INTRA VENOUS SEDATION IN DENTISTRY COMPLICATIONS
THEIR TREATMENT AND PREVENTION

C. LAMBERT
A REVIEW OF COMPLICATIONS AND THEIR TREATMENT
RESULTING FROM THE INTRAVENOUS SEDATION
TECHNIQUE OF DIAZEPAM, METHOHEXITONE SODIUM
AND ATROPINE SULPHATE WITH LOCAL ANAESTHESIA

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Colin Lambert. 9.12.77.
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Finally, thank you to my patients and staff who aided me in my administrations and to my examiners for their final detailed evaluation.
"The care of the human mind is the most noble branch of medicine." (GROTIUS)
(Quoted on the title page of the American Journal of Psychiatry, Vol.121, 1964-65.)

"Ideal therapy should be self limiting and thus have an end-point. That this ideal cannot always be attained is recognised in the old therapeutic saw, 'to cure occasionally, alleviate often, to comfort always'." (PARGITER 1977)

"Concerning psychotropic drugs; it is ill judged to try to teach a drowning man to swim when what he needs is a life belt. Some will only need the belt a short time while being taught to swim, others longer. And may there not be those who will never learn to swim, no matter how skilled the instructor?" (PARGITER 1977)
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INTRODUCTION AND OUTLINE OF THE REVIEW

This review was prompted by the writer's personal experience of the occurrence of complications associated with the intravenous administration of diazepam, methohexitone sodium, atropine sulphate and local anaesthesia for anxious dental patients. A current text (Intravenous Anaesthesia 1973) does not mention in detail the treatment of certain complications, for example the accidental intra-arterial injection of drugs.

The aim of the work is therefore to review the available reports of complications and to report my own experiences. As the dental literature concerning sedation complications is limited, and because the use of the technique (intravenous diazepam, methohexitone sodium, local anaesthesia and atropine sulphate - 2ml diazepam (10mg) are diluted with 0.5ml atropine sulphate (0.3mg)) cannot guarantee that a patient is conscious at all times, the review has been extended to include the relevant medical and general anaesthetic literature.

The pharmacology of diazepam and its use in dentistry are reviewed. Complications which may follow its use are then considered.

Patients occasionally are very restless and uncooperative when given diazepam intravenously. The reason for such an untoward response is unknown but there is some evidence to show that certain types of personality are prone to exhibit such reactions. Some psychiatric personality types are described with reference to diazepam. This may enable the dental surgeon to predict a poor response to diazepam sedation so that a difficult treatment
may be avoided and an alternative method used.

The pharmacology and complications of methohexitone sodium administration are discussed. Its various uses in anaesthesia in dentistry with comparative doses used are reviewed with evaluation of one popular technique. The aim is to relate the doses used in other techniques to the small doses used in dental sedation.

Atropine sulphate is a drug of established safety. References in the literature to its pharmacology are not recent but have been included for the sake of completeness.

Sedated patients in their more suggestible state may retain inadvertent post-hypnotic suggestions. They may hear and retain subconsciously statements or attitudes concerning them made during their treatment which may in the future produce adverse dental attitudes and fears. This complication may be avoided by minimising background conversation and alerting surgery staff to be careful of their conversation. Examples of patients hearing and remembering conversations concerning themselves during general anaesthesia are reported to reinforce the importance of this complication relevant to dental sedation.

Local complications of the intravenous administration of drugs are considered with reference to venepuncture complications, accidental intra-arterial injection of drugs and thrombophlebitis. With the cooperation of the Department of Anatomy, Sydney University, I undertook a dissection of the left cubital fossa and dorsum of the left hand. This subsection is included in Part V.
The eyes are more vulnerable to damage both from foreign bodies and the drying of secretions, especially under the influence of atropine during intravenous sedation. These problems are reviewed as are dangers from glaucoma.

The major complications of cerebral damage or cardiac arrest may occur. As the best course of action is prevention, the background to the causes of these disastrous complications is reviewed to enable earlier recognition of warning signs by the dental surgeon. All facts should be gleaned from anaesthetic and sedation deaths so that future anaesthetic and sedative techniques may be made safer.

A search of the literature disclosed only a limited number of post sedation patient questionnaire surveys of complications. In view of this lack of information I undertook an investigation of complications arising in my practice. Two hundred and sixty one patients were asked to report changes they noted from their normal behaviour as detailed in a questionnaire (p.310). Their responses were then analysed for the incidence of untoward reactions to the sedation technique employed. The results of the survey are assessed and presented in tables and graphs and conclusions are drawn (Part X).
PART I
DIAZEPAM
CHAPTER 1.

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CHAPTER 2.

DIAZEPAM COMPLICATIONS.

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CHAPTER 1.
PHARMACOLOGY OF DIAZEPAM.

Diazepam is the primary agent I use to sedate unduly anxious patients undergoing extensive dental treatment. The pharmacology of diazepam will now be briefly reviewed to establish limits to the safe use of the drug by the dental surgeon.

A. Nervous system.

Diazepam first became available for general use in 1963. It is classified as a minor tranquilizer, and its most obvious pharmacological effect is that of causing muscular relaxation and the reduction of skeletal muscle tone (Parkes, from Knight and Burgess 1968; Randall et al 1961). Diazepam disrupts reflex interneural transmission, tends to prevent convulsant activity and impairs recall of events after its intravenous administration.


B. Cardiovascular system.

Diazepam's effects on the cardiovascular system generally are minimal. The main effect is hypotension and reduction in cerebral blood flow in high dosage, otherwise in the supine patient the effects are minimal when usual doses are given (10 - 20 mg). Effects on blood pressure and pulse rate are also insignificant in the dosages used in dentistry (Dalen et al 1969; Healey et al 1970).

Brown and Dundee (1968) commented on the relative
stability of the cardiovascular system in doses generally used (0.6 mg to 0.8 mg per kg body weight). Heart rate is decreased in anxious patients after the administration of diazepam intravenously. Chambiras (1972) observed a brief heart rate rise of up to 40 beats per minute in 19 of 27 dental patients receiving local anaesthesia with 2 per cent lignocaine and adrenalin 1 in 80,000 under intravenous diazepam sedation. This was not seen where local anaesthesia with felypressin was used. (Aellig et al 1970).

The onset of sedation is often accompanied by noticeable vasodilatation of the peripheral blood vessels (Chambiras 1970). This dilatation is not accompanied by blood pressure changes in the supine patient. A vasodilating effect on coronary blood vessels has been reported by Abel et al (1970).

C. Respiratory system.

Diazepam produced central respiratory depression affecting tidal volume only (Hunter 1967). Respiratory depression is accentuated when diazepam is used with opiates in premedication and may even cause apnoea. Intravenous doses of 0.66 mg per kg of diazepam do not affect the respiratory response to carbon dioxide (Steen et al 1966).

The use of diazepam in dentistry with regard to its safety has been favourably reported on by many authors (Dalen et al 1969; Brown and Dundee 1968; Katz et al 1967; Steen et al 1966; Hollis 1969; Knight and Burgess 1968; Schechter et al 1970; Rollason 1968; Driscoll et al 1972; Keilty and Blackwood 1969; Healey and Robinson 1970; Rattray 1968; Foreman 1970; Litchfield 1971).
D. Metabolism of diazepam.

The slow metabolism and excretion of diazepam are its main disadvantage when used in outpatient dental procedures. Its minimal effects on respiration and the cardiovascular system, its amnesic properties, relaxant and anxiety-reducing properties make diazepam an invaluable agent in the treatment of anxious patients. However, it has a long plasma half life and delayed recovery, depending on dosage, is frequently seen.

Schwartz et al (1965) using radioactive labelled diazepam (H3) found that in man (2 subjects) only 10 per cent of an oral dose was found in the faeces. This indicated that the administered dose was almost completely absorbed and also that if any secretion back into the gastrointestinal tract did occur the dose so secreted was reabsorbed. The half life of the urinary excretion rate in man was 2.7 days. Their studies indicated that the half life of compound 4 (which was later found to be the demethylated metabolite of diazepam) was much longer than that of diazepam in human blood. The rapid appearance and fall-off of H3 (diazepam) in the blood of the two subjects during the first day, together with the excretion of less than 20 per cent of the labelled drug during this period suggested that the drug was taken up by the tissues.

They found a distinct plateau in both level fall-off and the rate of urinary excretion of H3 (diazepam) in one of the subjects. This finding raised the possibility that in a certain percentage of patients treated with diazepam there may be a retention of drug or metabolite in some depot, followed by release into the blood at a rate which compensated for the loss of metabolites by urinary excretion.
Schwartz et al concluded that the two subjects given 2 mg of H3 (diazepam) orally excreted an average of 71 per cent of the dose in urine and 10 per cent in the faeces. They estimated that peak levels of diazepam in the blood at 2 to 4 hours averaged 0.07 micrograms per ml. The fall-off of ether extractable blood radioactivity in the first patient was characterized by a fast component (half life of 10 hours), a plateau from 1 to 4 days, and then a slow component (half life of 2.7 days). In the second patient the fast component (half life of 7 hours) was followed immediately by a slow component (half life of 2.6 days) which was comprised of diazepam in compound 4 (demethylated diazepam).

Randall et al (1965) showed that the metabolites of diazepam are pharmacologically active having similar actions to diazepam but not being as potent. Their studies were on rats and monkeys and they tested chlordiazepoxide as well as diazepam and concluded that these drugs form pharmacologically active metabolites.

De Silva et al (1966) tested the effects of short-term oral doses of diazepam (10 mg) as well as intramuscular and intravenous modes of administration. A long-term regimen of the drug given orally in two cases was studied and both these cases showed a slow drop-off of both diazepam and its major metabolite (N-desmethyl diazepam), although the metabolite drop-off curve was much longer than that of the diazepam (Ref. Graphs 1,2,3,4 p.10-11).

The patterns indicated a redistribution in the blood of diazepam and its metabolite which were previously stored by tissues. Chronic massive dose
GRAPH 1

Blood level fall-off curve in man following a single oral 10-mg dose of diazepam.

GRAPH 2

10-mg iv.

GRAPHS 2 & 3 - Blood level fall-off curves in man following a single 10-mg dose of diazepam in a parenteral formulation by i.v. and i.m. routes.

GRAPH 3

10-mg im.

(Reproduced from DE SILVA (1966) p. 697.)
Blood levels of diazepam and its metabolite (Ro 5-2180) from a human given 150-200 mg/day orally for 8 weeks followed by gradual withdrawal of medication.

(Reproduced from DE SILVA (1966) P. 699.)
levels of diazepam averaged 1.6 micrograms per ml (after one week of continuous dosage), while N-desmethyl diazepam continued to increase until an apparent equilibrium was reached at a ratio of diazepam to desmethyl diazepam of 1 to 2.5. Only traces of the urinary metabolites oxazepam and 3-hydroxydiazepam were identified in the blood.

In investigating the relationship of behaviour changes to changes in diazepam blood concentration after diazepam administration in monkeys, Coutinho et al (1973) reiterated the finding that initially the absorption of diazepam was very rapid. They showed the presence of diazepam and its major metabolites as early as a quarter of an hour after a dose and that the N-desmethyl derivative predominated throughout the 24 hour period. The concentration of diazepam in all three tissues, blood, brain and muscle fell relatively faster than its metabolites. Correlation of behavioural changes with tissue concentration of diazepam and its metabolites suggested that behaviour paralleled changes in concentration of unchanged diazepam rather than its metabolites.

In a study in man of a pharmacokinetic profile of diazepam following single intravenous and chronic oral administrations Kaplan et al (1973) fitted their intravenous blood level data into a three compartment open model system containing both a shallow and deep peripheral compartment. The apparent half-life of elimination of diazepam following intravenous administration ranged from 21 to 37 hours. The rate at which diazepam returned to the central compartment from the deep peripheral compartment was shown to be the rate
controlling factor in the elimination of diazepam and in the formation of desmethyldiazepam.

E. Extended effects of diazepam.

In 1972 Baird and Hailey commented on the observation by van der Kleijn et al (1971) of the absorption of diazepam metabolites in the gastrointestinal tract following intravenous administration of diazepam in mice and dogs. Baird and Hailey suggested an enterohepatic process to account for the irregular fall-off of diazepam initially followed by a peaking rapid reappearance of the drug at about 6 to 10 hours with a further drop, then a further peaking at 50 hours. There was a concurrent gradual increase in desmethyldiazepam. They suggested that this coincided with the subjective reports by their subjects of drowsiness and sleepiness at these particular time periods.

They concluded that there is the possibility of an enterohepatic cycle as gradual release of diazepam from adipose tissue would be expected to result in a plasma level curve with a plateau rather than a peak as was found.

Baird and Hailey (1973) carried out a study of the plasma levels of diazepam and its major metabolite after intramuscular administration of diazepam and noticed a similar peaking of the drug at about 6 to 10 hours after an initial rapid decrease of plasma levels of diazepam. In each case they found a gradual rise in diazepam's major metabolite, desmethyldiazepam, in man.

Their experiments have been criticized by Ghoneim et al (1975) on the grounds of inadequate experimental design and limited numbers of subjects, thus possibly invalidating their conclusions.
In 1975 Eustace et al studied the biliary excretion of diazepam in man but found that in the time 6 to 10 hours after administration of the diazepam, the concentrations in the bile were too small to account for the dosages in the plasma. Diazepam (10mg) was administered intramuscularly to four patients who had biliary t-tube drainage. Blood and bile diazepam metabolite concentrations were measured for 12 hours. The expected fluctuations in blood diazepam concentrations were seen, and conjugated diazepam metabolites were present in human bile. However, bile diazepam concentrations were insufficient to account for an enterohepatic circulation.

Korttila and Linnoila (1975) suggested from their study that there were large inter-individual variations in serum concentrations of diazepam within each dose level. The increases in serum concentrations of diazepam after the intake of food support the concept of an enterohepatic cycle for diazepam. Here we have authors whose impressions tend to support the idea of Hailey's et al of an enterohepatic cycle for diazepam. Ghoneim et al (1975) suggested that in their study there was no rebound effect in plasma concentration or increase in plasma concentration of diazepam. Also there were not any subjective reports by patients of recurring symptoms after their initial recovery period. From presently available data one can conclude that the mechanism of re-release of diazepam still awaits elucidation.

F. Test of recovery from sedation.

Newman et al (1970) used a dot-joining test to determine the time of recovery from a combined diazepam and meperidine mixture. They concluded that diazepam and meperidine appeared to be a potent combination
significantly affecting psychomotor functions for short durations and at relatively low doses. The drugs were administered intravenously and the general conclusion was that the use of the Trieger test in measuring recovery in the dental clinic was suitably demonstrated and that it showed the relative duration and effect of various sedative agents on psychomotor functions.

This test may be used as a measure of recovery and thus facilitate the release of recovered patients and the economic use of recovery facilities in outpatient offices and clinics. The recovery time for diazepam with meperidine was 60 minutes after the patient had left the chair. No tests were done for periods after 60 minutes. A questionnaire to determine the patients' subjective effects following the sedation appointments was not arranged by these authors.

The effects of diazepam on psychomotor and other skills following its administration will be reviewed in the next section. It is important at this point to note that there is a delay in the excretion of diazepam and its metabolites from the body after intravenous injection and that the drug effect may recur. Holland (1977) commented that there is a marked dose response variability seen with diazepam - this is not so evident where methohexitone sodium is used as a supportive amnesic agent at the time of the appointment but it may become more apparent post sedation (ref. Part X, p.308).
CHAPTER 2

DIAZEPAM COMPLICATIONS

Complications reported following the use of diazepam are reviewed in the medical and dental literature. The knowledge of complications as reported may prevent recurrence of similar problems during subsequent appointments involving the use of diazepam.

A. Effects on psychomotor skills.

Diazepam has been extensively prescribed in the general community and authors have evaluated effects of diazepam on psychomotor skills related to driving ability and its effect in combination with ethanol. This was done to see if the patient is at risk in normal situations (i.e. driving) while taking diazepam.

Lawton and Cahn (1963) investigated twenty male subjects for the effects of diazepam and a diazepam/alcohol combination utilising both psychological and psychomotor tests. Their results showed a small but statistically significant tendency for psychomotor performance to be influenced by diazepam medication whether with alcohol or placebo. They found no evidence to suggest a decrement in performance with a combined dosage of diazepam and alcohol. Their study was conducted long-term. Dosage conditions began with three days of medication with placebo or 5mg diazepam three times daily, followed by a single tablet dosage on the morning of the fourth day. Testing and alcohol were given on days four, eight, twelve and sixteen.

In 1973, Haffner et al studied the performance of eight healthy young males tested by means of eight psychological and psychomotor tests 1 3/4 and 4 1/2 hours
after the administration of either ethanol (30 per cent v/v), diazepam (10 mg or 20 mg), or placebo. The method of administration of the diazepam was by 2 mg tablets.

Diazepam produced stronger subjective sensations of relaxation and reduced concentration than ethanol. The test subjects experienced a similar subjective depressing effect on motivation and effectiveness after ethanol and after the largest dose of diazepam (20 mg). Both diazepam and ethanol reduced the scores in the following tests: memorizing; sorting (of coloured tablets); complex coordination and critical flicker fusion frequency. The scores in letter cancellation and mirror tracing tests were also reduced by both drugs, but in different ways. Ethanol made the test subjects attempt more but increased their number of errors, while diazepam, on the other hand, slowed the subjects, so that they made fewer mistakes, but attempted less. Diazepam (20 mg) also reduced their time evaluation ability, while ethanol did not affect it significantly. Judged by clinical examination diazepam had a less marked effect on proprioception and speech and balance than did ethanol. The effect of diazepam on the flicker fusion and mirror tracing tests could still be recognized 4½ hours after administration of the drug.

In discussion these authors mentioned some of the differences between the effects of alcohol and diazepam on their series of tests relative to driving performance. Firstly, the effect recorded by subjective evaluation of mood varied. After the administration of 10 mg of diazepam, and especially after 20 mg of diazepam, the test subjects reported that they were more
relaxed and at ease, than after alcohol intake. They experienced a similar depressing effect on motivation and capability after 20mg diazepam as after ethanol. These findings are in agreement with the results obtained by Jäättelä et al (1971) who found that 10mg diazepam made the test subjects significantly more inactive and in addition, the male subjects more euphoric.

The effects of alcohol might be due to the well-known initial reduction of inhibition with extinction of self-criticism. In their limited material Haffner et al (1973) showed that diazepam did not appear to induce this effect in the same way as alcohol but the subjects acted more slowly. The slowness could either be due to the altered appreciation of the passage of time as shown by the results of the evaluation tests, or it could be due to slowness of motor performance. If this could be confirmed in a larger study it would be of importance in the evaluation of the motor traffic risk represented by diazepam.

Intellectual or mental capacity was reduced by both alcohol and diazepam. In this respect the effect of alcohol and 20mg diazepam appeared to be about equally effective in memorizing tests, even after 10mg diazepam. The memorizing ability was impaired; this agreed with the findings of Jäättelä et al (1971) in their test on repeating number series. They used a dose of 8mg of diazepam whereas Hughes et al (1965), who used 6mg diazepam and nine verbal or arithmetic tests, did not obtain any significant influence on the
performance score.

The sorting test involved integrated mental and intellectual functions such as alertness, memory and evaluation in addition to psychomotor performances. Diazepam 20mg made the subjects significantly less fitted for this test, but alcohol impaired their ability even more.

The discrimination of flicker fusion frequency has proved a valid test regarding the effects of drugs on central nervous functions (Simonson and Brożek 1952). Haffner et al (1973) found that 10mg diazepam significantly depressed the ability to discriminate flicker to about the same degree as the dose of ethanol given. Similar findings have been reported by others (Holmberg 1971). A decrease in flicker fusion frequency probably reflects a disturbance in the integrative action of the central nervous system, and therefore seems to be a sensitive test for the influence of diazepam on the central nervous function.

In small doses diazepam is believed mainly to alter the mood, especially by relieving anxiety and tension, probably acting on structures in the central nervous system controlling the emotions. However, in the doses given in the present study diazepam also affected psychomotor performances. Speech, gait and balance were little affected as compared with the effect of alcohol. More affected were the results of the sorting test, the complex coordination test and the mirror tracing test. These tests require integrated
reflex activity of the central nervous system and coordinated movements of the limbs. Diazepam impaired the test results, probably mainly by slowing down the activity and by increasing the time required to execute the responses.

Since it has been shown in all experiments that diazepam does not significantly affect monosynaptic reflexes and the peripheral nervous muscular transmission unless large doses are given, the action is probably on central nervous mechanisms involving polysynaptic reflexes (Hamilton 1967; Przybyla and Wang 1968) presumably on the brain stem reticular formation.

Haffner et al (1973) concluded that since the results of their tests showed that the effects of diazepam especially in high doses, are in many respects comparable with those of alcohol, it would be expected that both driving and flying ability are also reduced under the influence of diazepam. In addition, probably the most dangerous effect with regard to traffic safety is the sedative effect of diazepam, which might induce sleep in the driver and thereby cause accidents. The test subjects in the present experiments were obviously sleepy after diazepam intake. They were liable to fall asleep even after such inconvenient procedures as venepuncture.

