may increase the risk of an epileptic attack, it will decrease the chance of regurgitation. As the epileptic attacks produced seem to cause no permanent harm, the rules of fasting should not be relaxed (see Section 1-10-1).

1-9-5: DIABETES

Diabetes affects 1.5-2.0% of the population (Bennett 1974o) and perhaps one in one hundred is an undiagnosed diabetic (Jolly 1967).

Diabetes does not alter a patient's response to anaesthesia, nor is it a contraindication to methohexitone, but in middle age there are associated cardiovascular degenerative changes. Bourne (1967k) recommends that the initial dose of methohexitone be reduced.

The main problem is that uncontrolled diabetes, or those on insulin or other hypoglycaemic agents, could develop a hypoglycaemic coma during a general anaesthetic (Cawson 1970b).

Uncontrolled diabetics must not be treated, but Bourne (1967k) suggests that the controlled diabetic should have his normal regime till midnight, then nothing on the day of treatment; he then can be treated as a normal patient.

Buxton (1971a) suggests that they be treated at the end of the morning or afternoon session, after a normal breakfast or light lunch (see Section 1-10-1).

See conclusions in Section 1-9-12.

1-9-6: CARDIOVASCULAR DISEASE

1-9-6a: Myocardial disease

The American Dental Association and the American Heart Association Conference (1964) concluded that patients suffering from ischaemic heart disease should be treated in hospital.

A recent coronary occlusion within 14 weeks is a contraindication but after one year, the patient can be treated as a normal risk (Buxton 1971a).

Mann et al (1971) state that it is unwise to use unsupplemented methohexitone on patients with cardiac disease because of the tachycardia produced with the M.I.T. (see Section 1-7-6).

Coleman & Green (1960) state that it can be safely used as an induction agent in such cases.

Elliott et al (1974) used premedication, local analgesia and methohexitone in 800 patients for outpatient oral surgery. However, *poor risk patients such as those with recent myocardial infarcts and aged individuals received methohexital only during the injection of the local anaesthetic solution . . .*

Drummond-Jackson (1975c) believes that the M.I.T. is preferred

in these cases and, because it is smooth and minimal, it has advantages over the more problematical inhalation techniques - especially if the patient is nervous or frightened.

Thus the very anxious hyperactive patient with heart disease will have this type of treatment strongly indicated, in order to reduce the stress on the heart caused by dental treatment (Holmes 1976). See conclusions Section 1-9-12.

1-9-6b: Hypertension

Hubbell & Royer (1963) recommended the use of methohexitone for middle-aged patients taking drugs for hypertension. Jorgensen (1966) has found that his technique is useful in such cases and he has found that blood pressure stabilises at a slightly lower level during treatment, compared with that measured preoperatively.

The joint conference of the American Dental Association and American Heart Association (1964) recommended that sedatives should not be given to patients who are on ganglionic blocking agents because dangerous hypotensive episodes or orthostatic hypotension could develop. Such drugs will also prolong the action of the sedative.

Because antihypertensive drugs reduce peripheral vascular tone, there is the added danger of methohexitone reducing peripheral vascular tone also. The effect will be further potentiated if the patient is taking a diuretic.

Bourne (1967k) gives half the usual induction dose of methohexitone and tests the pulse rate as a guide to the effect on peripheral vascular resistance. See conclusions Section 1-9-12).

1-9-7: PATIENTS RECEIVING SPECIFIC DRUGS

1-9-7a: M.A.O.I. Antidepressants

These drugs produce an increased sensitivity to barbiturates and their action can last up until two weeks after they have been withdrawn (Bourne 1967k; Jolly 1967).

The M.I.T. should be safe because dosage can be reduced accordingly (Blatchley & Drummond-Jackson 1971g).

If these patients are premedicated with pethidine (see Section 1-11-6f(iii)), hypotension and deep, even irreversible coma could develop (Cawson 1970b).

1-9-7b: Major tranquillizers

Methohexitone could provoke a hypotensive episode (Cawson 1970b). See also Section 1-9-12.

1-9-7c: Hypnotics and minor tranquillizers

Either the patient will be more resistant to methohexitone or potentiation and delayed recovery will occur (Cawson 1970b).

1-9-7d: Tricyclic antidepressants

Staccia (1966) observed no potentiation when these patients received methohexitone for E.C.T.

1-9-7e: Anticoagulants

Levin, W.G. (1975) discusses anticoagulants and states: *It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. The patient on anticoagulant therapy*

must be followed by means of prothrombin time tests and observed carefully for any development of bleeding tendency.