Linnoila (1973) also studied the drug interaction of psychomotor skills related to driving with regard to hypnotics and alcohol. He concluded that since all the hypnotics studied interacted with alcohol taken the next morning many of these combinations were deleterious for driving. Among the hypnotics that he studied were nitrazepam and diazepam.
Diazepam (10 mg) had additive effects with alcohol on the reactive and coordinative skills of the young subjects, with oral administration. This interaction appeared before the peak blood-alcohol concentrations after a single oral dose of diazepam (10 mg) as with the interaction after simultaneous administration of diazepam and alcohol. These results agree with the observation of Kleijn and Wijffels (1971) that diazepam remains in the brain for several hours. The diazepam alcohol interaction may take place at the receptor level as previously suggested (Linnoila and Mattila 1973). Diazepam may increase the sensitivity of the brain to alterations in blood alcohol concentration, as suggested by Dundee et al (1971). Linnoila (1973a) concluded that diazepam (10 mg) and also other tranquilizers taken orally at night can impair driving skills the next morning, particularly in combination with alcohol. Of special significance he noted that middle aged and older subjects may be more sensitive to the effects of benzodiazepines.

In a further study Linnoila (1973b) compared the effects of diazepam, chlordiazepoxide, and other tranquilizers and alcohol on psychomotor skills related to driving. Once again he remarked on the strong interaction of benzodiazepine with alcohol and that this effect should be considered in medical practice particularly in treating neurotic patients who often use drugs in combination with alcohol. Linnoila discussed the effects of benzodiazepines with alcohol on psychomotor skills. He compared the effects of diazepam with chlordiazepoxide and found that for different skills the two drugs reacted differently with alcohol.
Published reports differ about the interaction of benzodiazepines with alcohol. Dundee et al (1971) showed that diazepam potentiates but chlordiazepoxide antagonizes the effects of alcohol given intravenously. Keilholz et al (1969) showed that 20mg of chlordiazepoxide had additive effects with alcohol in real driving situations. Large oral doses of chlordiazepoxide have proved additive, or have been potentiated, with alcohol (Burger 1963; Ditt and Pauer 1965). No clear antagonism between diazepam and alcohol has, however, been found; either no major inter-reaction has been reported (Hughes 1965; Lawton 1963) or it has been proved additive or potentiating (Dundee 1971; Morselli et al 1971). The nature of the benzodiazepine alcohol inter-reaction depends on the doses of both agents concerned (Dundee 1971; Linnoila 1973) as well as on psychomotor skill measured. So diazepam, chlordiazepoxide or nitrazepam have additive effects with alcohol on reactive and coordinative skills - such as response orientation, concentrated attention, control precision, multi-limb coordination and greater control (Eklund 1970 and Moskowitz 1968) - while diazepam and chlordiazepoxide may slightly antagonize the deleterious effect of alcohol on divided attention (Moskowitz 1968). Other possible factors influencing the benzodiazepine-alcohol inter-reaction are the sex and age of the subjects. (Jäättelä et al 1971 and Linnoila 1973).

Korttila and Linnoila (1975) have more recently studied the recovery of skills relating to driving after intravenous sedation with reference to dose/response relationship for diazepam. Their study returns
25 mg) were tired at twenty-four hours after the injection. On the other hand, Brown and Dundee (1968) found that with a greater dose of diazepam (0.45 mg per kg), 30 per cent felt dizzy at twenty-four hours after the injection. The incidence (Korttila and Linnoila 1975) of tiredness or drowsiness was about the same with the two small doses (0.15 mg per kg and 0.3 mg per kg) and only one subject injected with 0.45 mg per kg of diazepam felt tired ten hours or later after the injection. However, the performance of this subject on the tests at ten hours was as good as before the injection.

(ii) Clinical recovery.

Clinical recovery as assessed by Romberg's test was thirty-six minutes with 0.30 mg per kg and 0.45 mg per kg of diazepam (Korttila and Linnoila 1975) while Baird and Hailey (1972) found 40 per cent of their volunteers to have ataxia and a positive Romberg's test one hour after the injection of 20 mg of diazepam. Clinical tests of recovery were previously reported to be unreliable in assessing patients' psychomotor skills (Linnoila and Matilla 1972b).

(iii) Serum concentration of diazepam.

Korttila and Linnoila (1975) noted that with each dose of diazepam serum concentrations of diazepam increased after taking food. This might be the result of the possible enterohepatic cycle of diazepam (Baird and Hailey 1972; Korttila and Linnoila 1975). Thus, although the increases were not statistically significant and the serum concentrations of the diazepam did not correlate well with performance, fatty meals which can be expected to increase bile secretion should be avoided after sedation with diazepam.
Korttila and Linnoila (1975) concluded that for skills related to driving (the ability to discriminate the fusion of flicking lights, and hand and foot proprioception) measured in a double blind study in thirty-four healthy volunteers before and after three doses of intravenous diazepam that the effects of diazepam were most harmful to coordination. With doses of 0.15 mg per kg, 0.30 mg per kg and 0.45 mg per kg of diazepam the impairment of coordinative skills was statistically significant \((P < 0.05)\) up to two, six and eight hours respectively. No impairment of performance on any tests was measurable at six hours after 0.15 mg per kg or at ten hours after 0.30 or 0.45 mg per kg of diazepam. There were large inter-individual variations in serum concentrations of diazepam within each dose level. The increases in serum concentrations of diazepam after the intake of food support the concept of an enterohepatic cycle for diazepam. It was concluded that patients should not drive or operate machinery for at least six hours after 0.15 mg per kg of intravenous diazepam and at least 10 hours after 0.30 mg per kg and 0.45 mg per kg diazepam.

B. Effects on ill, elderly or alcoholic patients.

Rao (1964), Gundlach et al (1966), McDowall et al (1966) and Ryan et al (1968) reported increased depression and suicidal thoughts and tendencies in patients taking diazepam. Holbrook (1966), noted a variety of side effects in two hundred patients in a medical practice, including increased sensitivity to and prolonged effects of the medication in the elderly. Hallberg and Associates (1964) and Daly and Kane (1965) reported acute toxic psychoses associated with diazepam and Barten (1965) reported similar manifestations when diazepam was withdrawn.
Hall and Joffe (1972) noted six patients who demonstrated aberrant responses to diazepam which were manifested as a cluster of symptoms consisting of tremulousness, apprehension, insomnia and depression followed by suicidal ideation. The syndrome was abrupt in onset and marked in severity and appeared in individuals who had been previously emotionally stable. All the patients had been taking more than the maximum recommended doses of diazepam (that is, more than 40 mg daily), primarily for medical conditions.

The significance of this syndrome lay in the quality of the suicidal ideation, which negated the usual indicators of suicidal intent so that recognition of the possibility of suicide was difficult. The appearance of any of the preliminary symptoms of this syndrome is therefore an immediate indication for the withdrawal of diazepam and the protection of the patient against suicidal impulses. Furthermore, it was strongly suggested that physicians adhere to the maximum recommended doses and be aware of the possibility that peripheral vascular disease and age may be a factor in the appearance of cumulative toxic effects.

Where many patients are referred for anxiety control in dentistry a proportion have on occasion some psychiatric problem which is under control by daily diazepam maintenance. If they are subjected to high dose intravenous basal sedation of diazepam these toxic reactions may manifest themselves and therefore, where possible, another drug should be used.

Daly and Kane (1965) reported two severe reactions to benzodiazepine compounds. Their second reported case is relevant as diazepam was used in conjunction with
chlordiazepoxide. This patient was not elderly (30 years) but demonstrates the syndrome very well. He was admitted to hospital following episodes of disorientation, querulousness and display of paranoid delusions for about a week. On the night prior to admission he was seen to be surreptitiously taking chlordiazepoxide, to which he had unlimited access. He had been hospitalized in the same centre in the early part of the year when he had an acute Korzakoff-like brain syndrome with confabulation, memory loss, impaired attention, labile affect and generalized interference with intellectual function but with no evidence of psychosis. This patient was diagnosed as having toxicity effects and with hospitalization recovery progressed over the next three months. Full recovery ensued in his case with no abstinency syndrome seen on the withdrawal. This case reinforces the recommendation of wariness when dealing with patients who are taking large doses of maintenance sedative drugs.

C. Effect on depressed patients.

A report by Ryan et al (1968) referred to an increase in suicidal thoughts and tendencies in depressed patients associated with diazepam therapy. He quotes seven cases in which there was an association in time between the institution of diazepam therapy and the onset of suicidal thoughts and tendencies, which tended to be concealed by patients who were at the time receiving psychiatric treatment. An additional patient demonstrated deepening of depression while receiving diazepam. Ryan et al recommended that physicians should consider the possible adverse depressive effect of diazepam when prescribing it as an anti-anxiety agent. This recommendation applies equally to the dental surgeon using diazepam sedation.
the review to intravenous diazepam and its use in dentistry. They commented that diazepam is generally used as an intravenous sedative drug for outpatient anaesthesia. Although rapid recovery after diazepam, measured by a paper and pencil test, has been reported (Driscoll et al 1972), it is commonly believed that recovery after intravenous diazepam was delayed (Baird and Flowerdew 1970; Baird and Hailey 1972; Fox, Wynards and Bhambhāmi 1968). Advice against driving for twenty-four hours after intravenous sedation has been recommended (Dixon and Thornton 1973; O'Neil et al 1970).

Since reports about delayed recovery and the recommendation not to drive after diazepam are mostly based on subjective assessments of patients by anaesthetists, an investigation (Korttila and Linnoila 1975) was conducted in order to provide objective data by measuring skills related to driving after three different doses of diazepam (0.15 mg per kg, 0.3 mg per kg, 0.45 mg per kg). The doses of diazepam were based on those found in the literature (Baird and Flowerdew 1970; Brown and Dundee 1968; Dalen et al 1969; Dixon et al 1973; Dundee and Haslett 1970; Fox, Wynands and Bhambhāmi 1968; Rao et al 1973) and performance in the test used bore an approximate relationship to driving ability (Eklund 1970; Häkkinen 1958).

(i) Subjective recovery.

The literature about subjective tiredness or drowsiness after intravenous diazepam is controversial. Baird and Hailey (1972) reported a recurrence of clinical sedation at six hours after injection in five volunteers who were given diazepam 20 mg. Three of their volunteers who were given diazepam 0.36 mg per kg (approximately
Reports in the literature of an increase in suicidal thoughts and tendencies in individuals who have been treated with diazepam include that by Rao (1964). In one patient out of the eight in his group receiving diazepam, depression developed with suicidal tendencies during trial diazepam therapy. With the administration of imipramine hydrochloride the depression lifted. In a study reported by Gundlach et al (1966) emergent suicidal impulses and thoughts developed in nine patients, seven of whom were receiving diazepam, and two of whom were receiving placebo.

In the study by McDowall et al (1966) two patients discontinued diazepam therapy, one because the drug made him feel ill and the other because the drug made him feel depressed. These reports are at variance with the enthusiasm expressed for diazepam by most writers. The major adverse side effects were considered to be the possible development of ataxia and confusion. However, the report by Feldman (1962) of the progressive development of dislike and hate in some patients, manifested in one by an overt act of violence, may not be totally unrelated to the problem. In two of the cases referred to by Ryan et al (1968) suicide did take place.

The comment by Ryan et al (1968) on their cases is interesting and will be described in detail.

Of eight patients, two were considered to have a psychotic depressive illness initially. The condition of one of these quickly improved, and this patient was not regarded as having basically a psychotic illness. The six other patients were regarded as having psychoneurotic illnesses when they presented. The
diagnostic impression in case one was revised to a psychotic process after the patient's suicide attempt. This kind of revision in diagnostic thinking also occurred after patient three did commit suicide. The other individuals continued to be regarded as having adequate ego strength and were not considered to have had underlying psychoses or borderline psychoses. This point is made because, while diazepam is no longer recommended as a useful drug in psychotic illness, it is recommended for the alleviation of anxiety in individuals suffering from psychoneurosis.

Five patients showed improvement in a matter of three or four days after the discontinuation of diazepam therapy and the institution of treatment with antidepressant drugs, either imipramine or amitriptyline. The improvement was considered to be associated in time with diazepam withdrawal rather than the onset of antidepressant medication, as neither imipramine nor amitriptyline was believed to contribute to the lifting of depression in this short a time span.

Ryan et al (1968) believed that in several of the cases presented there occurred the insidious onset of suicidal ideation and intent as seen in smiling depressions in association with the use of diazepam. A smiling depression is a façade manifested by some severely depressed individuals in which the use of denial tends to conceal the underlying depressed effect. This aspect was a cause for concern to these authors which prompted the reporting of their experiences.

There has been no clear warning that diazepam may have this kind of adverse effect in psychiatric patients, only that it cannot be expected to do the job of
the accepted antidepressants in patients with severe depression. It would seem that caution should be exercised in the use of diazepam in all patients in order to promptly detect adverse depressive effects. The use of diazepam in even mild depressions, in their view, requires consideration of the potential hazard of the onset of suicidal thoughts and tendencies which may not be readily recognized. Diazepam must be used with caution in psychotic or severely depressed patients.

D. Paradoxical reactions.

Paradoxical reactions are so called because on administration of diazepam, instead of the patient becoming tranquil, rested and quiet, the patient becomes agitated, distressed and disturbed to varying degrees. This reaction is not reported in the literature at length and possibly requires the experience of a number of cases before it is seen. As this is a most disturbing complication, references in the literature will be detailed. References to these types of reaction in the psychiatric literature are reviewed in Chapter 3.

Each author who encountered this complication has given his own interpretation of the situation and its cause. Glazer and Small (1972) reported a case in which a seventeen year old girl was given intravenous sedation on previous occasions with no untoward reactions. Her weight was 105lb, her medical history was non-contributory, her blood pressure was 130/80mm Hg and she had a pulse of 100 per minute. She had previously been treated twice with a modified Jorgensen technique (pentobarbitone and pethidine) and once with diazepam intravenously.
The patient was given 10 mg of diazepam slowly into a wrist vein, following this, local anaesthesia with prilocaine hydrochloride and 1 in 200,000 epinephrine was injected. All the carious teeth were prepared in the next thirty minutes. The patient began to weep uncontrollably and would not respond to questions from the operator. Shortly thereafter, she began to thrash about in the chair, necessitating two nurses to restrain her arms and legs. After five or ten minutes of uncontrollable movements and no response to questions, 100 mg of pentobarbitone intravenously was administered which took immediate effect, the movements ceased.

Communication with the patient was impossible, all dental work was abandoned and the patient moved to the surgery recovery room. Fifteen minutes later the patient was still in an almost trance-like state, but now her breathing had become very irregular and she was beginning to show slight colour changes (type of change not documented). Her blood pressure was now 140/80 and the pulse was regular at 140 per minute. Her respirations were aided with an air viva with oxygen supplied. Her colour quickly changed back to normal and one hour and fifty five minutes later she finally began to respond to questions. She had no memory of the events which had taken place previously and her vital signs were once again normal. These authors offer no explanation for this very unusual reaction except to state that if the girl did "dabble with drugs" recall of a past hallucinatory experience might have occurred.

The problem of an adverse reaction is an inherent possibility when utilising any form of drug
sedation. Therefore, no practictioner should attempt any form of sedation without adequate training, staff, equipment, and facilities in order to ensure that these continuing privileges and the safety of these treatments are maintained. (Glazer and Small 1972.)

The second case reported was by Litchfield (1975). The patient was a female, aged fourteen and a half years, who had 20 mg of diazepam injected intravenously for an apicoectomy. The patient appeared normal at the commencement but soon after the diazepam was injected she exhibited strange and unusual body movements and began to speak in pronounced, obscene tones, "which made one think that she was repeating the words and body actions used by the person 'possessed' in the film 'The Exorcist'." In fact, these actions and words were almost identical to those used by the actress in the film. This unusual behaviour continued through most of the operation and also for some two hours afterwards. The operation was completed and the patient had no recollection of the event. However, the unusual behaviour of the patient caused a good deal of concern and embarrassment to members of the staff, especially as it continued for such a long period afterwards. On questioning the patient some time after the operation the dental surgeon found that she admitted having seen the film "The Exorcist", even though she was under age. On a subsequent appointment for post-operative treatment the patient appeared normal and had no memory of her unusual behaviour.

Litchfield (1975) suggested that this case history highlighted the extent to which emotional and psychological factors can manifest themselves when
sedative and psychotropic drugs are used. Proper handling and care of such persons until they have recovered from the affects of the drug becomes a very important matter. If a further sedation session is necessary another drug or less of the same drug would be desirable. This may be an example of an abreaction produced by a hypnosedative drug. (ref. Part IV)

A third report of unusual adverse behaviour on injection of diazepam intravenously was reported by Driscoll et al (1972). They reported similar situations to an experience of mine. The most distressing single side effect noted was the paradoxical or reverse psychological reactions seen in a few patients. These patients became fearful and more anxious for a short period after receiving diazepam, rather than becoming calm and relaxed. On retrospective questioning it was noted that none of these patients had ever been inebriated or had taken any alcohol containing beverages. They had avoided alcohol because they were afraid of losing any degree of psychological control over their actions and thoughts. When they experienced this loss of control under diazepam, fear rather than relaxation was initially experienced. This appeared to be a non-specific effect, unrelated to the particular drug (diazepam) being studied.

Driscoll suggested that this psychological complication might be prevented by better screening of patients for diazepam sedation. Those few patients who indicated a reluctance to relinquish any self-control possibly could be reassured before administration of the drug. They may be also given a test session
of nitrous oxide inhalation sedation, with its rapidly reversible effect that will expose them briefly to such sensations and thereby possibly remove their fears. However, some patients may not be suitable for intravenous sedation and may require other methods of anxiety control.

Hypnosedative drugs are used in psychiatric practice to initiate exposure of repressed traumatic experiences by the patient. This behaviour by the patient is referred to as an abreaction and may occur spontaneously under the effect of a hypnosedative drug. The patient becomes very distressed, agitated and may cry uncontrollably. Treatment is to use an authoritarian hypnotic technique to reinduce the patient or to administer more of the sedative drug. (Collison 1977.)

E. Venous irritation and thrombophlebitis.

In my experience venous irritation and thrombophlebitis is a frequent complication. A review of this complication of diazepam is in Chapter 14. The irritation is thought to be due to the special solvents needed to dissolve the diazepam. The possibility of precipitates causing thrombophlebitis was considered by Jusko et al (1973).

Assuming that the solvent system is responsible for these complications an alternative formula has been prepared replacing the glycoferol-alcohol-benzoic acid with cremophor E.L. Siebke et al (1976) found a significant reduction in the incidence of thrombophlebitis using diazepam in the new solvent.

F. Diazepam and cardiac arrest.

Relkin (1966) found no reported fatalities due to diazepam.
He reported on a twenty year old Caucasian male who was admitted to hospital with a clinical diagnosis of dystonia musculorum deformans of progressively worsening type.

In an effort to relieve the patient's painful leg spasms therapy with diazepam 10 mg orally every six hours was instituted. The dose of diazepam was increased to 15 mg every six hours. Two days later the patient stated that the spasms were slightly less severe. Although the drug caused sedation, which was especially marked during the last four days of administration, it did not significantly diminish the leg spasms and tremors and therefore was discontinued. The spasms and tremors then exceeded their original intensity and the patient was found to be profusely diaphoretic with dilated pupils, a temperature of 102 degrees Fahrenheit and a tachycardia of 190 per minute. Although there was no apparent cause for the fever, penicillin was given later that day as the temperature rose from 102 to 106.6 degrees Fahrenheit. However, the therapy was without effect and the patient died.

Post mortem examination disclosed no septic foci or significant changes in any organ other than the brain. The brain revealed changes of an unclassifiable neuronal lipid storage disease. Most severely affected were the caudal nucleus and putamen, where most of the nerve cells seemed to be greatly distended with a pale staining substance strongly reactive for lipid. Similar alterations were seen in some cells in the cerebral cortex, thalamus, hypothalamus, brain stem and cerebellum but these alterations were not as great as those noted in the basal ganglia.
Relkin hypothesised that the patient developed an excessive hypothalamic discharge on withdrawal of diazepam and that this alone or in combination with a basic inability of such patients with basal ganglia disease to respond normally to fever caused hyperthermia, exhaustion and death. He recommended that diazepam be carefully tapered prior to withdrawal when using high doses.

Sherman (1974) reported on a thirty-five year old woman with a fracture of the left side of the body of the mandible. The patient had been involved in an automobile accident and was a known alcoholic.

On the second hospital day the fractures were temporarily stabilized using diazepam and methohexitone sodium for sedation and lignocaine for anaesthesia.

Six days later the patient was given intramuscularly, 50mg pethidine and 0.4mg atropine sulphate. Forty minutes later 10mg diazepam were given intravenously. During this time, 260mg lignocaine with 1 in 100,000 epinephrine was given submucosally.

Splints and suspensionary wires were easily placed, the patient being well sedated. About forty-five minutes after the procedure was started, cardiorespiratory arrest occurred.

Within 9 to 120 seconds, precordial thump, cardioversion, closed chest cardiac massage, endotracheal intubation and intermittent positive pressure ventilation produced strong peripheral pulses, normal blood pressure, normal pulse rate and a normal electrocardiogram. The pupils were fixed and dilated. Arterial PO₂ was 69mm mercury, PCO₂ was 26mm mercury and the pH
was 7.4.

Profound neurological deficit resulted and the patient died four days later. Since this episode, the authors learned through personal communication of at least four other fatal cases of oral surgical and orthopaedic closed reductions of fractures in which diazepam given intravenously, with or without local anaesthesia, was implicated in cardiopulmonary arrest. A definite contributory action by diazepam was not shown, although the fact that it was one of the agents used was interesting. Care in its use in patients at all times must be observed and not only in the elderly, but also in the injured, shocked, alcoholic or psychiatric patient.

G. Apnoea and hypotension.

References to hypotensive or apnoeic effects of diazepam also are infrequent in the dental literature. Rollason (1968) reported cardiovascular collapse in a patient undergoing anaesthesia where diazepam was used as an induction agent. However, this was the only report where diazepam was found on its own to cause an emergency situation of this type. The patient was elderly.

Buskop et al (1967) reported an untoward effect of diazepam. Once again the patient was elderly; an eighty-one year old man of average build and otherwise healthy, was referred for operation. During the course of sacral anaesthesia he became restless; 10mg diazepam was administered intravenously. The patient lost consciousness and became apnoeic, his blood pressure and circulation were restored by artificial ventilation without any other measures, but it had to be continued for three to four hours before he was fully conscious again.
Later that evening the patient was again restless and 10 mg of diazepam was given intramuscularly. Within ten minutes he was apnoeic and cyanotic again, and the pulse weak. Artificial ventilation was instituted and was again necessary for three hours. On the other occasions when diazepam was used as a sedative during endoscopies, depression of respiration was observed, and sometimes even a short period of apnoea was suspected. This occurred in elderly, weak subjects, and the dosage of diazepam varied from 5 to 15 mg. Buskop et al suspected that some unpredictability of effect may be expected with 5 to 60 mg of diazepam especially in the elderly.

Greenblatt and Koch-Weser (1973) reported on adverse reactions to intravenous diazepam. Of 14,344 hospitalized medical patients monitored in which many patients had advanced or terminal organic disease the overall mortality was nearly 25 per cent. Adverse reactions were attributed to intravenous diazepam in six patients. Three reactions, confusion in two patients, transient hypotension (in one) were minor. The other three adverse reactions were life threatening (apnoea and coma in two patients, hypotension and coma in one); these occurred in two patients with terminal disease and in another who received large doses of chlor diazepoxide. The results suggested that serious adverse reactions to intravenous diazepam are uncommon even in the seriously ill. However, intravenous sedatives and tranquillizers should always be administered with caution, particularly in patients with hepatic decompensation, advanced cardiac or pulmonary disease, and in those receiving other central nervous system depressant drugs concurrently.
Greenblatt and Koch-Weser (1973) stressed that patients receiving endoscopy or cardioversion were a healthier group. There were no deaths and no adverse reactions to the drug among these individuals.

Several case reports described apnoea or hypotension following intravenous diazepam (Bell 1969; Doughty 1970; Buskop 1967; from Clinical Anaesthesia Conference 1971). In all these reports the patients were elderly, had serious underlying disease, or had received other central nervous system depressant drugs concurrently. Several authors have emphasized the hazards of parenteral administration of multiple anti-convulsant drugs to individuals with intractible seizure activity (Brett 1970; Taylor 1969). Combinations of barbiturates, paraldehyde and diazepam may produce coma and apnoea in such patients. There is some evidence to suggest that the propylene glycol solvent used as an injection vehicle for intravenous diazepam may be partly responsible for adverse haemodynamic and respiratory effects (Bianco 1971; Sharer 1971).

The commonest serious complication encountered in hospital practice is aspiration pneumonitis following diazepam sedation for endoscopy (Holland 1977).

It would seem then, that in dosages used in dental practice, 10-20mg intravenously for an average sized adult who is healthy and not taking other central nervous system depressants, possible hypotensive and apnoeic effects are highly unlikely.

II. Amnesic action of diazepam.

In dental practice, the amnesic effects of diazepam are not a complicating factor as it is this
property which enables a general anaesthetic-like effect to be produced during treatment and is, therefore, desirable for the patient. Unfavourable aspects of treatment are not remembered. Long term amnesia, if it occurred, would be a problem. Patients twenty-four or forty-eight hours later may forget actions or dealings that they make or may forget what they have done with valuables or even what they may have done with their children.

Kahler et al (1967) noted diazepam induced amnesia in cardioversion and Clarke et al (1970) also noted the amnesic effect of diazepam in a study using intelligent male volunteers. A more extensive study in dentistry has been done by Gregg et al (1974) in which third molar teeth were removed under diazepam in conjunction with local anaesthesia. However their study did not extend into the day after the diazepam administrations.

A personal experience demonstrates the problems of unwanted amnesia. A healthy male patient 21 years of age received 20 mg of diazepam and 250 mg of methohexitone with local anaesthesia for a two hour restorative procedure. Two days later he delivered parcels at work during the morning and on returning to work at lunch time could not remember where he had been all morning. This complication would be most alarming to a patient.

I. Thrombocytopenia.

Baumes (1971) reported the presence of an antibody against thrombocytes due to intravenous diazepam in one case. This antibody was responsible for serious
thrombocytopenia which was treated by repeated transfusions of fresh platelets. The antibody was particularly labile and was not found eight months after the incident.

J. Respiratory arrest, diazepam and poliomyelitis.

Brown et al (1975) reported the occurrence of respiratory depression in a patient who suffered from an obscure neurological problem which rendered her paraplegic. Pentazocine and diazepam were given with local anaesthetic and when the procedure was completed she had difficulty in breathing, which required assisted ventilation. These authors suggested that some subclinical respiratory embarrassment was made acute by the respiratory depressant effects of pentazocine and diazepam. Further details obtained by personal communication with one of the authors were interesting. The respiratory distress worsened when the patient sat up (Main 1976). Care must be exercised when treating patients with history of weakness of the musculo-skeletal system.

K. Diazepam and the foetus.

Two considerations must be assessed where a woman is pregnant, anxious about dental treatment and who may require the assistance of sedation with diazepam. These are: the effect of diazepam on foetal formation during the first three months of pregnancy and the subsequent depressant effects of diazepam on the foetus during the remainder of the pregnancy and early after birth. References to these two possible effects of diazepam in the literature are few.

(i) Chromosomal effects.

A literature review did not disclose reports of aberrant effects of diazepam on chromosomes which caused malformation of the foetus. White et al (1974)
studied chromosomal aberrations by means of blood samples drawn several days before surgery, immediately before sedation, and forty-five minutes after sedation, in 20 patients who received diazepam immediately before surgery. It was given intravenously at a rate not exceeding 5 mg per minute in a dose of 12 mg to 20 mg depending on the amount needed to achieve a standard level of sedation. Blood levels of diazepam for all 20 patients were averaged at each time point and were expressed as mean percentage of cells with chromosomal aberrations and mean number of aberrations for each person. A total of four thousand cells were analyzed for each time and a total of twenty thousand for the entire study.

They concluded that their failure to demonstrate a positive effect confirmed the results of most previous studies. They could not detect significantly increased aberration rates after administration of diazepam in combination with other agents. The negative results, granted the fact that various other drugs were used in all the patients, provided reassurance that this commonly used therapeutic measure is not associated with genetic damage as measured by chromosomal analysis. These results do not suggest that diazepam should be administered with abandon to women in the first trimester of pregnancy. Past experience with drugs (for example, thalidomide) has shown what seriously damaging effects on foetal development that drugs may exert and all possible care must be taken not to administer any drug unnecessarily to a woman in the first trimester of her pregnancy. Treatment is best postponed until after the first three months of pregnancy where possible.
Safra and Oakley (1975) suggested that there may be a risk of higher incidence of cleft lip with or without cleft palate in babies whose mothers ingested diazepam in the first trimester. They concluded that their survey lacked sufficient numbers of cases to show a definite correlation. However, the possibility that the association was causal was supported by an independent investigation from Finland.

In a large case-control study of oral clefts, Saxén (1975) noted a threefold relative risk for cleft lip with or without cleft palate without associated malformations among infants of women exposed in the first trimester to antineurotic drugs, mostly diazepam. Saxén and Saxén (1975) extended their analysis to show that the association remained when the antineurotic preparations were limited to the benzodiazepines.

(ii) Diazepam and direct depressant effect on the foetus.

Idänpään-Heikkilä et al (1971) studied placental transfer and foetal metabolism of diazepam in early human pregnancy. They found that the maternal blood level of diazepam increased rapidly following an intramuscular injection of 5 mg of diazepam and the drug crossed the placenta without delay. After six hours the cord blood levels with diazepam were about twice as high as those found in maternal blood. The peak concentrations in foetal tissues were obtained in one hour; the foetal liver and brain diazepam level remained quite unchanged during six hours. In forty-eight hours 86 per cent of the dose was recovered in maternal urine. Neither the premature placenta, term placenta, foetal brain nor foetal small intestine metabolized diazepam. A constant
enzyme activity metabolizing about 3 per cent of added diazepam was found in the foetal liver supernatant.

Scher et al (1972) studied the effect of diazepam on the foetus during labour and the levels of the drug in the maternal and foetal circulations in twelve cases. They found that diazepam caused loss of beat to beat variation of the foetal heart rate pattern within two minutes of intravenous administration of 20 mg of diazepam. This effect lasted an average of sixty-five minutes. It was not associated with significant alteration of foetal pH or Apgar score (a method to assess the general condition of the new born soon after birth) at birth. High foetal plasma levels did not appear to affect the foetus adversely in labour or at birth. Rapid placental transfer occurred and the maternal and foetal blood ratios were variable.

Mofid et al (1973) were concerned with two questions - (a) what were the effects of diazepam on the uteroplacental and foetal circulation as well as on oxygen transfer when the drug was given to the mother, and (b) what were foetal cardiovascular and metabolic responses to this pharmacological agent when injected directly into the foetus. The effects of diazepam on uteroplacental and foetal circulation and on oxygen consumption were investigated in near-term ewes. When injected into the mother in doses between 0.1 and 0.5 mg per kg, diazepam did not alter uteroplacental haemodynamics and oxygen transfer; doses greater than 0.5 mg per kg produced a slight fall in maternal arterial pressure and uteroplacental blood flow. Foetal haemodynamics and oxygen consumption were not altered by any other doses administered to
the mother. Administered intravenously to the foetus with intact umbilical circulation, in doses varying between 0.5mg per kg and 8.0mg per kg diazepam did not alter the foetal cardiovascular functions or oxygenation.

Erkkola et al (1973) also studied the transfer of diazepam across the placenta during labour. A 10mg dose of diazepam was given intramuscularly to thirty-seven patients during the first stage of labour, five minutes to four hundred and one minutes before delivery, after which blood samples were immediately collected from the umbilical cord of the maternal vein. Diazepam was found in all the plasma samples with very great individual variation in the concentrations. Neither the diazepam concentrations in the cord plasma nor the foetal to maternal ratios of the concentrations had any significant influence on the Apgar scores of the newborn. The cause of the diazepam accumulation in the foetal circulation was unclear. The better binding of diazepam with the foetal plasma proteins was discussed. The importance of individual drug doses to parturients according to their weight was emphasized. The conclusion may be drawn from these studies that for the anxious, expectant woman, diazepam may be used with care after the first trimester of pregnancy to facilitate her dental treatment.

(iii) Post partum depression.

Another adverse effect possibility is depression of the baby due to excretion of diazepam in maternal milk in the postnatal nursing period. This is unlikely to have dangerous effects on the newborn apart from a better sleep than usual for the infant - provided doses are kept to a minimum when treating the mother. No studies have been found to substantiate this in the literature,
however, from studies of effects on the foetus from diazepam administered during labour it would appear that diazepam for the new born if provided through breast milk would be unlikely to have any serious effects although, once again, minimal dosages must be provided for anxious mothers who are breast feeding their children. Post natal brief sedation for the mother is usually beneficial. This is a clinical observation.
CHAPTER 3

AVOIDANCE OF UNWANTED PSYCHIATRIC BEHAVIOUR RESPONSES TO DIAZEPAM

This chapter has been included to suggest that difficulties which arise in patient treatment following intravenous diazepam may be predictable with knowledge of the personality type or psychiatric history of a particular patient. In my practice where very anxious patients are treated routinely, the number of patients with various forms of psychiatric disturbance is probably higher than in general dental practice. Some of these patients react poorly to sedation. It would be advantageous to both the dental surgeon and the patient if an initial unsatisfactory appointment involving poor patient cooperation could be eliminated and a more satisfactory treatment technique followed.

Constant and Gruver (1963) reported on a preliminary evaluation of diazepam in psychiatric disorders. They classified their patients into groups: anxiety reactions; anxiety with depression; obsessive compulsive reactions; affective reactions (depressive), schizoaffective disorders; schizophrenia and chronic brain syndromes. They studied a total of 183 patients whose ages ranged from fourteen to seventy-eight years.

Symptoms included anxiety, tension, gastrointestinal complaints (e.g. nausea and cramping); crying spells, loss of interest, hyperirritability, increased capacity for fatigue, muscle spasms, depression, insomnia, feelings of futility, loss of appetite, headache, rage, phobias, obsessions, compulsions, suicidal
thoughts and tendencies, paranoid delusions and auditory hallucinations.

Most patients had previously received a wide variety of drugs including phenobarbital, reserpine, chlordiazepoxide, meprobamate, phenylethylhydrazine, isocarboxazid, chlorpromazine, amphetamines, and electroconvulsive treatments.

Diazepam was administered in divided doses, the total daily dose ranging from 6mg to 30mg per day. The duration of treatment ranged from two days to eleven months, and approximately half the patients received the drug for eight months. Thirty-one patients manifesting depressive components received diazepam with monoaminooxidase inhibitors or imipramine hydrochloride or iproniazid or tranylcypromine or amitriptyline or carphenazine or insulin or electroconvulsive treatments where required. Psychotherapy was continued as usual.

Evaluation of results was based on relief of symptoms and responses were classified as excellent, good, fair and poor. Improvement was graded according to the following criteria:

(i) Excellent - either complete disappearance or marked reduction in intensity of symptoms;
(ii) Good - moderate reduction in symptoms;
(iii) Fair - mild reduction of symptoms with some continuing discomfort; and
(iv) Poor - no change or an increase in intensity of symptoms.

The patients in all but one of the diagnostic categories responded to some extent. Those who responded
best were the patients with psychoneuroses: anxiety reactions, anxiety with depression, obsessive compulsive reactions and affective reactions (depression). Diazepam was effective to some degree in the affective and schizo affective disorders. It also reduced neurotic symptoms in the pseudoneurotic schizophrenic patients. Overall effectiveness regarding reduction in symptoms was 77 per cent. It did not affect the second order of schizophrenic symptoms such as autism, paranoid delusions, and hallucinations. In the two patients with chronic brain syndromes, diazepam was not effective in reducing anxiety depression and hyperkinesis.

Beerman (1964) in a controlled study of the use of diazepam in psychiatric outpatients found that diazepam was more effective in patients in the psycho-neurotic categories also. It benefited those patients with psychotic disorders although their response was more moderate. One failure occurred in a woman aged forty-one years with chronic phobia reaction with hysterical features. After her first and second dose of 5 mg of diazepam she complained of blurred vision and left the study. The eight patients with phobic reaction had, on the whole, the least successful responses.

Merlis et al (1962) found that diazepam did not influence chronic schizophrenic patients treated for one month with a dose of 30 mg daily. Diazepam was beneficial as far as anxiety symptoms were concerned in general medical cases. McDowall et al (1966) agreed with the pattern reported above (Beerman 1964) that showed diazepam to be an effective sedative for patients showing neurotic anxiety symptoms.
Raskin et al (1974) in a double blind study of seven weeks duration compared the effects of 30 mg of diazepam or 45 mg of phenelzine on patients who were divided into depression subtypes and studied their responses to phenelzine, diazepam and a placebo. There was a significant number of anxious depressive patients who were diazepam responders, that is, their symptoms subsided on this treatment and became worse when this drug was discontinued.

In contrast, diazepam was a poor treatment for the hostile depressions. These patients were restless, anxious, negativistic, suspicious and irritable when they entered the study. These symptoms persisted on diazepam and improved on either phenelzine or a placebo.

The comments by Raskin et al (1974) are of interest. Initially, the negative effects of diazepam for the hostile depressive patients seemed to fall into the category of paradoxical reactions, especially as this drug had beneficial effects for the patients with anxious depressions. However, there is a fairly extensive literature on such paradoxical reactions as increases in rage, hostility, anxiety, excitement, depression, paranoid symptomatology, and suicidal ideation associated with either diazepam or another benzodiazepine derivative, chlordiazepoxide. (Di Mascio 1969; Feldman 1962; Gundlach 1966; Hollister 1963; Salzman 1969; Ryan 1968; Rao 1964; McDowall 1966; Tobin 1960; Ingram 1960; Kay 1970; Jäättelä et al 1971; Gardos 1968; Di Mascio 1971.) It was interesting that a third member of this class, oxazepam, did not appear to provoke these reactions. Since oxazepam is a major metabolite of diazepam, diazepam's potential for
provoking these reactions may be related to unusually slow metabolic conversion of diazepam to oxazepam in certain individuals. These untoward effects have been observed in normal subjects (Salzman 1969; Jäättelä et al 1971; Di Mascio 1971) and schizophrenics (Feldman 1962; Gundlach 1966; Hollister 1963) as well as in depressed patients (Ryan 1968; Rao 1964; Kay 1970).

Di Mascio et al (1969) have hypothesized that it may be only in those patients with a history of poor impulse control or aggressive destructive behaviour that the paradoxical rage reaction occurs. They suggest that rather than being paradoxical this may be viewed as an expected or predictable reaction in these individuals.

In the investigation by Raskin et al (1974) diazepam did not provoke rage reactions or evoke other forms of hostility. In a small study, Rao (1964) observed the effects of diazepam over a six weeks course of 30mg down to 10mg per day in eight patients suffering from obsessive compulsive disorders. Findings of the trial indicated the usefulness of diazepam in patients suffering from symptoms of anxiety, phobias, obsessions and compulsions. His success rate was six patients out of the eight on his rating scale for various aspects of obsessive compulsive manifestation.

Conclusions relevant to dental sedation and prevention of complications.

General conclusions to be drawn from the reports of the previous authors suggest that patients who may best respond to intravenous diazepam sedation would be those showing psychoneurotic tendencies, anxiety reactions, anxiety reactions plus depression, obsessive
compulsive behaviour, affective reactions and phobic reactions. Those who may be worse after intravenous diazepam administration would be patients showing paranoid delusions, chronic brain syndromes, hostile depressions, suspicious restless negativistic depression and possibly also schizo-affective disorders. This has not been proven but may be an indicator which may eliminate unsuitable treatment for those patients suspected of falling into a particular psychiatric group. Recognition of disorders would be based on past experience by the dental surgeon of the patient or by a psychiatric history provided by the patient's physician or psychiatrist.
PART II

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CHAPTER 4.

PHARMACOLOGY OF METHOHEXITONE SODIUM.

To appreciate the advantages and dangers of methohexitone sodium the dental surgeon must be familiar with the pharmacology and properties of this drug. Possible complications may then be avoided. Controversy concerning the safety of methohexitone sodium as an anaesthetic agent will be reviewed with relevance to the small doses used in the supplemental technique with diazepam and local anaesthesia.

Methohexitone sodium is used in combination with diazepam and atropine, and local anaesthesia, to ensure amnesia towards the end of longer cases. This enables reduction in the dose of diazepam since the prolonged drowsy and hypotensive effects of increased dosages of diazepam may be more of a danger to the patient than are very brief periods of unconsciousness provided by small amnesic doses of methohexitone sodium (5 mg to 10 mg) at the time of the appointment.

Properties of this ultra short acting barbiturate are reviewed.

A. Metabolism and excretion of barbiturates.

These characteristics of barbiturates are extensively covered by Goodman and Gilman (4th Ed. p.111 - 112, 1970). However, no detail is provided with reference to methohexitone sodium.

Brand et al (1963) studied plasma and adipose tissue concentrations in humans following the administration of exceptionally high doses of at least 1200 mg. Their results indicated that the elimination rate of methohexitone sodium from plasma was faster than that of
thiopentone. However, definite conclusions could not be drawn since concentrations could be measured only up to five hours, because of the limited sensitivity of their ultra violet assay method. Sunshine et al (1966) developed a gas chromatographic method to measure blood concentrations after clinical doses (1.5 mg to 2 mg per kg) but the sensitivity of their procedure did not allow the measurement of drug concentrations for more than ten minutes following intravenous injection.