Jolly (1967) said that barbiturates are suspected as being antagonistic with anticoagulants. However, I cannot find any specific contraindication mentioned in the literature.

1-9-7f: Steroids

Foreman (1967) lists adrenocortical insufficiency and steroid therapy as a relative contraindication to methohexitone.

However, it is usually thought sufficient to double the dose of steroid on the day and for 3-4 days afterwards, in addition to giving 100mg hydrocortisone hemisuccinate the morning before and the evening after treatment (Cawson 1970b).

Cawson & James (1973) discuss the handling of these patients, who may be at risk if they have been taking systemic corticosteroids for more than a few months, or if a longer course of treatment (more than one year) has been given within the past two years.

1-9-7g: Acidic drugs

The intensity of C.N.S. depression of barbiturates can be increased by acidic drugs such as aspirin or sulphonamides which displace barbiturates from the plasma protein (Harvey 1975).

1-9-7h: Drugs of abuse

1-9-7h(i): Alcohol

Although barbiturates are potentiated by alcohol, the alcoholic may show a degree of excitement.

In the alcoholic, the main problem is liver damage, therefore methohexitone should be administered with caution and in reduced doses (Harvey 1975); recovery will be delayed (Woods 1974).

These problems arise because methohexitone is metabolised in the liver (see Section 1-6-3).

Thornton (1970) suggested using propanidid instead of methohexitone, because it is not metabolised in the liver.

1-9-7h(ii): Marijuana

Campbell et al (1976) gave atropine, fentanyl, diazepam, methohexitone, nitrous oxide and oxygen, and local analgesia to ten surgery patients; five of whom smoked marijuana. They state: *There seemed to be a correlation between postoperative tachycardia and the incidence of smoking marijuana in four of the five patients.* They suggest that clinically significant drug interactions may occur between atropine, methohexitone and marijuana if smoked within 48 hours prior to surgery (see conclusion; Section 1-9-12).

1-9-7h(iii): Others

1. Opioid drugs are discussed in Section 1-11-6f.
2. Smoking is discussed in Sections 1-7-2d(iii) and 1-7-1e(v).

1-9-8: SOME OTHER MEDICAL CONDITIONS

1-9-8a: Thyrototoxicosis

It is rare to see an untreated thyrotoxic patient. These patients would require extra methohexitone for the same effect because of an

increased metabolic rate (Buxton 1971a). Also see Section 1-9-10 and Conclusions in Section 1-9-12.

1-9-8b: Haemophilia, etc.

Mulkey (1971) prefers to treat controlled patients with methohexitone and local analgesia and as outpatients rather than with hospitalisation and intubation. He says that intubation may be potentially hazardous. See Conclusion, Section 1-9-12.

1-9-8c: Anaemias

These patients have a reduced haemoglobin content. In cases of anoxia, the traditional cyanotic colour may be absent. Jacobi (1975) recommends hospitalisation.

Cyanosis is discussed in Section 1-7-5d.

Sickle Cell anaemia is discussed in Section 1-9-3c.

1-9-8d: History of fainting

See Section 1-7-11d.

1-9-8e: History of allergy

Patients with a history of allergy to methohexitone should not be given the drug again (see Section 1-8-2e(4)).

Patients who have general allergies account for half the reported allergy reactions to methohexitone (see Table 8-1, Section 1-8-2b).

1-9-9: PREGNANCY1-9-9a: When safe to give methohexitone

Blatchley & Drummond-Jackson (1971e) give methohexitone to pregnant patients but restrict treatment to short duration emergencies. During the 10-16th week they will not give methohexitone without a prior medical consultation because of the danger of miscarriage.

A symposium at Southend Hospital (Cato 1976), concluded that the first and third stages were safe provided nitrous oxide and oxygen were also administered.

Quinn (1973) uses small quantities of methohexitone, 50:50 nitrous oxide and oxygen, and local analgesia. He does not give methohexitone in the first trimester or late in the pregnancy.

1-9-9b: Danger of methohexitone in early pregnancy

There is some evidence that if a mother became anoxic in the first trimester, a malformation of the child could occur (Macintosh et al 1971). (The role of methohexitone in anoxia is discussed in Section 1-7-5.)

Mothers receiving barbiturates in the early weeks of pregnancy have shown a small increase in producing children with cleft palate and cleft lip (Jarvie 1976).