Breimer (1976) developed a sensitive method using gas chromatography with nitrogen selective detection for the accurate measurement of methohexitone sodium in plasma in concentrations less than 0.05 mg per ml. Methohexitone (3.0 mg per kg) sodium was infused into healthy volunteers and plasma concentrations measured during and after infusion. The decrease in the plasma concentration of methohexitone sodium could be described by two compartment kinetics. The terminal elimination half-life of the drug was relatively short (seventy to one hundred and twenty-five minutes), which was a result of a high metabolic rate (657 to 999 ml plasma per min.). It was concluded that uptake of the drug by adipose tissue did not contribute significantly to its pharmacokinetics in man. In addition to the initial redistribution of an anaesthetic dose of methohexitone sodium, the rapid recovery of patients was a result of rapid metabolism of the drug.

B. Cardiovascular and respiratory effects.

Taylor and Stoelting commented on these properties of methohexitone sodium in 1960. The amount of methohexitone sodium required for induction of
anaesthesia varied from between 20 mg and 250 mg by intravenous administration of a 1 per cent solution. Their average dose of the drug required for induction was 70 mg. Transient apnoea occurred occasionally lasting up to three minutes; when the drug was injected rapidly the frequency of apnoea increased.

Hypotension occurred in five hundred and thirty-four of three thousand three hundred and forty patients following the administration of the initial dose of methohexitone sodium. The systolic blood pressure fell by 10 mm to 20 mm of mercury in four hundred and one patients and 30 mm to 40 mm in one hundred and thirty-three patients. This hypotension was transient and usually returned to the pre-operative level within five minutes. No period of severe hypotension could be attributed to methohexitone sodium. Forty-five patients with a history of asthma received methohexitone sodium during anaesthesia or as an induction agent. None developed bronchospasm nor did it occur in any of the other patients included in the study.

Mild laryngospasm occurred in only twenty-eight patients, of three thousand three hundred and forty administrations and could be relieved by further injection of methohexitone sodium, and the removal of any exciting stimulus (mucus). Insertion of oral airways in patients receiving methohexitone sodium rarely caused laryngospasm. Taylor and Stoelting obtained the clinical impression that patients recovered more promptly after the use of methohexitone sodium than after the use of thiopentone sodium and thiamylal.

The publications of Stoelting (1957), Redish et al (1958), Wyant and Chang (1959) and Taylor and Stoelting (1960) all confirmed the greater potency of
methohexitone sodium as compared with thiopentone sodium.

Concerning the incidence of complications following induction with methohexitone sodium, Stoelting (1957) noted only one instance of coughing and one of laryngospasm in his initial series of two hundred and eighty-five patients. In their more recent paper dealing with three thousand three hundred and forty administrations, Taylor and Stoelting (1960) reported a 1 per cent incidence of spontaneous coughing and a slightly lower incidence of laryngospasms. About 3 per cent of patients experienced hiccoughs during induction. Compared with these low figures there was a 41 per cent incidence of hiccough reported by Wyant and Chang (1959). Wyant and Barr (1960) found that when thiopental and methohexital were combined with nitrous oxide/oxygen, hiccoughs did not occur in fifty-five patients.

Cardiovascular depression was not a feature of the early reports but when hypotension occurred it was transient. Barron and Dundee (1961) considered that due to this relative lack of depression of the cardiovascular system as compared with thiopentone sodium, methohexitone sodium may well become the drug of choice in the elderly hypertensive subject.

Apnoea and respiratory depression have been reported with methohexitone sodium by a number of workers. Wyant and Chang (1959) and Wyant et al (1957) found a high incidence of apnoea with methohexitone sodium while Taylor and Stoelting (1960) reported apnoea of up to three minutes duration with this drug. On the other hand, Coleman and Green (1960) who employed methohexitone sodium in dental anaesthesia under similar conditions to
those of the present study, report an absence of marked respiratory depression. The lack of apnoea in the present work and in that of Coleman and Green (1960) may be accounted for by the smaller dosage used and by the omission of premedication. It has been shown that apnoea and respiratory depression will be more obvious when opiate premedication has been employed (Eckenhoff and Helrich 1958) or when large doses of barbiturates are employed (Dobkin and Wyant 1957; Swerdlow 1958).

Dundee (1964) showed that some anaesthetic doses of methohexitone sodium produced increased sensitivity to somatic pain in a manner qualitatively similar to thiopentone sodium. However, the duration of analgesia after recovery from large doses was much shorter than after comparable doses of thiopentone sodium.

In a study using methohexitone sodium in conjunction with regional anaesthesia in eight hundred surgical patients Meagher (1964) concluded that the major advantages of methohexital sodium were ease of control, lack of severe cardiorespiratory depression and lack of accumulation. He suggested that its main disadvantage was the higher incidence of extraneous muscle movements and vascular irritation after its use.

C. Extravascular injection.

Recant (1960) noted that extravasation of 1 per cent methohexitone sodium did not injure the tissues. Barron and Dundee (1961) also found that inadvertent subcutaneous injection of up to 100 mg of methohexitone sodium produced no sequellae. Weyl et al (1958) also noted this lack of local irritation following extravascular injection.
D. Pain on injection.

Taylor and Stoelting (1960) remarked on the frequency of a complaint by the patient of the intensity of the pain of the injection of methohexitone sodium into the vein. Wyant and Chang (1959) did not mention this complication at all in a series where methohexitone sodium was used alone. In a series of over six hundred administrations there was complaint of pain following the use of a 2 per cent solution in doses up to 950mg (Barron and Dundee 1961).

E. Tachycardia.

Rises in pulse rate have been reported in patients receiving methohexitone sodium (Christenson et al 1961; Rowlands et al 1967; Wise et al 1969; Shafto 1969; Mann et al 1970) usually of the order of 40 per cent after a single anaesthetic dose (Allen et al 1969).

F. Recovery.

Recovery from methohexitone sodium is more rapid than after equivalent doses of thiopentone sodium. Wyant et al (1957) noticed the absence of hangover following methohexitone sodium as compared with other drugs.

In a series of minor gynaecological procedures in which either methohexitone sodium or thiopentone sodium was used as sole drug, the same conclusion was reached by Wyant and Chang (1959). Using a blind technique and combining a barbiturate with nitrous oxide/oxygen for the operation of dilatation and curettage, Wyant and Barr (1960) confirmed a more rapid rate of recovery from methohexitone sodium. It has been frequently suggested that the drug would be very suitable for outpatient anaesthesia in view of this rapid recovery and absence of hangover (Barron and Dundee 1961).
With reference to recovery after methohexitone sodium Doenicke and Kugler (1965) in an investigation of the electroencephalogram (EEG) for twenty-four hours after methohexitone sodium or propanidid noted that the test subject was tired for many hours with various sleep patterns on the EEG following methohexitone sodium administration. The reasons for the tiredness and hangover was presumably the fact that the metabolism of methohexitone sodium amounted to only about 15 per cent to 17 per cent of the initial dose per hour (Zindler 1965). Within the clinical range of dosage each increase in dosage of the drug resulted in linear increase in sleeping and full recovery time (Swerdlow and Moore 1969). Methohexitone sodium thus showed some evidence of accumulation. Therefore the initial recovery to consciousness is rapid but sleep effects still linger. This is in disagreement with Breimer (1976) (ref. p. 57.).

Korttila et al (1975) tested patients recovery on a driving simulator two, four, six and eight hours after a single anaesthetic dose of thiopentone sodium, methohexitone sodium, propanidid and alphadione. The tests were done double blind and compared to pre anaesthetic tests. The driving performances remained significantly worse than in a control group for six hours after thiopentone and for eight hours after methohexitone. These authors suggest that in the doses they used (2 mg per kg for methohexitone sodium) that patients should not drive or operate machinery for at least twenty-four hours after the anaesthetic because of the severity of disturbances found at eight hours. This effect of methohexitone sodium is similar to that of diazepam so that these drugs used together would be expected to potentiate
each other and to adversely affect psychomotor performance well into the post sedation period.

G. Nausea and vomiting.

Nausea and vomiting are relatively rare after methohexitone sodium used for induction and followed by nitrous oxide and oxygen. Dundee (1965b) quotes figures of the order of 2 per cent to 3 per cent. With propanidid the frequency of these complications was more than three times as great.
CHAPTER 5.

METHOHEXITONE SODIUM COMPLICATIONS.

Complications from the use of methohexitone sodium as a supplemental sedation drug are rare as reported in the literature. Patients may receive an accidental intra arterial injection of the drug or respond allergically to the drug.

A. Intra arterial injection.

Brown, Lyons and Dundee (1968) considered that methohexitone sodium was safer than thiopentone sodium if inadvertently administered intra arterially. This safety is directly related to the potency of the agent. The more diluted the solution which can be used clinically, the less is the likelihood of intravascular clotting. Other factors being equal, an oxybarbiturate such as methohexitone sodium should be preferable to a thiobarbiturate. Miller et al (1976) reported on the inadvertent intra arterial injection of methohexitone sodium (20 mg) with a successful outcome after the injection of procaine into the brachial artery.

B. Allergic reactions to methohexitone sodium.

One of the great advantages of methohexitone sodium shared by diazepam is the low frequency of reported allergic reactions in patients even after repeated dosage. Mason and Frew (1963) reported on a twenty year old apprehensive patient who was given 90 mg of methohexitone sodium slowly intravenously. Less than thirty seconds after this injection he sneezed violently three times. This was followed rapidly by coughing, flushing of the face and marked nasal congestion. Breathing became laboured with a respiratory wheeze. His
colour remained good, pulse normal and he quickly recovered. The rhinitis persisted and he was still flushed and having mild respiratory difficulty twenty minutes after the injection. There was no history of allergy. These authors recommend careful investigation of allergy history and if there is any suspicion to give a small test dose.

Reichert et al (1972) reported a rare allergic reaction to methohexitone sodium. In their situation the patient developed itching of his thighs after administration of 14 ml of 1 per cent methohexitone sodium approximately four minutes later while in the recovery room. Shortly thereafter angioneurotic oedema was seen in his lips and about the periorbital areas. A gradual increase in redness of these regions as well as of the face, trunk and extremities occurred. Concurrently, the patient's hands and feet became oedematous. After ten minutes his entire body was uniformly bright red; this condition was accompanied by itching. At this time diphenhydramine hydrochloride 50 mg was administered intravenously. The itching sensation subsided. Hydrocortisone sodium succinate 100 mg was administered intramuscularly. Within twenty minutes the urticaria and angioneurotic oedema began to subside. Approximately an hour post-operatively, the patient was nauseated and had slight emesis. Half an hour later the patient experienced slight chills. By this time all signs of urticaria and oedema had disappeared.

The patient received no medication and did not use drugs, he did have a history of sensitivity to sulphonamide drugs. He was given a letter to his physician describing his allergic reaction and was cautioned
against the use of all barbiturate-type general anaesthetics. This most important aspect of sedation work involving drugs which may produce allergic reactions must be followed through.

Driggs and O'Day (1972) during their experience in administering forty three thousand consecutive general anaesthetics in which methohexitone sodium was the primary agent, treated six patients who exhibited signs of acute allergic reaction. Judging from the literature they suggested that such observable reactions were not being reported or were misdiagnosed and remained unrecognized. All their cases recovered following recognized treatment for allergic reactions.

In the six cases they presented, hypotension was an early sign that persisted until the patient recovered from the reaction. Hypotension secondary to anaesthesia was the diagnosis in two of their patients; the patients were essentially treated for that. The cause of the allergic reactions in two patients was discovered when, at a later date, methohexitone sodium was again administered to them with similar physiologic sequelae.

This type of reaction responded favourably to the prompt application of standard treatment for anaphylaxis, that is, oxygen, vasopressors, epinephrine, steroids and antihistamines. They believed that delay in treatment was the most dangerous aspect of this clinical phenomenon. Rapid diagnosis and institution of therapy are essential.
Comments.

Methohexitone sodium as a primary agent in anaesthesia has a remarkable record of usefulness and safety (Driggs 1972). It is interesting that in the two cases reported by Driggs, the first signs that something untoward was occurring was sneezing and rhinorrhoea and that in the other cases the patients initially became restless and the reaction sometimes occurred soon after completion of surgery. Therefore, the initial warning signs which may present must be carefully noted and acted upon.

My experience of one patient (ref. photograph p.68) who developed urticaria and itching over her neck, face, trunk and abdomen could not be attributed only to methohexitone sodium. The reaction occurred after one hour, not as soon as the drugs were given. Treatment was intravenous antihistamine (Phenergan 10mg). The rash subsided on the following day. There was no previous allergic history to any food or drug.
Photograph 1

Allergic rash extending from forehead down the neck to the abdomen (see p. 67).
Photograph 2

Higher magnification of the patient's neck.
Photograph 3

Allergic reaction extending onto the patient's abdomen.

(Clinical photographs 1, 2 and 3 from the clinical survey reported in Chapter 24)
CHAPTER 6.

USES OF METHOHEXITONE SODIUM IN DENTISTRY.

A. Minimal incremental technique.

Methohexitone sodium is used in dentistry as an ultra short acting anaesthetic agent to enable rapid painful procedures to be accomplished. It may be used after the technique of Drummond-Jackson (1962) described as a minimal increment technique in which a sleep dose of methohexitone sodium is administered and the patient maintained at a light level of sedation and amnesia for the completion of small amounts of conservative dentistry with maximum dosage held at 250 mg of methohexitone sodium and a working time of no longer than twenty minutes (Drummond-Jackson 1973, p.203).

Foreman (1965) refers to the advantages of the minimal incremental technique in dentistry. These advantages include the presence throughout of all normal protective reflexes, an especially valuable factor in heavy cigarette smokers who had proved difficult under deep anaesthesia due to coughing attacks. The procedure with such patients was to remove the mouth prop and allow the patient to clear his throat. He could then usually be asked to swallow and even to open his mouth for the reinsertion of the prop, following which a further minimal dose of methohexitone sodium was administered and the operation resumed. Recovery was also rapid, and patients were virtually in full possession of their faculties on leaving the chair. For the majority of the procedure the patient responded to commands of opening the mouth and to questions as to their comfort and that a great amount of work could be done with
the eyelash reflexes present. In experienced hands this would appear to be an admirable technique for short procedures.

Methohexitone sodium and its application in dental anaesthesia was reported on by Thornton (1970) who commented that several cases of epileptiform seizures have been reported in association with the administration of methohexitone sodium (Galley 1966; Goldman 1966; Boston and Unkles 1969; Ryder 1969; Mann et al 1970). It would appear unwise to administer the drug when a history of epilepsy is elicited in either patient, his parents or siblings.

Thornton (1970) commented that in assessment of depth of anaesthesia methohexitone sodium, like other barbiturates, will produce surgical anaesthesia only at the expense of generalised central nervous system depression. It has been suggested that the presence of an eyelash reflex was associated with safety in that respiratory obstruction does not occur and that the cough reflex is not impaired. (Foreman 1965.)

The eyelash reflex could be very misleading (Mann et al 1970) being sometimes absent in those not fully anaesthetised and often being present in those who do not react to painful stimuli. It would appear from comments such as this balanced against Foreman's reports of very extensive experience in administration of methohexitone sodium that there is a discrepancy in points of view regarding the value of the presence of the eyelash reflex in patient monitoring.

Thornton (1970) commented on the minimal incremental methohexitone sodium technique for conservative
dentistry and referred to recent studies by Wise et al (1969) and Mann et al (1969). Both these studies were carried out in the environment of a dental teaching hospital and both studies employed a separate administrator who was a trained anaesthetist. Both these studies have led to a better understanding of the risks involved in employing the minimal incremental technique and until detailed studies are forthcoming from dental practice (that is, results obtained by the operator/anaesthetist technique), conclusions must be drawn from this reported work.

It is an interesting observation that while these studies were done in the environment of a dental teaching hospital and both studies employed a separate administrator who was a trained anaesthetist, they did not state that the dental surgeon involved was experienced in working with this technique. Unfamiliarity with any technique tends to increase the time period required to do any procedure. Consequently, the drug dosage required to maintain a given state of sedation or anaesthesia is increased. Detailed physiological studies of the effects of methohexitone sodium administration in dental conservative work will be considered later. Thornton's comments relating to these studies will then be presented.

The minimal incremental technique was criticized by Wise et al (1969). They studied broad physiological parameters affected by the technique used in an overdose situation.
(i) Criticism of the minimal incremental technique.

Wise et al (1969) did an extensive physiological trial of the effects of methohexitone sodium when used in a technique claimed to be the minimal incremental technique. Their data showed their usage to be a study of the drug used in overdosage.

The mean range of dosages used were 400 mg to 500 mg with a maximum of 800 mg and operating times up to one and a half hours. They studied thirty subjects classified as nervous or impossible to treat under local anaesthesia. Of interest were their electrocardiogram (ECG), blood pressure and peripheral circulation readings which showed that the patients' peripheral circulations were severely depressed and that to maintain blood pressure the cardiac output increased significantly.

In response to painful stimuli the blood pressure rose dramatically in some cases. It was found that the peripheral tissues were not being adequately perfused with oxygen, the venous oxygen content rose and the venous pressure increased dramatically as the myocardium became more depressed and cardiac output dropped. An increase in the lactate/pyruvate ratio even after the procedure was terminated, indicated that the peripheral tissues were not being adequately perfused with oxygen. Checks on depths of anaesthesia were carried out using an electroencephalogram (EEG) and patients were found to fluctuate in and out of surgical anaesthesia. At times the specialist anaesthetist could not detect respiratory obstruction despite careful observation of the patient. This seems difficult to understand as a specialist anaesthetist would be expected to notice all outward signs of respiratory obstruction.
Wise et al (1969) concluded that although one or two doses of methohexitone sodium caused no severe physiological upset, repeated doses severely depressed cardiovascular and respiratory integrity in spite of the recumbent position. They reported that they had studied the technique as used in dental surgeries and suggested that they tested high dosages on seeing these dosages used in private dental practices. Consequently, the inference from these authors was that the technique was being misused and that patients were being subjected to excessive dosages of this drug routinely in private dental practice contrary to the technique as described by Drummond-Jackson (1973, p.203).

(ii) Criticism of Robinson et al's study.

Foreman (1969) commented in a letter to the British Medical Journal on the study of Wise et al (1969). He referred to the article as a study of the technique used in an extreme overdosage. He agreed with the authors who stated that it would be unfortunate indeed if an excellent drug fell into disrepute due to its misuse which he concluded is precisely what had been achieved by their study. Foreman's main criticisms of the study were that on several points there had been no comparisons made with other drugs being used for comparison of untoward effects as follows.

Wise et al (1969) showed that 45 per cent of their patients treated supine swallowed contrast media placed on the tongue and this media entered the bronchial tree as revealed on later chest radiographs. Apart from the figure of 8.5 per cent quoted by workers of the University of Sheffield (Foreman 1969) (itself a widely differing result) and the unsubstantiated statement by the Birmingham authors (Wise et al 1969) in the British M.
Journal of 3rd June, 1969, who quoted "this manoeuvre does not result in contrast media being found in the chest of normal subjects", no real evidence has been documented to my knowledge (Foreman 1969) showing that contrast media was never found in the bronchial tree of conscious patients undergoing prolonged treatment under local anaesthesia (where mouth packing is seldom carried out) or other methods commonly used (for example, nitrous oxide and oxygen). Without such comparisons, it is difficult to accept that such findings are restricted solely to methohexitone sodium for conservation, even in the large dosages employed in the present study, where it would be surprising indeed if depression of the laryngeal reflexes did not occur (Foreman 1969).

Wise et al (1969) proposed that a recent death that (quoted by them of a fatal subarachnoid haemorrhage) had occurred during the use of intermittent methohexitone sodium was possibly due to the large swing in blood pressure which resulted in the reception by the patient of a painful stimulus when the peripheral circulation was depressed. Foreman suggested that if the peripheral vascular tone is obtunded then it would be difficult for it to respond in such a dramatic matter to a powerful stimulus. In a similar case in which the death occurred in New Zealand of a patient who suffered a subarachnoid haemorrhage after the administration of a local anaesthetic containing adrenalin, it would seem that one should tread warily before making inferences of this kind, particularly as subsequent correspondence revealed further details of this case including the fact that the patient had a pre-existing cerebral aneurism and was also given a local anaesthetic containing noradrenalin.
While Foreman has some valid points in his evaluation of the study of Wise et al, their study is an extremely valuable physiological evaluation of the technique which probably has been abused in the past. If it is abused in the future the practitioner must then be aware of the physiological trespass he is subjecting his patient to.