1-9-9-c: Danger in late pregnancy

Methohexitone may precipitate labour. If the patient is supine, the pressure of the gravid uterus on the inferior vena cave may prevent return, there is then a risk of supine hypotension (Stubbings 1972), embarrassed breathing and hypoxia (Buxton 1971a).

Coleman & Green (1960) gave methohexitone, as an induction agent only, in 68 maternity cases and found no incidence of variation of the foetal pulse or subsequent depression of infant respiration.

Wilkinson & Wilkinson (1960) gave methohexitone prior to nitrous oxide and oxygen for extraction in one patient at the third month, and one at the eighth or ninth month of pregnancy, without complication.

1-9-9d: Methohexitone crosses the placenta

Marshall (1964) took serial samples of human umbilical-cord blood during caesarian section with the infant remaining in the uterus. Peak umbilical venous levels of methohexitone occurred 2-3 minutes after maternal injection. Umbilical venous levels were directly related to maternal dosages. Placental transmission of methohexitone seems to be almost instantaneous.

Similarly, diazepam should not be administered (Foreman et al 1968) and neither should pentazocine (Kurland 1971).

A conditional dilemma arises in determining the appropriate dosage which the undeveloped systems of the foetus can cope with (Office of Health Economics 1976).

Clarke (1971b) suggests increasing the calculated induction dose by 10mg for the pregnant patient!

1-9-9e: Conclusion

Methohexitone should not be used on pregnant patients.

1-9-10: CONTRAINDICATIONS TO THE USE OF ATROPINE

Atropine is frequently used with methohexitone (see Section 1-11-5), therefore it is important to discuss specific contraindications to its use.

Patients suffering from glaucoma should not be given atropine because of the danger of loss of vision due to an increase in intraocular pressure (Drug Profile 1976).

Because atropine produces tachycardia, it should not be given to patients suffering from cardiovascular disease unless their physicians have been consulted (American Dental Association & American Heart Association 1964).

Similarly, patients suffering from Wolf-Parkinson-White syndrome should not be given atropine because of the risk of intractable tachycardia which could be fatal (Hannington-Kiff 1972b).

Similarly, atropine should be avoided in thyrotoxicosis (Foreman 1970a) and in the elderly (Litchfield & Gerard 1971).

1-9-11: CONTRAINDICATIONS TO THE USE OF DIAZEPAM

Diazepam is frequently used with methohexitone (see Section 1-11-6h), therefore it is important to discuss specific contraindications to its use.

- (i) Myasthenia gravis is the only real contraindication (Woods 1974).
- (ii) The elderly are more subject to respiratory depression and hypotension with, even small doses, of diazepam.
- (iii) Patients undergoing treatment for depression should be treated

with caution because diazepam may intensify the effect of their medication.

1-9-12: CONCLUSIONS

1. The use of methohexitone implies an expertise in patient assessment new to dental practice.
2. Providing patients are healthy enough to reach the surgery, detailed medical reports are probably not essential - unless some specific disease is suspected.
3. Any condition (see Section 1-9-2f) that increases the metabolic rate will increase the rate of biotransformation of methohexitone - hence patients will start to recover more quickly and may become restless in the presence of pain or some other discomfort.
4. If a patient is unable to breathe through his nose (see Section 1-9-3a) he should not be given methohexitone - the presence of the pack will prevent mouth breathing and the patient will be unable to breathe at all. (The pack is discussed in Section 1-10-7d.)
5. There is no reason to give methohexitone to a patient who has sickle cell anaemia, even in an emergency (see Section 1-9-3c).
6. The conclusions concerning epilepsy are in Section 1-9-4g.
7. Uncontrolled diabetics must not be treated.

Controlled diabetics may be treated, provided they have eaten their regular meals but comply with the fasting rules. (See Section 1-10-1.)

8. Patients with myocardial disease should not be given methohexitone. The danger of tachycardia is too great.
9. Patients who are hypertensive should not be given methohexitone if they are taking ganglionic blocking agents.
10. Patients who are on antidepressants, tranquillizers and drugs of abuse must be treated with caution.
11. Thyrotoxic patients are in extreme danger with any anaesthetic technique - methohexitone must not be given.
12. Whilst the haemophiliac may not be in any danger from the effects of methohexitone per se, he may be from the effects of dentistry. These patients should be treated in hospital and under correct drug regime.
13. I feel that pregnancy should be an absolute contraindication.
14. Where ever there is doubt about a patient's health, methohexitone should not be used.