Drummond-Jackson (1969) replied in the British Medical Journal to this report of Wise et al's (1969). He objected, not to the physiological measurements, but to the physiological treatment given to these patients. The controversy then moved into the nebulous area of the reporting of deaths from dental procedures with or without anaesthesia. Drummond-Jackson stated that Wise et al were worried by the dismissal by Bourne (1969) of any deaths associated with the technique. He called for these authors (Wise et al) to give details of the several deaths of which "only they appeared to have knowledge". It was suggested that methohexitone sodium killed about one in every seven thousand or eight thousand people on whom it had been used, which was about one patient every two or three months. However, no details of these deaths were forwarded. On these grounds and the fact that this report had been taken to the press Drummond-Jackson proceeded with a libel suit against the British Medical Journal. The results of the libel suit were inconclusive.

In the same correspondence Cutler (1969) suggested that it was abundantly clear that the good faith of all concerned in this discussion was not in doubt and there was a certain well defined, albeit small, proportion of dental patients who benefited from this approach in anaesthesia. He suggested that there was no
criticism of the method itself by Wise et al but that practising dentists should take due note of it.

Loeber (1969) reiterated the observations of Wise et al that because of the progressive fall in the peripheral vascular resistance, two effects took place as the length of anaesthesia was increased. The venous blood became arterialized and hypoxia was not reflected by cyanosis. Hypoxia may be present but quite unnoticed due to the peripheral vasodilatation. The blood pressure only remained normal by virtue of a large increase of cardiac output. Under these circumstances the challenge produced by hypoxia could not be met by increased cardiac output. Hence, as the length of time increased, patients were subjected to a progressive degree of a condition physiologically resembling high output cardiac failure.

Hatt et al (1971) carried out a study of conservative dentistry under a minimal increment of methohexitone sodium technique in which they maintained dosages closer to those recommended by Drummond-Jackson, SAAD (1973, p.203). These dosages were around the 250 mg total and operating time no longer than twenty minutes. This study appeared to concentrate primarily on operating facility for the surgeon and compared quality of work done under local anaesthesia to that done under methohexitone sodium.

I would criticize this study primarily because the patients allocated to the methohexitone sodium group were not patients who could not be treated under local anaesthesia but included many patients who would normally be treated quite well under local anaesthesia. Also these studies were carried out by clinicians unfamiliar
with the technique, therefore these workers would have more difficulty working under this technique than with local anaesthesia. This point is mentioned by the authors in their conclusion with reference to mouth packing which they found to be effective in only 70 per cent of their cases.

In their hands and in conditions under which the investigation was carried out, the minimal increment methohexitone sodium technique for conservative dentistry was inferior in almost all aspects to the local anaesthetic techniques. Advantages claimed for the technique were not substantiated by the results.

Although the mean number of completed restorations per administration was greater under methohexitone sodium, the quality of the completed restorations was not as good. Treatment had to be abandoned in 13 per cent of methohexitone sodium administrations due to adverse working conditions. There was also a comparatively high incidence of side effects and after effects.

I suggest that the primary value of methohexitone sodium is as a supportive sedative agent in small amnesic doses to facilitate the administration of local anaesthesia or to supplement local anaesthesia and diazepam for longer cases.

Methohexitone sodium in small amnesic doses is a useful drug which may be used to decrease the dose of drugs which have prolonged recovery times (diazepam). In small doses up to 250 mg it has minimal effects on the cardiovascular and respiratory systems in healthy patients.
(iii) Summary relevant to sedative uses.

Relevant to Wise et al's study doses of methohexitone sodium as used in supplemental methohexi-
tone sodium with diazepam and local anaesthesia (where the dosage is kept to 250 mg total reaching this value on rare occasions spread over a two or three hour appointment) would be highly unlikely to cause any gross physiological upset or trespass to a normal healthy patient (Litchfield 1972).

B. Supplemental methohexitone sodium, diazepam and local anaesthesia.

Methohexitone sodium may be used to reduce diazepam dosage in longer conservative cases where the methohexitone sodium is used in very small increments of 5 mg to 10 mg to ensure amnesia during brief periods of discomfort towards the end of long conservative appointments. This technique is described by Brown et al (1968). It has since been described by Litchfield and Gerard (1971) and Litchfield (1972). It must be again emphasized that these small doses of methohexitone sodium potentiate the effects of the basal sedation of the diazepam and the patient occasionally becomes unconscious. Even though many of the patient's reflexes are present he is not able to respond to verbal command.

C. Uses in light anaesthesia.

Most reports in the literature on the dental use of methohexitone sodium refer to its use in the ultra light minimal increment technique or its use in dental anaesthesia supplemented with nitrous oxide and oxygen. These references will be discussed to note the dosages used, the duration of anaesthesia produced, the recovery rate and any other complications where methohexitone
sodium was used in considerably high dosages in a relatively short time. This may be compared with the very small dosages used over a very long period of time when it is supplemented with diazepam and local anaesthesia.

Coleman and Green (1960) aimed at obtaining quiet dental anaesthesia without hypoxia and with a rapid recovery. Following insertion of a mouth prop, methohexitone sodium was given intravenously as rapidly as possible at a dose of 5 mg per stone body weight. This dose was a minimum which experience showed produced sleep for two minutes. As soon as the patient was asleep a mixture containing 15 per cent oxygen and 85 per cent nitrous oxide was administered with a nasal mask. One and a half to three minutes were required in a majority of cases to establish satisfactory conditions for operation. At this stage the oxygen percentage was increased to 20 per cent. These authors concluded that recovery following methohexitone sodium was a notable feature being rapid, complete and utterly free from side effects.

Methohexitone sodium has great promise for use in outpatients provided it is used solely as an induction agent in the small doses required. The rate of recovery of the patients seemed to be quicker than from any barbiturate previously investigated.

Although the time taken to prepare the patient for dental extraction was longer than with pure nitrous oxide, the smoothness of the procedure and the absence of hypoxia more than compensated for this. Outpatients seemed to welcome this type of anaesthesia.
Coleman and Green considered 100 mg as a small dose when given at once. Extrapolating from this then 250 mg of methohexitone sodium given in small increments spread over two to three hours on a basal sedation of 15 mg of diazepam would be unlikely to cause any serious depressant effects.

Danziger (1962) commented on the use of methohexitone sodium in tracheal intubation for anaesthesia in the dental chair. Methohexitone sodium had all the merits lacking in thiopentone sodium. The excellent toleration of a nasotracheal tube in light anaesthesia afforded by methohexitone sodium-succinylcholine induction was noted. There was no breath holding or straining on the tube as was seen after thiopentone if nitrous oxide was not supplemented, and there was no post extubation spasm of the larynx or bronchi. Danziger recommended methohexitone sodium as the induction drug of choice for all cases requiring intubation.

D. Methohexitone sodium and intramuscular premedication.

Miller and Stoelting (1963) reported a preliminary communication on the sleep-producing effect of intramuscular methohexitone sodium in the pediatric patient. This is an interesting article in the situations where an excessively unruly or apprehensive pediatric patient may be rendered cooperative and sleepy by intramuscular injection of methohexitone sodium without resorting to other long-acting oral premedicants. They found that when given by intramuscular injection in a dose of 3 mg per pound body weight (6.6 mg per kg) methohexitone sodium was safe, rapid and pleasant in the induction of sleep in the pediatric patient. There were apparently no limitations in the use of intramuscular methohexitone sodium other than those limitations placed
on the use of any barbiturate. There were four hundred and eighty patients in this series and the ages of the patients ranged from a few hours to sixteen years. The injection was given in the upper outer quadrant of one buttock. A single injection of a 2 per cent solution of methohexitone sodium in normal saline was used for the intramuscular injection.

Goldman (1966) commenting on general anaesthesia for children's dentistry referred to the paper of Miller and Stoelting. He tried intramuscular methohexitone sodium for premedication with children. He also concluded that when premedication was required that this technique resulted in admirable sedation, for the child was sleeping lightly as a rule within six minutes following a dose of 3 mg per pound of body weight using a 2 per cent solution.

E. Use in neurolept anaesthesia.

Methohexitone sodium has also been used combined in an anaesthetic technique utilising droperidol, fentanyl, and methohexitone sodium for outpatient oral surgery. This combination is reported on by Elliott et al (1974). Combination of a respiratory depressant or potential respiratory depressant like methohexitone sodium with a known narcotic respiratory depressant (fentanyl) would seem to be an extremely dangerous procedure.

In the dosages used by these administrators the incidence of side effects was low in approximately five hundred patients. The technique was recommended for use only by practitioners adequately trained in general anaesthesia. In this procedure local anaesthetic was also used. The combination was to provide safety,
rapidity of onset, effectiveness, controlled duration and rapid postoperative recovery. The mean dose of methohexitone sodium was 10.5 ml of a 1 per cent solution. The ranges were large as might be expected due to varied patient population and involving procedures consisting of one to thirty extractions, one to four impactions, removal of tori or closed reduction of a fractured mandible. Less than 1 per cent of patients required treatment for respiratory depression. All patients recovered within sixty seconds after administration of levallorphan 1 mg intravenously and artificial respiration with a bag resuscitator. Elliott et al noted that with experience impending respiratory depression was recognised easily and treated prophylactically with levallorphan. In summary the incidence of side effects was low and most patients were responsive to spoken commands but amnesic for the procedure. Because of the potency of the drugs used and the seriousness of the complications that may develop, the technique was recommended only for those with adequate training in general anaesthesia.

Summary.

In experienced hands methohexitone sodium is a useful anaesthetic and sedative drug with a good margin of safety due to its short duration of action. This only applies where the patient is not overdosed and is constantly observed for signs of respiratory depression and obstruction.
PART III

ATROPINE SULPHATE.
## CHAPTER 7.

**PHARMACOLOGY AND COMPLICATIONS OF ATROPINE SULPHATE.**

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CHAPTER 7.

PHARMACOLOGY AND COMPLICATIONS OF ATROPINE SULPHATE.

The properties of atropine sulphate (atropine) are well established. Consequently, most of the references are not recent. The literature on atropine and its relevance to dental sedation is reviewed with reference to its pharmacology and physiological effects.

A. General properties.

Parasympatholytic agents also described as anticholinergic agents such as atropine, inhibit the responses to stimulation of post-ganglionic cholinergic nerves, particularly those of the parasympathetic nervous system which innervate exocrine glands and smooth muscles. They prevent acetylcholine from exerting its usual action on the receptor cells; they do not diminish the production of acetylcholine.

Parasympatholytic effects include: paralysis of ocular accommodation; dilatation of the pupil; increase in heart rate; decreased production of saliva, sweat, gastric and intestinal secretions; decreased intestinal motility, and inability to urinate. In addition to its parasympatholytic actions, atropine stimulates the medulla and higher cerebral centres, manifested by mild central vagal excitation and respiratory stimulation, and causes depression of certain motor mechanisms, particularly those associated with the extrapyramidal tract (Martindale 26th ed., p.273).

There is considerable variation in atropine effectiveness (Eger 1962). Post ganglionic endings of the parasympathetic system are particularly susceptible while autonomic ganglia and the skeletal neuromuscular endings are much less susceptible to actions of atropine.
(Dale 1930; Duke Elder 1930; Luco 1943; Trendelenberg 1929). This has led to the concept that atropine blocks the muscarinic actions of acetylcholine (the actions at vagal endings in general) but does not block the nicotinic responses to acetylcholine (skeletal neuromuscular junction, autonomic ganglia). There is a continuous range of responsiveness to the effects of atropine (Eger 1962).

The parasympathetic innervation of salivary glands is affected by a low dose of atropine, while two and a half times the dose produces the same degree of inhibition of the cardiac vagus and ten to twenty times this dose produces the same degree of inhibition of accommodation (Herxheimer 1958; Ursillo 1961). Eger (1962) makes the point that the problem of potency is certainly complicated by the appearance of tachyphylaxis with atropine (Gray 1955, Quigley 1937).

B. Effect on metabolism.

In man, decrease in oxygen utilization is slight (Stoll 1948); atropine elevates the threshold for renal excretion of sugar and prolongs the elevated blood sugar level obtained in a glucose tolerance curve (Cullumbine 1955; Eda 1927; Robinson 1955). The symptoms of hypoglycaemia (sweating, weakness, trembling and anxiety) due to insulin injection can be eliminated by atropine (Quigley 1937). There is no effect on lactic acid metabolism (Lundholm 1959; Wilber 1958).

C. Absorption.

Intravenous administration of atropine results in more rapid onset of action but only slight increase in potency over subcutaneous injection (Severinghaus 1955; Tønnesen 1948). Both of these routes of
application are far more rapid than oral administration (Schriftman 1957, Unna 1950).

Up to 50 per cent of atropine is transported in blood, loosely bound to protein (Tønnesen 1956). Atropine maintains a fairly even distribution throughout the body (Evertbusch 1956; Gosselin 1955; Kalser 1957; Tønnesen 1948).

D. Metabolism.

Man utilizes neither conjugation nor hydrolysis as a means of metabolising atropine (Gosselin 1960). The means by which atropine is altered is not known. Liver is the main organ of detoxification in most animals and would likely be the same in man (Stoll 1948). Consequently, liver disease may predispose to prolonged effects of atropine.

E. Elimination.

The kidney eliminates most of both altered and unaltered atropine (Evertbusch 1956; Gosselin 1955; Gosselin 1960; Kalser 1957). A small amount is lost in faeces (Evertbusch 1956; Gosselin 1955; Kalser 1957) and little or none in expired air (Evertbusch 1956; Gosselin 1955). In man, the major portion of elimination occurs in four to eight hours. 20 to 50 per cent of an injected dose of atropine may be recovered unchanged in twenty-four hours from the blood (Gosselin 1960; Tønnesen 1950) while another 35 per cent is excreted in urine after metabolic alteration (Gosselin 1960).

F. Tolerance.

Numerous reports of atropine and scopolamine intoxication in man may be found (Dameshek 1937; Hoefnagel 1961; Hoffman 1959; Morton 1939; White 1929). Treatment of belladonna intoxication is mainly symptomatic (Eger 1962).
The innocuousness of large doses of atropine in unanaesthetized man is demonstrated by the use of large doses of atropine in toxicity therapy of other drugs (Forrer 1956; Goldner 1956; Miller 1956; Miller 1958; Wada 1960). Injections of 400 mg of atropine three times a week are not unheard of and doses of 30 mg to 50 mg have been routinely used. Recovery from coma is spontaneous and complete in six to nine hours (Miller 1958). These doses are not advocated for routine use in anaesthesia or sedation but do underline the relative safety of doses used by anaesthetists in unanaesthetized man (Eger 1962).

Tolerance may vary between various groups. Mongoloids are supposedly more sensitive to the mydriatic effects of atropine (Berg 1959; O'Brien 1960), although this has not been substantiated. Blacks develop little or no initial bradycardia with small doses of atropine compared to whites, but develop comparable tachycardia at higher doses (Heinekamp 1922; Paskind 1921). The young are described as having more, less and similar tolerance to atropine than adults, depending upon the investigator (Pilcher 1934; Schlossmann 1937). Probably the very young who have incomplete liver development are less tolerant (Schlossmann 1937). Nevertheless, a sixteen to twenty week human foetus, given 0.01 to 0.2 mg into the umbilical vein showed little or no increase in heart rate or any significant changes in the electrocardiogram (Stern 1961). Beyond one month of age, the atropine required to reduce secretions is directly related to weight (Unna 1950). However, muscular subjects appear to respond less while thin subjects are more sensitive to atropine (Nalefski 1950).
G. Effect on respiratory system.

Both atropine and scopolamine may cause an increase in minute volume and some authors have attributed respiratory stimulating properties to these drugs (Hawk 1943; Regelsberger 1926; Wangeman 1942; Waters 1938). In part, the increase may be due to the increase in physiological dead space that occurs following atropine, although this increase is small compared to the increase in anatomic dead space (Butler 1960; Edsall 1914; Kilburn 1960; Severinghaus 1955).

In addition to dilating the bronchi, atropine reverses broncho-constriction caused by serotonin (Herxheimer 1953; Kilburn 1960), acetylcholine (Herxheimer 1953), pilocarpine (Gillespie 1931; Sollman 1937) and similar drugs (Steinberg et al 1957). It does not protect against effects of histamine (Gillespie 1931; Sollman 1937). The normal subject's airway conductance is increased after atropine (Butler 1960). In the asthmatic patient, atropine is of slight or no benefit (Dautreband 1959; Hume 1961) causing side effects without achieving the same degree of relief obtained with isoproterenol (Hume 1961).

H. Atropine and arrhythmias.

In unanaesthetized man, doses of atropine less than 0.3 to 0.6 mg may produce slowing of the pulse rate but above these doses tachycardia appears (Crawford 1923; McGuigan 1921; Morton 1958; Rudolf 1924). Maximum slowing occurs at doses of 0.2 to 0.3 mg intravenously (Morton 1958). Slowing of the pulse is probably due to central vagal stimulation (Heinekamp 1922; Henderson
1936; Heymans 1946), while tachycardia results from peripheral vagal blockage (Henderson 1936) and perhaps also from facilitation of excitation of cardio-accelerator fibres (Chauchard 1937). It has been suggested (Jones et al 1961) that this initial slowing effect of atropine on the heart is also associated with arrhythmias and, therefore, is possibly of some danger to the patient. Arrhythmias have been demonstrated during minor oral surgical procedures under local anaesthesia (Williams et al 1963). Their importance has been assessed by Hughes et al (1966).

Other authors (Morton and Thomas 1958) have shown that the appearance of this slowing of the pulse by atropine is dependent upon the speed of the injection and the concentration of atropine given, and that it is almost imperceptible when the injection is given quickly intravenously. Only when the injection is given slowly and over a longer period of time is this actual slowing detectable. Consequently, where the dose of atropine is given up to 0.6 mg this arrhythmia and slowing effect is probably negligible. A normal, conscious patient experiences arrhythmias on administration of local anaesthesia even when this injection is not made intravascularly (Hughes et al 1966; Williams et al 1963).

In normal awake subjects, cardiac arrhythmias may occur on intravenous or subcutaneous injection of atropine. Besides sinus tachycardia, atrioventricular dissociation, atrioventricular block and even ventricular extrasystoles have been seen (Averill 1959). However, during anaesthesia, intravenous atropine is sometimes followed by marked and dangerous arrhythmias (Jacobson 1954; Johnstone 1952; Jones 1961; Pooler 1957).
Arrhythmias do not occur to any appreciable extent in subjects anaesthetized with nitrous oxide and sodium thiopentone or with ether (Jones 1961).

Atropine also is effective in the prevention and treatment of arrhythmias caused by intravenous calcium or acetylcholine (Loomis 1955; Malinow 1954) or epinephrine (Roberts 1955; Wilburne 1947).

Where local anaesthesia incorporating adrenalin is used in sedation techniques atropine can increase the hypertensive effect of adrenalin (Geffen 1956; Sarnoff 1954; Trendelenberg 1929; Wilber 1958). This effect could possibly occur with any vasopressor and atropine and probably results from block of reflex bradycardia that occurs with induced hypertension.

Jones and co-workers (1961) studied the effects of electrocardiographic alterations which frequently follow the administration of atropine to normal man. Atrioventricular dissociation was first reported by Wilson in 1915 and more recently has been described in detail as the electrocardiographic alteration most frequently noted following the intravenous administration of atropine to normal man (Averill and Lamb 1959). Other types of arrhythmias also occur, including nodal and ventricular extrasystoles.

Atropine can, depending on dose, either stimulate or block vagal activity and the arrhythmias noted after its administration may be attributable to these actions. Jones et al (1961) found an incidence of ventricular arrhythmias in over 50 per cent of patients anaesthetized with cyclopropane contrasted with their complete absence in unanaesthetized subjects given atropine and in subjects anaesthetized with ether and
oxygen or thiopentone, nitrous oxide and oxygen. On the other hand, supraventricular arrhythmias were frequent in conscious subjects, but much less so during general anaesthesia. As concluded by Hughes et al (1966) these arrhythmias are not significant.

Atropine does not prevent the pressor effect of endotracheal intubation in lightly anaesthetized man (Devault 1960). The increased pulse rate normally seen following intubation is abolished. The bradycardia sometimes seen following intravenous succinylcholine or pharyngeal manipulation may be prevented or treated with small doses of atropine (Leigh 1957).

An important contra-indication for the use of atropine for sedated patients may be mentioned here.

Where sedation results in reduction of stress for a patient and is therefore of benefit in patients who may be under treatment for conditions where the heart has reduced capacity to withstand stress, for example, for those patients with a history of myocardial infarction or hypertension or for patients who have been treated for angina pectoris, then any increase in pulse rate puts an additional workload on the heart which contra-indicates the use of atropine.

I. Reduction of salivary secretion.

In dental sedation procedures, pharyngeal and oral secretions are reduced by atropine, thereby minimizing the possibility of mucous irritation of the larynx. Operative procedures in the mouth are facilitated by placement of restorations in a dry field. This procedure must not endanger the patient in any way and in the author's experience of relatively routine use of atropine premedication, the benefits have outweighed the
complications (post sedation dry mouth and throat).

Herxheimer (1958) showed that the different effects of atropine occurred with different doses and that the reduction in salivary secretion of between 40 per cent to 80 per cent occurred before an excessive increase in heart rate. The actual increase in heart rate seen with 0.6 mg of atropine intravenously is not marked, compared with the amount of drying of secretions.

Atropine reduced salivary secretions that followed stimulation with carbachol or lemon juice. The importance of minimal secretions lay not only in avoidance of obstruction from mucous and saliva, but also in prevention of stimulation of the larynx by these secretions (Eger 1962). Since the incidence of laryngospasm is lowered by reduction of secretions (Eger 1961) indirectly atropine or scopolamine help to prevent laryngospasm. The dose required to achieve dryness varies from patient to patient and from one anaesthetic to another (Mushin 1953).

To test comparative antisialogogue effects of atropine and related drugs, Wyant and Dobkin (1958) on a small sample of four healthy volunteers, compared atropine with L-hyoscyamine, promethazine, methantheline bromide, hexocyclium and oxyphenonium bromide. They found the drying effect in decreasing order of effectiveness as follows: L-hyoscyamine 0.3 mg - 99.5 per cent effective, L-hyocine 0.2 mg - 97 per cent effective, atropine 0.6 mg - 96 per cent effective, methantheline bromide 5 mg - 95 per cent effective, hexocyclium 1.5 mg - 93 per cent effective, oxyphenonium 0.5 mg - 90.5 per cent effective.
They concluded that atropine sulphate had little effect on the cardiovascular system and was a satisfactory drying agent, but must be given in doses of at least 0.6mg to be thoroughly effective. One of the disadvantages of atropine was that individual variations, which occurred with all agents, seem to be more marked with atropine than with any of the other drugs. This unpredictability of the drug acting on the autonomic nervous system has been reported by others (Stephen et al 1956).

J. Postural effects.

Eger (1962) in a summary of the general effects on the cardiovascular system in man stated that in recumbent man, atropine caused an increase in pulse rate if the venous return was adequate (and it tended to be because of venous constriction), stroke volume did not diminish and cardiac output increased. The tendency towards an increase in blood pressure was balanced by a decrease in peripheral resistance. At the same time, the body was less able to compensate for stresses such as tilting. This postural non-compensation may be due to ganglionic blockade in part as well as to vagal blockade.

K. Blush effect.

It is interesting that following intravenous injection of atropine and the sedative drugs, patients occasionally show a marked reddening in the blush region of the upper thorax and neck. This sometimes appears speckly and may be thought to be an allergic reaction. This rash does not progress down the trunk of the patient (photograph p.97). Eger (1962) noted that atropine and scopolamine administration was sometimes followed by an
Photograph 4

Fine erythematous rash (anxiety or atropine induced) on the patient's neck and upper thorax but not found on the abdomen and lower thorax.

(Clinical photograph from clinical survey, Chapter 24)
Photograph 5
Rash shown on previous photograph at a higher magnification.

(Clinical photograph from clinical survey, Chapter 24)
active vasodilatation of the cutaneous blood vessels in the blush area (Goodman 1955). The cause of this is not known, although it may be related to the release of histamine.

L. Central nervous system effects.

Moore and Dundee (1962) found that intramuscular injection of atropine 0.6mg produced a slight but significant increase in sensitivity to somatic pain detectable twenty minutes after administration. This effect passed off within a further twenty minutes. It also decreased the analgesic action of pethidine and pethidine-phenothiazine mixtures in a similar time relationship. The incidence of excitatory phenomena following methohexitone sodium 1.6mg per kg was significantly increased.

Atropine would appear to be most effective in blocking interneurones (Curtis 1960; Eccles et al 1954) in the reticular activating system (Rinaldi 1955). This augments the effect of diazepam which also acts on the reticular activating system, tending to impair reflex patterns of behaviour. Atropine can produce hallucinations and illusions, also ataxia, drowsiness, slurred speech, impairment of recent memory and attention span (Ostfeld 1960; White 1956). Sedation is a desirable side effect of anaesthetic premedication and for this purpose scopolamine is superior to atropine (Eger 1961; Freeman 1959) being some five to fifteen times more potent (Ostfeld 1959; Ostfeld 1960; White 1956).

M. The eye.

The belladonna drugs have long been noted for their mydriatic action. Both atropine and scopolamine are effective topically or systemically in this regard (Goodman 1955; Krantz 1958). Because of this action, it
is suggested that caution should be exercised in administering atropine, and especially scopolamine to known glaucoma sufferers (Leopold 1948). There is evidence that in the doses used in premedication, neither drug causes an increased intra-ocular pressure in the presence of glaucoma (Schwartz et al 1957). Its use is not advised by intravenous injection for patients prone to acute glaucoma (Chapter 15).

N. Allergic reactions.

One report of suspected allergic reaction to atropine is by Turner et al (1972). A twenty-nine year old woman developed anaphylaxis after injections of propanidid, atropine and suxamethonium. The patient had previously been exposed to suxamethonium and atropine but the episode reported had occurred after initial exposure to propanidid and atropine. The patient's leukocytes eight weeks after anaesthesia released histamine in vitro in the presence of both propanidid and atropine. Histamine release, however, could not be demonstrated at seventeen and twenty-two weeks after anaesthesia, hence the adverse reaction in this context was transient in nature. The abnormal response to these drugs did not appear to be dependent upon immunological mechanisms but was, in all probability, idiosyncratic (Turner et al 1972). This is the only report of an allergic like reaction involving atropine that was found in an extensive search of the literature.

O. Attitudes for and against atropine use.

From articles by Allen (1970), Holt (1962) and Levy (1964) it would appear that the use of atropine in anaesthetic practice is widespread and almost a routine procedure, where a compatible anaesthetic technique is being used. These authors all commented on the
need to assess carefully the situation and the indications before using atropine.

Allen (1970) summarised his cautions on the indiscriminate use of atropine. The safety of atropine appeared to have been demonstrated by the fact that up to 400 mg has been given in a single dose. There may be merit in the concept that atropine, by reducing the arresting phase in cardiac cycle, reduced the time period in which abnormal stimuli could allow development of cardiac arrhythmias. However, it is not entirely innocuous, and as suction can more than adequately clear all secretions, the noted hazards should be considered and atropine should not be used on an indiscriminate basis. Allen's indications for its use are: when repeated doses of succinylcholine are to be given; if neostigmine is to be administered; to counter traction reflexes, or if the anaesthetic technique is such that in order to prevent secretions due to hypercarbia and hypoxia, the drug is needed.

Levy (1964) was similarly against the routine use of belladonna drugs including atropine and studied one thousand six hundred and fifty patients who were anaesthetized without preoperative atropine. Circulatory and respiratory complications were observed. She concluded that atropine did not protect against circulatory reflexes during anaesthesia. The incidence of significant secretions was reduced from 7.5 per cent without atropine to 3.2 per cent with atropine.

The use of atropine as a routine would seem undesirable (Levy 1964). The drug should be reserved for a particular purpose - for example, to block the carotid sinus reflex. The energy wasting effect of
atropine on the myocardium makes its use dangerous in
the anginal patient (Holt 1962; Pender 1953; Dawson 1960)
and atropine is contraindicated in mitral stenosis
(Pender 1953; Dawson 1960).

Wyant (1962) believed that "to deride atropine
because it was not an anti-emetic and because it did not
counteract respiratory depression caused by narcotics, or
because someone had said that it aggravated glaucoma,
which was doubtful if given in the usual clinical doses
by the intramuscular route, bordered on the ridiculous".
On balance, atropine does much more good than harm, has
a wide safety margin, and a wide area of applicability.
Even if one accepts the theory that its use increased
the incidence of sore throat and may cause parotitis,
many more difficulties would arise if the use of this
drug were restricted. Wyant knew of no incident where
the administration of atropine had cost a patient his
life, surely a remarkable safety record for any drug.

P. Treatment of toxic effects.

Toxic effects of atropine ingestion are de-
cribed by Goodman and Gilman (p.534).

Physostigmine is the rational therapy for
atropine poisoning. Injected intravenously, intramuscu-
larly or subcutaneously, it antagonizes the peripheral
effects of the poison, and rapidly and effectively
reverses the central nervous system manifestations, which
are the major sources of danger (Goodman and Gilman
p.535). Forrer and Miller (1958) reported that injec-
tion of 1 mg to 4 mg of physostigmine rapidly abolished
the delirium and coma following 200 mg of atropine.
Conclusion,

Atropine sulphate may be used in intravenous premedication to protect the patient from emotional or fear induced bradycardia. It is also effective in producing a dry field for the placement of dental restorations as well as reducing pharyngeal secretions which may disturb the sedated patient's larynx. In the normal healthy population its use may be routine, limited only by drugs it may potentiate or medical conditions it may complicate. Adverse effects to its use are rare.
PART IV

CONSCIOUS AND SUBCONSCIOUS

PATIENT COMPLICATIONS

"Be careful, the patient is listening."

(CHEEK 1966)
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CHAPTER 8.

PERCEPTION AND THE UNCONSCIOUS PATIENT.

An aspect of dental sedation which has not been considered previously and which has not in the past received extensive review in anaesthetic or dental literature is whether generally anaesthetized patients can hear and whether or not this is significant for amnesic sedated dental patients. Limited work has been done by Cheek with generally anaesthetized patients (Cheek 1959, 1960a, 1961, 1962a, b, c, 1964, 1966) and also by Levinson (1965) and Oswald et al (1960). Cheek's work consists of clinical reports and are reviewed in detail.

Cheek (1959) reported on the unconscious perception of meaningful sounds during surgical anaesthesia as revealed under hypnosis. He considered it an error to judge the anaesthetized patient as being asleep and unable to hear or understand just because such an individual may have no subsequent conscious memory for events during this period of unconsciousness. Meaningful (that which has a direct bearing on the subject's subconscious well being) sounds, meaningful silence, meaningful conversation are registered and may have a profound influence upon behaviour of the patient during surgery and for many years after. The anaesthetized patient may lose all motor reflexes, lose all ability to communicate with the outside world, lose all sense of pain, but the anaesthetized patient may hear and remember important events at a deep level of subconscious thought. This level can be uncovered and the events recalled by hypnotic techniques as described by Le Cron (1954).
The modern trend of anesthesiology is towards maintaining the surgical patients at lighter planes of anaesthesia than used to be the custom. Tranquilizing drugs are being used to diminish apparent reactions to environment (for example, intravenous dental sedation), and much use is being made of combinations of drugs which sedate and paralyse motor activity at the same time. Now more than ever, should we be careful of what our patients hear. Not only are their fundamental sensoria affected to a lesser degree by anaesthetics but the patients today have been subjected to more medical education through more channels than ever before. The resulting potential for dangerous and unrecognized fears originating in and about our operating rooms is of enormous magnitude.

Cheek (1959) followed several hypnotized subjects through two or more remembered anaesthetic experiences. Fears originating during an earlier operation reappeared as the subject was reliving the later induction into surgical anaesthesia. These fears produced changes in heart rate and respiration. From the standpoint of behaviour it would seem from the available evidence that the point of prime importance was not whether the patient actually hears but rather that the patient believes he has heard. In the light of the findings it seemed of the utmost importance that we know before administering an anaesthetic or sedative what attitudes the patient has carried over at a subconscious level from previous real or imagined operative experiences.

Cheek suggested that the preoperative patient to worry about was the one who showed no conscious level evidence of fear and who asked no questions. This is the
patient who may be the most subconsciously terrified. He wondered for fifteen years why some patients took a disliketo a previous surgeon without knowing just why they did so. Conversational methods with age regression in hypnosis failed to uncover retention by the patient of thoughtless remarks heard during anaesthesia. However, ideomotor response techniques showed that memories of operating room experiences were preserved at levels of awareness so deep that they could not be reached with ordinary conversational techniques during the time usually available for investigation. It was suggested that it may take four or more hours to train the subject to speak without his awakening from a deep trance. Muscular responses of adaptation to environment are learnt long before the complicated mechanisms of thought translation into articulated sounds are learned. Muscular responses are, for the most part, unconscious in origin, while those of speech are related to effort and evolve at a more conscious level in response to more complicated stimuli.

In exploring possible traumatic memories with age regression it was necessary to respect the decision of the subconscious mind regarding release of information. An "I don't want to answer" should be a signal to leave that recollection alone after dropping the suggestion that perhaps the experience could be reviewed later in different circumstances without emotional dissociation. Subjects with hypertension and all who are over forty years of age were requested to consider themselves a nurse or orderly in the hospital situation rather than being the patient experiencing the anaesthetic. Although the subconscious would probably protect the organism in the hypnotized state from critical reactions, there was
clinical evidence (Wolff 1950) that emotional stress could initiate cerebral haemorrhage or coronary artery occlusion and that it seemed unwise to tempt fate in the exploration of operative experience.

A study of patients' retention of operative-room conversation during surgical anaesthesia using ideomotor questioning of obstetrical patients showed a repeated demonstration of hypersensitivity to pessimistic remarks which had been picked up from lay people and given a stronger value than the reassuring statements of physicians. This should lead to more careful screening of preoperative patients with bad attitudes (Cheek 1959) and to a more subtle form of reassurance than usually is employed by surgeons and anaesthetists.

Most of the subjects in this study (Cheek 1959) demonstrated that the subconscious was acutely sensitive to nuances of voice inflection. Sometimes it was difficult to be sure that this perception was based only on minimal cues. Patients under surgical anaesthesia are just as aware of deceit and attempts to avoid the truth as are patients with malignancy or a critical illness. There are ways of telling unpleasant truths which do not close the door to hope. Cheek had yet to find a patient who had not seen through a lie or failed to resent, at a subconscious level, the failure of his physician to trust him with the facts.

The power of the effects of hypnosis were demonstrated by Raginsky (1959), where he induced temporary cardiac arrest under hypnosis. The experiment was conceived to discover whether syncope could be induced by hypnosis. It was not contemplated that cardiac arrest would follow the suggested syncope. It was anticipated
that if a fainting episode could be induced under hypnosis some relatively minor electrocardiographic changes might be recorded but this supposition was based on observations made while experimenting with the production and elimination of extrasystoles in hypnotic states. Raginsky was not at all prepared for the complete cardiac arrest which followed the hallucinated episode. When the patient was first told to visualize his fainting attacks he became upset and restless but did not attain a real attack. It might be termed a simulated attack of faintness or, at best, a mild faintness. It was only when he suddenly blanched and became limp, as was apparent clinically, that he was really capable of reliving a previous attack.

To their knowledge, the production of temporary cardiac arrest by means of hypnosis had never been recorded in the literature. Summarizing, Raginsky described the experiment in which the symptoms of syncope and temporary complete cardiac arrest were induced under hypnosis in a patient who had been operated on for a so-called Adams-Stokes syndrome and who had, until the time of the experiment, remained free of such symptoms.
CHAPTER 9.

HYPNOTIC COMPLICATIONS ARISING FROM
ANAESTHESIA OR SEDATION

A. General considerations.

The dental surgeon must be aware of the psychological properties of the hypnosedative drugs that he is using. He must be aware of fundamental complications involved in hypnotic therapy so as to protect his patients from them (abreaction, unfulfilled post hypnotic suggestion, foolish post hypnotic suggestion and masked symptoms - Meares (1972) & from experiencing complications due to careless conversation within earshot of the sedated patients (Cheek 1960).

Patients are vulnerable to inadvertent suggestions while under the influence of tranquilizers and sedative drugs (Watkins 1951; Bingham 1964; Burgess 1977). Hypnosis has been induced in a subject who was firmly trying not to become hypnotised (Watkins 1951) and inadvertent hypnotism has been reported by Dumas (1964).

Cheek (1958) suggested that more harm could be done with ignorance of hypnosis than with intelligent use of the forces of suggestion. For example, Chapman et al (1959) observed in a hypnotised patient following standard amounts of noxious stimulation on the forearm a decrease in the inflammatory reaction and tissue damage when it was suggested that the subject's arm was insensitive and numb and would not be hurt, (anaesthetic) as compared to the reaction and tissue damage of the other arm which was suggested to be normally sensitive. The individual's perceptions and attitudes seemed relevant to neural activities that engendered or enhanced inflammatory reactions.
Enhanced inflammation was effective in combating invasion by micro-organisms and in the rapid elimination of tissue breakdown products of injury. Therefore, the present alterations indicated that man includes among his adaptive and protective devices, neural reactions integrated at the highest levels that heighten inflammation in the peripheral tissues and increase the local susceptibility to injury thus enhancing the protection of the whole organism at the cost of the integrity of a part. Such adaptive reactions at times may be essential to survive, but if evoked inappropriately or excessively may contribute to disease since non-noxious stimulation become noxious and mildly damaging stimuli result in greater injury. On the other hand, the observations reported by these authors (Chapman et al 1959) suggested that activity of the highest integrative functions may also prevent excessive or inappropriate responses and may initiate appropriate tissue reactions.

They concluded that neural activity involving the segmental or axon levels, the brain stem and hypothalamic levels, as well as the sub-cortical and cortical levels could alter the reactions in the peripheral tissues subserved in such a way as to augment inflammation and increased local tissue damage in reaction to noxious stimulation. Proteolytic enzymes and a bradykinin-like polypeptide were implicated in these enhanced reactions. Effects of surgery may be improved or worsened depending on the suggestions given to the patient.

B. Characteristics of subconscious mentation applied to anaesthesia and sedation.
(i) Thought processes go on independently both at the conscious level and at a more child-like literal subcon-
scious level while we are awake. The objective, inductive type of thinking is blocked off in serious illness, during fear and when the individual is unconscious, regardless of the reason for unconsciousness.

(ii) The subconscious mind puts together associations of thought that are senseless to the conscious mind, and equally senseless identifications of the self with real or imagined unfortunate people.

(iii) Reassurance as it is usually given by physicians and relatives is often worse than useless. It may be accepted at a conscious level but may also be completely rejected at a subconscious level.

(iv) Indirect reassurance, on the other hand, is almost always accepted at the subconscious level, and this is the strongest weapon the anesthesiologist has against potentially dangerous fears. Most anesthesiologists seem to sense this fact, and will talk calmly about the preparation for anaesthesia, and also about what the patient is to do when he awakens. This is accepted as meaning that all is well and that there will be a post operative survival. But common error seems to be based on the uncritical belief by anesthesiologists that the hearing sense is necessarily discontinued when the patient has become seemingly unconscious with an anaesthetic.

The anesthesiologist can mitigate the possible damage of careless conversation of the surgeon and assistants by explaining the intended meaning or by directing the patient's subconscious attention to constructive acceptable instructions in a louder voice in order to channel all auditory awareness toward what he is saying.

(v) Hypnosis may occur spontaneously in the presence of fear, sensory or postural disorientation and in loss of
consciousness. Cheek concluded that anaesthetized and traumatically unconscious human beings may be considered hypnotized.

(vi) The subconscious mind is able to perceive pain without necessarily passing the awareness along to the conscious part of the mind. The physiological manifestations of inflammation associated with trauma, or infection, may be mediated by subconscious awareness of pain (Cheek 1962b).

In discussing the dangers of hypnosis for the subconscious mind Cheek (1962b) considered that it was not dangerous for a human being to enter hypnosis spontaneously during a time of stress provided that there was freedom from frightening suggestions during the time that he was in hypnosis. The person in charge must be fully aware of what was happening to his patient and qualified to utilize it to the patient's advantage. It was also reasonable to assume that such spontaneous hypnosis unrecognized and ignored by those properly responsible, could be a source of danger, not in itself but developing from a professional unawareness of significant changes in the patient.

Hypnosis with its diminished oxygen requirements, its diminished capacity for feeling pain, its diminished tendency for bleeding, its diminished voluntary muscular activity, and its exclusion of all non-meaningful stimuli could be used to great advantage by every surgeon and every anesthesiologist. For these reasons, among others, we should know when to expect its presence, how to recognize its manifestations and how to utilize it for the benefits of our patients. Unrecognized, it can be a detrimental force.
C. Simulated catastrophes and hypnotic trance.

An hypnotic trance is deepened by any sudden sensory perception which is out of context with the environment of the moment (Cheek 1962b).

Cheek's following suggestions have not been widely supported or disproved but are included for their relevance to a collapse situation. Crasilneck and Hall (1975) (p.83) support Cheek's warnings regarding psychological care of the unconscious patient. A deeper trance may be produced by anything that disturbs the individual's normal position relationship in space. It may occur when a paralysed and lightly anaesthetized person has had his head forcibly hyperextended for introduction of a laryngoscope prior to intubation. It may occur when an anaesthetized person is unceremoniously dragged or jolted into the gall bladder, kidney, lithotomy, laminectomy or Trendelenburg position. The sudden dropping of an unconscious patient from the operating table into a carriage, or from the carriage into the bed can produce an hypnotic state so deep that it simulates the suspended animation of the oriental religious men. At such time the behaviour of the patient may so simulate death that the attendants become frightened. This in turn, the acutely sensitive subconscious part of the patient's mind may perceive, and this communicated alarm can then produce dangerous physiological responses or even complete collapse. Stimuli tending to deepen an hypnotic state in an anaesthetized person may produce a very deep trance in the anaesthetized patient. At such a time the patient can seem to stop breathing, become pulseless and lose readable electrical discharge from the myocardium. Information is lacking with regard to how much the actions of the surgical team, confronted with this situation, might contribute to true cardiac
arrest or physiological collapse. Cheek suggested that it might be worthwhile to attempt talking authoritatively to the patient before pressing, thumping or incising the thorax.

D. Abreaction.

Upon entering hypnosis, or upon becoming unconscious, there may be a release of memory associations with earlier experiences in life which have been frightening. It is a fairly common experience in inducing hypnosis in timid or frightened subjects to have them, sometimes overwhelmingly, so experience a vivid recollection of a past traumatic or terrifying experience or even a whole series of past unhappy memories. The human being losing consciousness with sodium pentothal anaesthesia under pleasant surroundings at the age of forty-six may have a coronary occlusion during the emotional reliving of a traumatic ether anaesthetic for a tonsilectomy at the age of six. He may show no outward signs of dismay because of the muscular paralysis due to the anaesthetic. An adult patient may go into respiratory collapse during positioning for laminectomy as he is reminded of a similar jolting after loss of consciousness in an automobile accident which injured his back and contributed to the need for surgery. A patient, paralysed by a curare-like drug, may go into shock reliving the childhood panic experienced while wrapped in a rug by playful companions. (Cheek 1962b).

E. Careless Conversation.

The subjective mind, representing subconscious thought, is literal in its understanding of words. It interprets everything which could be significant as relating to itself. For these reasons, any conversation
overheard in the hallway of the surgical floor may be interpreted as applying directly to the patient.
CHAPTER 10.

PROTECTION FROM CARELESS CONVERSATION
AND IMPROVED POSTOPERATIVE CARE

Cheek (1960c) endeavoured to protect his patients from careless operative-room conversation by the use of preoperative hypnosis.

Patients would accept an amnesia for everything that was not addressed to them directly. This could be a helpful way of excluding careless conversation and possibly frightening suggestions. Conversely, suggestions could be given directly to such patients while anaesthetised and these suggestions could be helpful.

Since patients with cancer might feel that requested amnesia would prevent them from knowing about their condition, Cheek believed that they should be told in hypnosis to listen only to the surgeon and to the anesthesiologist. These two members of the therapeutic team should keep the patient posted regarding progress and should give optimistic thoughts regarding an eventual cure.

Cheek (1960a,b) showed that a surgically anaesthetized patient was tuned in to all meaningful sounds and could recall frightening conversation heard in the operating room. Careless conversation can be the cause of such untoward reactions as respiratory arrest and shifts from deeper to more superficial planes of anaesthesia. The anesthesiologist and the surgeon may help the patient by giving direct positive suggestions, or by speaking optimistically about the progress of surgery and prognosis.
Cheek (1961) said that during the past decade it had been possible to corroborate the observation of Esdaile (1957) that rejection of pain awareness at a subconscious level improved host resistance to infection and hastened the recovery from localized infection. Cheek's first glimpse of the possibility that this increased potential for combat might make the difference between life and death was offered by a patient with a spreading puerperal peritonitis which had not responded to chemotherapy (Cheek 1957). Observations with herpes simplex, persistent urinary tract infections, skin abscesses, perirectal abscess and acute vaginitis of several types convinced Cheek that this was more than a cortical like response which could dangerously remove the barriers to spread of infection. There had been no spread of infection in any case on which hypnosis had been used. Some research in Japan suggested that the human being in hypnosis may produce more effective immune responses to infection than is possible when energy is wasted in responses to pain and fear (Ikemi 1959).

With ideomotor questioning methods in hypnosis as a means of permitting detailed investigation of great areas of life experience and as a means of actively improving the adaptations of frightened, sick and depressed patients, we now may take another step forward in our understanding of human responses to stress. It is known that it is possible to use hypnosis to protect surgical patients from the dangers of careless conversation (Cheek 1960c). Little thinking about the behaviour of preparation attendants, orderlies, operating room personnel and nurses in the recovery room has been done by anaesthetists or dental surgeons. Cheek (1961)
believed that unprotected, unconscious, frightened patients were having their lives unnecessarily threatened in our hospitals every day.

Hutchings (1961) found favourable responses to careful use of hypnosis. He studied the value of suggestion given under anaesthesia and evaluated two hundred consecutive cases. He believed that patients could hear while under general anaesthesia, that they do hear and understand suggestions given while they are under anaesthesia, and that this method of suggestion during general anaesthesia had a useful application in the field of surgery. The major area of favourable results was in those cases where the abdominal cavity was not entered.

Postoperative care could be made easier by suggestions given during the anaesthetic state. Patients were more comfortable and more cooperative. Nausea and vomiting were decreased. Wound healing was apparently hastened, possibly because of an earlier meeting of the patient's nutritional needs.

Pearson (1961) studied responses to suggestions given under general anaesthesia. In a double blind trial using headphones and tapes he concluded that:
(i) Surgeons could not differentiate between patients who had received suggestions and those who had not.
(ii) There was no difference in the use of narcotics between the two groups postoperatively.
(iii) The patients who had received suggestions were discharged an average of 2.42 days sooner than the control group. This difference was statistically significant at below the 0.05 level.
Cheek (1962b) emphasized the importance of recognizing that surgical patients behave as though hypnotized. He commented that hypnosis was a naturally occurring body defence mechanism, an analogue of which occurred in animals confronted by danger situations. It appeared spontaneously in human beings when they were frightened, disoriented or in situations of severe violent stress, mental or physical, and quite possibly even when chemically or physically unconscious. He suggested that a state of mental activity of a subconscious or hypnotic character existed even in states of syncope or physical unconsciousness.

The anaesthetist or dental surgeon must show consideration for their anaesthetised or sedated patients. It was not necessary for the anaesthetist to demonstrate hypnotic phenomena nor was it necessary for him to learn any special formulae for talking. He need only extend his usual thoughtful consideration for the fears of his patient past the period when apparent unconsciousness occurred. He should be alert for the correction of possible misunderstandings caused by careless conversation in the operating room. He should advise the anaesthetised patient of any new manipulation or shifting of the patient's position. He should talk to the patient during general anaesthesia just as he would talk to a conscious patient under spinal anaesthesia. He should give simple directions about what he expects the patient to do on awakening and how to perform during the next few days of hospitalization (Cheek 1962c).

Some patients can verbalize their fears of death. Experience has shown that these people should not be reassured into continuing through the surgery, except under emergency conditions. They sometimes die.
Physiologically, the most dangerous type of fear is that which cannot be expressed verbally because it is too deeply repressed.

The subconscious fears of human beings are capable of causing grave physiological disturbances. This seems beyond any question of doubt and yet, because there has been no satisfactory way devised by the psychiatrists for discovering subconscious fears during the limits of time available for investigation, we have completely discarded all concern with this matter in the extensive literature dealing with anaesthetic complications (Cheek 1962). Thoughtful observers like Schroff (1959) wondered why 58 per cent of operating room and recovery room deaths at the Wadsworth Veterans Administration Hospital were in patients with elective surgery.

Berne et al (1955) said that "cardiac arrest was potentially avoidable, usually reversible ventricular asystole, with or without fibrillation, precipitated by the effect of anaesthesia alone, or surgery alone, or of these two in combination". No thoughtful consideration of possible contributory patient attitudes could be found in a survey of literature on surgical or anaesthesia mortality from 1952 to 1961 yet every good surgeon and every good anesthesiologist respected this factor, and would discuss it extensively in private. But it is a topic that warrants open not closed room consideration (Cheek 1962a).

Until all physicians know the available ways of discovering and correcting the potentially detrimental and even lethal subconscious attitudes of surgical patients it is possible to bypass some of them by learn-
ing some of the characteristics of subconscious thought, and respecting the capacity of the anaesthetized patient to hear. This respect must be extended to patients sedated for dental procedures and all the care and all the precautions and all the responsibilities with regard to protecting an anaesthetized patient must be carried through for the patient sedated who is even more receptive and even more aware of procedures being carried out during this sedation appointment even though amnesic for most of the procedure.
CHAPTER 11.

CONSCIOUS RECALL OF EVENTS UNDER GENERAL ANAESTHESIA

Most reports of the capacity to hear, understand and remember during the anaesthetic are reports where patients have been questioned under various hypnotic techniques to uncover unconscious memory (Cheek 1959, 1960b). Brunn (1963) reported a personal experience in which he was given a general anaesthetic consisting of a premedication of morphine and scopolamine, and an induction of a muscle relaxant (succinylcholine) and thiopentone for induction. He also received succinylcholine during the operation and nitrous oxide and oxygen for the entire fifty-five minute procedure. Brunn's experience and memory were corroborated by the operating staff entirely. He felt no pain but was aware of what was happening.

From this experience he was convinced that all those within hearing distance of the unconscious or anaesthetized patient should be aware of the very real possibility that the patient can hear, respond and remember and that simple courtesy demands proper conduct at all times in the patient's presence. Also, he was most strongly convinced that salutary remarks and suggestions by both surgeon and anaesthetist constitute a valid and often shamefully neglected part of the surgical procedure. He recommended that the patient undergoing an operation should have the benefit of the presence of someone well trusted such as the family physician. Helpful, constructive suggestions should also be made as legitimate a part of the operation as the scalpel and the sponge.
Erickson (1963) carried out a clinical trial with a patient to establish a relationship between hearing and memory in chemo-anaesthesia. The patient was asked various questions while in a state of surgical anaesthesia. Erickson discovered that the patient, when questioned at the end of the anaesthetic, could recall questions asked him in deep surgical anaesthesia. The only leading questions asked of the patient were, "were you asked something else?"; "what did you remember?"; and "what comes to your mind now?".

Erickson then described his own personal experience of having two teeth extracted plus curettage under a general anaesthetic. He was judged as being ready for operation by pupil assessment and was believed to be deeply anaesthetized. Erickson then startled the anaesthetist and the dentist by saying in a slurred voice that he was not. The anaesthetist gave more ether and then the dentist proceeded with the comment that with all that ether the patient could not feel a thing. Erickson states that the dentist was right. He could not feel anything. Neither could he move or even open his eyes. But he could hear. He heard the forceps clamped to the tooth but could not determine any sense of position. He heard the dentist tell the anaesthetist to hold his head firmer but could not feel it being done. He could hear what he reasoned to be the sounds of the tooth being loosened from its socket. He heard the scraping sounds of the curettage. The dentist remarked that the second abscess had ruptured into the first and he would do a curettage without a second extraction. He could hear more bone scraping sounds. Also he could hear someone breathing hard and spasmodically.
In brief summary Erickson (1963) stated emphatically that chemo-anaesthesia and mental functioning were as important fields of scientific inquiry as were the fields of chemo-anaesthesia in surgery. Also of equally intriguing interest was the observation that pain had an experience itself and that the knowledge and memory of a painful procedure could be rendered by chemo-anaesthesia into two separate items, only the latter of which was experienced.

Others (Blacher 1975; Brown 1976; Collison 1976) refer to this problem of patients experiencing mental trauma under general anaesthesia. Collison (1976) relieved a patient's distressing and significant symptomatology using age regression techniques as part of hypnotherapy. The patient's severe neurotic problems including severe phobias dated from surgery.

Brown (1976) reported a personal experience in which she experienced pain and the feeling of paralysis under anaesthesia. She could not move and the entire experience was "exceedingly horrifying and terrifying - and not at all what she had expected". In the succeeding months she had two nightmares which reiterated to some extent the terrifying experience she had had under anaesthesia.

Brown stated that she would be pleased to hear from any anaesthetist who would explain the pharmacological and neurological basis of the phenomenon and from any psychiatrist who would explain the psychological aspects.

Two cases of patients reporting mental trauma experienced under general anaesthesia came to my attention. The first was a middle aged male taxi driver who
twenty years previously experienced pain while under a general anaesthetic for a broken hip manipulation. He had also had a traumatic dental experience when his mandible had been fractured during a difficult dental extraction under local anaesthesia. This patient, as a consequence of these experiences, had not attended for dental treatment for twenty years. Before he presented for treatment he had closely questioned sixteen patients who had been sedated for their dental work and whom he had taken by taxi from the surgery. He responded well to an explanation of what he might expect from intravenous sedation.

The second patient had become aware during a general anaesthetic that a tube was in her throat, that she could not breathe herself and that she could not tell anyone of her predicament. She thought she would die and was very anxious that the same situation may develop with intravenous sedation. This patient also responded well to explanation that at all times she would be able to breathe herself. She found the experience pleasant.

Summary.

As a general conclusion the appreciation for the patient's vulnerability while he is sedated may reduce post sedation complications, may reduce post operative complications, may prevent serious complications of cardiovascular or cerebral type occurring during sedation and may establish confidence patterns for future operations. This is of great significance in dentistry.

If consideration for our patients' welfare is continued while they are sedated then the patients' confidence and their ego strength should be improving
with subsequent appointments. Also, with gradual conditioning and lighter levels of sedation, doses are reduced and the patient becomes more aware as part of the conditioning away from the need for sedative drugs for their treatment. No reference is made to these complications in current dental anaesthesia or sedation texts (S.A.A.D. 5th Ed., Drummond-Jackson 1973, Clinical Dental Anaesthesia - Bell 1975).
PART V

LOCAL COMPLICATIONS OF INTRAVENOUS ADMINISTRATION OF DRUGS.
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CHAPTER 12

VENEPUNCTURE COMPLICATIONS

Complications from venepuncture are pain on injection, extravascular injection and intraneural injection. These effects are poorly reported in the literature for intravenous sedation in dentistry.

A. Pain on injection.

Drummond-Jackson (S.A.A.D., p.169) recommended as a local obtundant of pain the use of ethylchloride drops. In a preliminary study of patient reaction to needle gauge Hamburg (1972) concluded that in intravenous anaesthesia the gauge of a needle and method of skin fixation played no part in patient acceptance and that only sharpness of the needle counted. Hamburg suggested that although his sample was statistically too small to be conclusive it clearly indicated that a topical anaesthetic in the antecubital fossa was not significant in the reduction of injection pain.

Rowlands (1969), in a study of four hundred inductions using 1 per cent methohexitone injected into a vein in the back of the hand, noted that forty-three complained of pain, discomfort or a feeling of warmth up the arm prior to falling asleep.

In a further four hundred inductions using an identical technique he found that by the addition of 1 mg per ml of lignocaine to the methohexitone solution pain was reduced (five patients reacted to pain, two of whom remembered it post-operatively).

In my experience pain on injection of diazepam, especially in small veins, is commonly reported by patients. This may be reduced by very slow injection, by
Photograph 6.

Chief veins and nerves of the right superficial antecubital fossa region.

k - basilic vein.
l - median basilic vein.
m - median cephalic vein.

(From Hollingshead - p.412)
Photographs 7, 8.

Common variations (a), (b), (c) and unusual distributions (c) to (f) of nerves of the dorsum of the hand.

(From Hollingshead - p.543)
Photograph 9.
A patient's left antecubital fossa showing the end result of poor venepuncture technique with haematoma formation. The patient also received a small amount of extravascular injection of methohexitone sodium. The enlargement of the region is on the following page.

(The reviewer's patient)
Photograph 10.

Enlargement of case from p.135

(The reviewer's patient)
selecting larger veins or by mixing the diazepam and the blood in the tubing of the infusion set.

Venepuncture in the dorsal aspect of the hand also, in my experience, produced a more marked painful reaction from the patient. This is not particularly surprising when the nerve supply to the back of the hand is considered. Anatomy for Surgeons (p.543) shows six variations in the radial and ulnar dorsal branches supplying the dorsum of the hand (photograph p.134). In the majority of cases, the area which is least densely innervated appears to be the middle of the dorsum of the hand. In practice the larger veins tend to lie in the lateral aspect or medial aspect of the dorsum of the hand in which there is also a higher density of nerves; consequently, venepuncture pain is difficult to avoid in these situations.

Conclusions.

Where possible use fine gauge sharp needles, inject slowly and into the largest veins available.

B. Extravascular injection.

With the drugs used in intravenous sedation routinely (methohexitone, diazepam) pain from extravascular injection is a temporary nuisance to the patient. Extravascular injection of diazepam or methohexitone produces pain in the area lasting one or two days after the appointment. According to S.A.A.D.(p.81) the production of this complication is considered to be negligence. However, in longer cases where small volumes of drugs are repeatedly being injected over a long period the lumen of the needle may be continually blocked by small blood clots thus precluding aspiration. The alternative is to inject a few drops of the solution
in an attempt to clear the blockage. If the patient has moved and the lumen of the needle no longer remains in the vein then small amounts of solution may be injected extravasously. As the best form of prevention in this case is to eliminate clotting in the lumen of the needle a method for prevention of clotting will be discussed under "Thrombophlebitis" (Augspurger 1974).

For small amounts of methohexitone injected into the tissues Drummond-Jackson (1973 p.81) recommended that the area be massaged immediately. Larger deposits must be diluted and dispersed by wide infiltration of the area with up to 10ml of 1 per cent procaine solution into which is mixed hyaluronidase (hyalase) 1,500 units. He does not say what a large amount is. Methohexitone 1 per cent solution and diazepam 0.5 per cent solution do not cause tissue sloughing at the site of injection. The patient's aversive reaction due to the pain that this produces in either case will warn the operator that something is amiss in the area. Large volumes of the drug should not then be injected extravascularly.

C. Intraneural injection.

The median cutaneous nerve, the lateral cutaneous nerve and the median nerve may be penetrated by the needle or irritated by solution injected extravasously in the antecubital fossa region. The lateral cutaneous nerve and the median cutaneous nerve are superficial and can often be impinged as they accompany the cephalic and basilic veins (photograph p.149). Irritation of these nerves results in paraesthesia and pain on the aspect of the forearm involved. When irritant drugs are injected into the median nerve more serious sequelae occur as this
Photograph 11.

Reproduction of the anatomy of the antecubital fossa region seen in cross-section.

(Reproduced from Eycleshymer and Schoemaker Sect. 59, p. 123)
is the main motor nerve of the muscles of the forearm and hand.

Median nerve.

The median nerve is derived from the sixth cervical to the first thoracic root. It innervates the pronators of the forearm, long finger flexors and abductor and opponens muscles of the thumb and is a sensory nerve to the palmar aspect of the hand. Complete median nerve paralysis results in wasting of the affected muscles and inability to pronate forearm or deviate the hand in an ulnar direction, paralysis of flexion of the index finger and the terminal phalanx of the thumb, weakness of flexion of the remaining fingers, weakness of abduction and opposition of the thumb, and sensory impairment over the radial two-thirds of the palmar aspect of the hand and over the distal phalanges of the dorsum of the index and third fingers (Harrison et al 1966, pp. 1880, 1918).

The ease with which the median nerve may be injured during attempted intravenous injection of drugs is illustrated in a short study by Pask and Robson (1954). It has sometimes been said that very ordinary caution would serve to prevent this injury since the direction of the needle necessary to make an injection into the median nerve must be much more nearly perpendicular to the axis of the arm than if the basilic vein is the objective (photograph p. 139). Consequently, the position of the syringe to which the needle is attached would clearly and obviously differ in the two cases. These authors compared the positions of a needle tip placed next to the median nerve and a syringe placed in the same or a similar angle but placed in the basilic vein.
Photograph 12.
Claw hand resulting from ulnar nerve paralysis.

(Reproduced from Hollingshead, p.519)
They concluded that the difference between the two positions of the syringe and needle was very slight. They were impressed by the fact that 0.2 ml of 1 per cent lidocaine was sufficient to affect the median nerve significantly provided that it was accurately placed.

It is very difficult indeed to appreciate the injection of this small quantity of fluid from a 10 ml syringe and one must recognize that if an irritant fluid such as thiopentone solution, methohexitone or diazepam was injected into the median nerve marked damage may be done to it. This experiment reinforces the argument against injection of irritant fluids into the veins in the medial part of the cubital fossa whenever possible.

At the same time Pask and Robson considered that if an injection must be made at this site, accidental damage to the median nerve could occur by mischance even though reasonable care was taken. For example, a slight movement of the patient might advance the needle at first satisfactorily placed in the vein a very short distance so that its point lay against the nerve. There would be no obvious change in position and the minute amount of solution presumably necessary to do damage might easily be injected before any sort of warning sign could be acted upon.

This complication is more likely to happen where syringes are used at a steeper angle of entry to the vein. With the butterfly sets (scalp vein sets) a flat level of entry can be made penetrating first skin, then advancing the needle tip to enter the vein. Going through the vein, through the aponeurosis and down to the median nerve without patient movement using the scalp vein set is highly unlikely. Possibility of damage to
the median nerve is more likely to occur with the scalp vein set when the vein is entered in the crease of the elbow in the cubital fossa. If the patient bends his arm slightly the needle may be passed deep to the vein through the aponeurosis close to the median nerve in which case aspiration of blood may be from a haematoma and injection of the drug next to the median nerve may cause damage. Consequently, the vein should be entered distal to the crease of the elbow in the cubital fossa such that if the patient does bend the arm the needle will stay within the vein.

Recognition of median nerve damage is important as a lesion of the median nerve can be alarming for the patient. Follow-up treatment and referral are a necessary continuation of treatment. To illustrate, Rana et al (1974) described a case of complete lesion of the median nerve in an eight year old child resulting from a traumatic injury. On examination there was loss of sensation in the distribution of the median nerve and loss of the power of the flexor pollicis longus, flexor digitorum profundus of the index finger, flexor digitorum sublimis and abductor pollicis brevis muscles. Needle electrode electromyograms from the abductor pollicis brevis showed profuse fibrillation and no response of motor units on voluntary effort. Electrical stimulation of the digital nerves in the median nerve distribution failed to evoke any sensory potential and there was no motor response to high intensity stimulation of the median nerve at the wrist, in the cubital fossa or in the axilla. Clinically, the boy had not been using his thumb or index finger. Upon active flexion of the digits of both hands there was no response from his thumb and index finger.
In my experience no marked injury to the median or superficial nerves has occurred. One patient experienced transient tingling in her thumb which lasted five days. If median nerve damage is suspected neurological consultation will be required.
D. Dissection of the antecubital fossa and the dorsum of the hand.

These dissections were done (p.147-160) to correlate the structures found with the same structures as presented in standard anatomy texts. It was felt that with an increased understanding of these regions my venepuncture technique would improve and be both more comfortable and safer for my patients.

A complete left arm and hand were provided by the Department of Anatomy, Dental Section, The University of Sydney. Related veins, arteries and nerves were displayed and serially photographed (ref. p.147-160).

Significant findings were:
(i) superficial nerves closely accompanied the larger veins both in the antecubital fossa and on the dorsum of the hand (p.148 and p.149). This may explain the occasional reports of discomfort by patients during penetration by the needle;
(ii) the thickness of the bicipital aponeurosis. This structure protects the underlying brachial artery and median nerve and in this specimen would have required a determined deep pressure of penetration on the needle to reach the underlying artery;
(iii) although the median nerve and the brachial artery are to a degree protected from needle penetration, they are still quite close to the overlying veins. Care is therefore required at all times during venepuncture.

I would conclude that familiarity with the anatomy of these regions increased both my confidence and my care for my patients. This exercise is recommended for those dental surgeons undertaking procedures
involving venepuncture.

My gratitude is expressed to Professor B.W. Barker, Mr P.L. Davies and Mr K.C. Parsons of the Department of Anatomy, The University of Sydney for making available the specimen and the facilities.
Photograph 13.

The left antecubital fossa region with the skin removed.

(Photographs 13 to 29 are serial dissections of the left cubital fossa and dorsum of the left hand by C. Lambert at the Department of Anatomy, Sydney University.)
Photograph 14.
The left antecubital fossa region from a medial aspect. The subcutaneous tissue has been removed. Shown are the median cubital vein (blue pin) with two accompanying branches of the median superficial nerve (yellow pins).
Photograph 15

The lateral aspect of the left antecubital fossa showing a median cephalic vein with the musculo cutaneous nerve (yellow medial pin).
Photograph 16

An enlargement of the previous dissection.
Photograph 17.

The medial aspect of the antecubital fossa showing the possible position of an artery (red pins) deep to the bicipital aponeurosis just under the median basilic vein (blue pins).
Photograph 18.

Enlargement of the previous dissection. Note the ease with which the median superficial nerve (yellow pin) may be penetrated during attempted venepuncture.
Photographs 19, 20.

Median superficial nerve again displayed with the musculo cutaneous nerve in the photograph below shown laterally (yellow pin).
Photograph 21.

More lateral view showing the musculo-cutaneous nerve medially and the lateral superficial nerve laterally.
Photograph 22.

Left antecubital fossa - bicipital aponeurosis outlined under the medial cubital vein. Deep to the bicipital aponeurosis is the brachial artery laterally and the median nerve medially.
Photographs 23, 24.

Progressive enlargements of the previous dissection.
Photograph 25.

The bicipital aponeurosis reflected and pinned.
Photograph 26

The relationship of the median cubital vein and the bicipital aponeurosis to the underlying brachial artery laterally and the median nerve medially.

Photograph 27

As above from the medial aspect.
Photograph 28.

Dissection of the dorsum of the left hand showing the relationship of the ulnar nerve to the five accompanying superficial veins.
Photograph 29.  
An enlargement of the previous dissection.
CHAPTER 13

INTRA-ARTERIAL INJECTION OF DRUGS

As this complication may result in the loss of whole or part of a limb (Cohen 1948; Brown et al 1968; Dundee 1956) care in prevention and, if necessary, successful treatment of this mishap are vital. A careful search of the literature on this subject produced only one reference to possible intra-arterial diazepam injection with loss of the limb (Schneider and Mace 1974) and one report of intra-arterial sodium methohexitone injection (Miller et al 1976).

A. Prevention.

Avoidance of intra-arterial injection necessitates careful venepuncture site selection in regions usually devoid of superficial arteries. A detailed knowledge of the anatomy of proposed injection sites is required. Usually the lateral aspect of the cubital fossa or the dorsum of the hand is selected (Ellis and McLarty 1961). Where the medial aspect of the cubital fossa is penetrated, the superficial radial and ulnar arteries may be encountered (Everett and Allen 1969). The proximity of the brachial artery deep to the bicipital aponeurosis which underlies the medial cubital vein is stressed. The brachial artery may divide into the radial and ulnar arteries proximal to the bend of the elbow and either of the divisions may become superficial in the cubital fossa.

Studies have indicated that approximately 18 percent of the population have superficial arteries at the elbow, and these were found to be bilateral in one-fifth of the cases examined (Gagnon 1966). Occlusion of a superficial ulnar artery by a tourniquet eliminates pulsation in that vessel distal to the point of application of the tourniquet. Consequently these regions
must be tested by palpation before the tourniquet is applied, otherwise this clinical sign will be missed and inadvertent injection may follow into an artery occluded by the tourniquet. Hazlett (1949) found that a well marked superficial vein usually accompanied a superficial artery on one side or another as a companion vein. The artery lacked the colour of a superficial vein, and pulsation was discernible on inspection in only four cases, but on palpation it was always felt with little difficulty. Of the five hundred and forty-two limbs examined by Hazlett in living subjects the superficial ulnar artery occurred with a frequency of 2.7 per cent which was lower than the frequency of both superficial radial and superficial ulnar arteries noted by Gagnon (1966), who studied a smaller group. The frequency of occurrence of superficial arteries detected in the cubital fossa which I have seen is also low. Only one patient was noted in a sample of two hundred and sixty-one in which a superficial ulnar artery was encountered. This particular artery was inadvertently penetrated but its nature became obvious by the speed and marked pulsation with which the blood moved down the butterfly tubing.

Palpation.

The second phase of prevention of intra-arterial injection is careful palpation of the target vessel before the tourniquet is applied.

If no pulsations are detected the tourniquet is applied and venepuncture completed. Aspiration is carried out to ensure that the needle is in the vein and then a small slow test injection of the drug is given to determine the patient's reaction. There are two reasons for the initial slow injection of a small amount of drug
in terms of prevention of intra-arterial injection. After the initial precautions have been taken, if an artery has been entered, a small dose of drug injected into the artery will not cause any serious complication. The patient will signify the event by complaining of pain radiating distally from the injection site. This will instantly arouse suspicion of intra-arterial injection. Secondly, it is important to inject a test dose of the drug to see if the patient is hypersensitive to the drug.

Summary.

In order to prevent the intra-arterial injection of drugs, the following precautions are recommended:

(i) Knowledge of the anatomy of the proposed venepuncture site must be known.

(ii) The lateral rather than the medial aspect of the antecubital fossa should be selected whenever possible.

(iii) Dependence should not be placed on the colour of withdrawn blood since dark blood can come from the artery as well as from the vein.

(iv) A momentary pause prior to injection to allow arterial pressure to push back the plunger or to course down the tubing of the butterfly infusion set before the syringe is applied to the end of the tubing.

(v) A small amount of the medication should be injected at first, waiting a few seconds for untoward reaction to occur prior to completing the injection.


The following reports deal with intra-arterial injection of thiopentone sodium and its sequelae as this drug demonstrates the worst outcome of intra-arterial injection. It has been well documented in the literature.
Kimmonth and Shepherd (1959) injected 5 per cent thiopentone sodium solution into the central artery of the rabbit ear and noted an immediate contraction of the vessel lasting about thirty seconds. This was followed by a rapid return to the original diameter after which a slight dilatation occurred for approximately one minute. No prolonged contraction of the vessel was observed nor anything which resembled spasm which follows mechanical trauma to an artery. On no occasion was anything other than transient contraction produced by thiopentone sodium solutions and alkaline solutions of equal pH never produced any change in arterial diameter.

Their study aimed to find the best treatment for accidental intra-arterial thiopentone sodium injection. They concluded that vascular damage was due to the direct action of thiopentone sodium and not as a result of a nervous reflex. Kimmonth and Shepherd showed with a constant dose of thiopentone sodium (20mg) that the extent and incidence of tissue necrosis decreased with decreasing concentration of the solution. This finding agrees with published accounts of clinical cases reviewed by Stone and Donnelly (1961).

In describing a clinical case Stuart (1961) believed, contrary to the previous authors, that the immediate sequel to intra-arterial injection of thiopentone sodium was intense arterial spasm, especially of the distal arteriolar tree with possible trapping of some of the solution. Such spasm may exist for at least twenty-four hours and was very easily precipitated when injection was made into a superficial ulnar artery as these vessels derived from the vasa aberrantia are like other superficial vessels and have a fuller nerve supply than deeper branches. Thrombosis was the essential pathological lesion although it was not clear why the arterial tree should
show such a vigorous reaction when venous thrombosis was relatively uncommon. Stuart commented that thiopentone sodium was a strongly alkaline irritant and the intima of the artery appeared to be particularly sensitive to solutions with such a high pH. Previous authors (Kinmonth and Shepherd 1959) tested and discounted this characteristic of thiopentone sodium as being the cause of the injury. Stuart stressed that treatment should be directed towards ensuring full vasodilatation of the limb.

An hypothesis was proposed by Waters (1966) to explain the occurrence of gangrene following the intra-arterial injection of thiopentone sodium. The small vessels were blocked by the precipitate which formed when thiopentone sodium solution was mixed with blood. Waters described experiments showing that precipitates were likely to form under clinical conditions and that the particles blocked a hypodermic needle. Post mortem perfusion experiments showed that circulatory occlusion could occur. This significant study showed that as arterial blood progressed to the peripheries, its volume diminished and the relative concentration of thiopentone sodium increased. The crystals of this drug began to form and actually blocked small vessels. Thus it may be inferred that thromboses formed at sites of mechanical damage of the endothelium reducing the lumen of the vessels. Arterial spasm possibly resulted where damage was gross, causing gangrene of that part of the limb supplied by the occluded vessels.

Burn (1960) found that gangrene resulted in the tails of mice after injection of thiopentone sodium and that it was accompanied by necrosis and ulceration at the site of injection. These changes were much less frequent in mice pre-treated with reserpine. The
administration of reserpine caused the disappearance of noradrenaline from the artery walls. Therefore, thiopentone sodium appeared to cause gangrene because of the local release of noradrenaline.

In view of the literature on factors related to intra-vascular thrombosis after accidental intra-arterial thiopentone sodium injection Brown et al (1968) listed previous theories as:
(i) Spasm of the vessel.
(ii) Internal damage and thrombosis (Kinmonth and Shepherd 1959).
(iii) Noradrenaline release (Burn 1960).
(iv) Arterial blockage of the small arterioles by crystals of thiopentone acid (Waters 1966).

It is difficult to see how thrombosis could result from spasm due to noradrenaline release alone, but it could conceivably be caused by crystals in the bloodstream (Brown et al 1968). Waters' (1966) evidence of formation of the crystals was indisputable but his explanation of the connection between this and thrombosis occurring on the basis of a mechanical blockage, is difficult to accept. Mather (1966) questioned whether 50 mg to 100 mg of thiopentone sodium could produce enough microemboli to be entirely responsible for the damage.

Brown et al (1968) extended and united these theories by discussing the causes of thrombosis or clotting within the blood vessel. Clotting occurred after a series of enzymatic reactions which led to the formation of insoluble fibrin from soluble fibrinogen. This required thrombin which formed from prothrombin under the action of thromboplastin. The latter may arise from an extrinsic tissue source or an intrinsic blood
source. The earliest events in the intrinsic pathway involved the inter actions of plasma clotting factor XII, with a foreign surface. This then reacted with plasma factor XI, to form a new reactive product which, in the presence of plasma factors V, VII, IX and X, with platelet phospho-lipids and calcium, led to the thrombo-plastin formation.

The foreign surface for the action of factor XII may be an area of endothelial damage but might be the surface of foreign matter present in the blood stream namely thiopentone acid crystals. Also, platelets will adhere directly to any area of endothelial damage and form a focus for thrombosis or they may adhere to the crystals. Finally, the platelets adhered and aggregated under the influence of adenosine diphosphate (ADP), released both from the platelets themselves (from its precursor adenosine triphosphate) and also from damage to red blood cells.

Thus, clotting could be caused by:
(i) a foreign solid material in the blood stream;
(ii) internal damage;
(iii) release of ADP from a damaged red blood cell or platelet.

It is conceivable that the crystals demonstrated by Waters in the blood stream could, by direct action, damage the formed elements in the blood and the vessel intima. Waters showed that by using 5 per cent thiopentone sodium the resulting range of blood concentrations would invariably result in crystal formation, red blood cell haemolysis and platelet aggregation. Any of these alone could initiate intra-arterial thrombosis and with all three present some degree of clotting was likely to occur. Although other mechanisms may be involved these factors could account for the undesirable sequelae of
the intra-arterial injection of thiopentone sodium.

In prevention of the condition it was concluded that it was less likely to occur with low concentrations. Thus, the more potent the drug the safer it should be with respect to the sequelae of intra-arterial injection as it can be used in more dilute solution.

C. Possible sequelae of vascular occlusion from intra-arterial injection of irritant drugs.

Sequelae of intra-arterial drug injection can vary from minor discomfort of a transient nature to gangrene of various parts of the hand, fingers and forearm resulting in amputation of that part of the affected limb.

Initially, following intra-arterial injection of an irritant drug, the patient complains of a burning, intense pain radiating distally from the point of injection (Swerdlow 1962; Stuart 1961). Also noticed will be a delay of onset of sedation or anaesthesia as the solution must negotiate the arterial tree, the capillaries and the venous complex before reaching the central nervous system. In the limb affected, slight flushing may be noticed or vasoconstriction with pallor. This may be followed by loss of either the ulnar or radial pulses and then gradual mottling, distal to the point of blockage of the affected artery. This mottling will continue to pronounced cyanosis as the tissue becomes more ischaemic. Eventually, dry necrosis and gangrene become established.

The patient will experience pain in the limb and where the blood supply affects the median nerve varying degrees of loss of motor function of the hand will be encountered. Movement becomes more and more limited. Oedema may also occur in the region of
ischaemia which, when present subfascially, further decreases the blood supply by fluid pressure on the vessels of the region. In the extreme case the patient will suffer from the loss of one or more fingers up to forearm amputation. When no part of the limb is lost, residual disability from degenerative nerve changes may ensue.

D. Aims of treatment.

The principal aim of treatment is to produce normality of function of the limb and the prevention of gangrene. Actual treatment differs from author to author and is aimed at maintaining the circulation to the region of the hand or the forearm affected by the arterial occlusion.

Hazlett (1949) attributed arterial damage to early or late thrombosis of the artery with distal or arteriolar spasm, following thiopentone sodium injection. His treatment aims, therefore, were directed towards clot minimization and dissolution or removal of the clot with alleviation of arterial spasm. Supportive treatment recommended was encouragement of vasodilatation in the affected limb. Contrary to this, Kinmonth and Shepherd (1959) concluded that as there was no evidence of prolonged arterial spasm then temporary spasm was the cause of the ischaemia following intra-arterial injection of thiopentone sodium and that intra-arterial injections of vasodilator drugs were ineffective. They concentrated their treatment on the removal of neural reflex mechanisms and in the dissolution of clot formation in the artery.

In reviewing a clinical case of intra-arterial thiopentone sodium injection and its subsequent treatment,
Stuart (1961) concluded that the immediate sequel to this mishap was the intense arterial spasm especially of the distal arteriolar tree with possible trapping or delay of some of the solution. He drew his conclusion from the fact that injection was made into a superficial ulnar artery and that these vessels, being derived from the vasa aberrantia had a fuller nerve supply than the deeper branches. He directed his therapy to continuous establishment of vaso-dilatation employing vaso-dilator substances both intra-vascularly and extra-vascularly. He took into account that thrombosis was the essential pathological lesion although his clinical observation supported vigorous treatment with vaso-dilator substances. Stuart (1961) concluded that treatment aims should not be the establishment of palpable radial and ulnar pulses since the pulse may disappear after a few hours, or it may remain full until shortly before the onset of gangrene where the pulse may disappear anything up to ten or sixteen days after severe intimal damage. Aims of treatment vary.

E. Treatment following intra-arterial injection of drugs.

As this accident occurs infrequently and is reported infrequently, there is no standardized treatment which is effective in all cases. Success of treatment is related to the speed and intensity of treatment and also to the period of time elapsed before the complication is recognized. Hazlett (1949) recommended immediate post-operative heparinization, possibly with injection into the affected artery. Sympathetic ganglion or brachial plexus procaine block was thought invaluable as in other cases of arterial thrombosis. Surgical intervention for the arterial thrombosis should take place if at all within a few hours of the accident and consisted of arteriotomy with clot extraction.
Subsequent therapy should consist of keeping the affected limb wrapped up at room temperature, immersing the opposite limb in hot water (Hazlett 1949), and covering the body with a heat cradle combined with the use of vasodilators, such as tetraethylammonium chloride or papaverine hydrochloride. This is no longer recommended as treatment (Holland 1977).

Stuart (1961) reported successful treatment of a case of intra-arterial thiopentone sodium injection. He immediately gave a brachial plexus block using 20ml of 2 per cent lignocaine and 10ml of 1 per cent lignocaine. On completion of the block 5ml of 1 per cent lignocaine were injected into the subclavian artery. At the conclusion of surgery 10,000 units of heparin were administered intravenously and repeated six hourly. Morphine 11mg six hourly was given for sedation and the limb elevated and swathed in cotton wool to aid venous return and to increase local circulation.

The brachial plexus block produced motor and sensory paralysis. Satisfactory vaso-dilatation was obtained, the limb became warm and pink with the presence of both radial and ulnar pulses. As the brachial plexus block wore off it was repeated using 50ml of cinchocaine. This was followed by intra-arterial tolazoline, an injection of 50mg in 1 per cent solution and heparin 5,000 units into the subclavian artery. Local infiltration of the left antecubital fossa and upper forearm along the course of the superficial ulnar artery using 20ml of 0.5 per cent lignocaine with 1,000 units of hyalase was given.

The affected limb was warm and pink well into the following day. The patient was maintained on oral tolazoline 25mg every six hours and the limb kept under close observation. The patient was discharged from
hospital thirteen days after the incident and the condition of the limb was satisfactory.

Webb and Lampert (1968) reported successful treatment following intra-arterial injection of meperidine and promethazine in which the symptoms were not recognized for four days after the injection. Examination revealed the thenar eminence to be cyanotic and cold with blotchy areas of cyanosis scattered over the forearm. The radial pulse was present. The patient did not mention these changes to the physician until three hours after the onset of the symptoms. After 50 mg of heparin was injected intravenously and 150 mg deep subcutaneous injection of heparin every twelve hours in addition to oral prednisone 20 mg every six hours, the patient showed marked improvement. She was placed on coumarin four days later and the prednisone dose was reduced to 10 mg four times a day and the patient discharged. Thirteen months later the patient was symptomless.

As the work of Engler et al (1967) suggested that early arteriolar damage was of an inflammatory nature, they suggested the use of cortico-steroids to limit inflammation. They concluded the most reasonable immediate treatment following recognition of the accident was intravenous heparin and cortico-steroids. These authors believed that the use of repeated brachial plexus blocks carried a rather high rate of complications. Their prognosis for a maximally irritated artery was very poor. Only those limbs with a minimal injury may survive without some tissue loss. In the case they presented, the time course of events suggested that the arteriolar damage was not maximal. Management was based upon the rationale of cortico-steroids to combat the inflammatory
process and heparin to minimize clot propagation in areas of sluggish flow.

Prognosis for long standing intra-arterial thrombosis is very poor. Engler et al (1967) described five cases of intra-arterial injection of drugs. In four cases, gangrene of a varying degree occurred and amputation was required, but on the basis of the successful treatment of one of these cases, the authors suggested the use of intermittent positive pressure to increase circulation as a possible aid in the treatment of the condition.

Engler's patient complained of intense pain in the left arm and was unable to move his left hand or fingers. His forearm muscles were hard while the arm and hand were oedematous. The fingers were cold and white and the skin was splotchy and purple on the forearm and up to the mid humerus. A pulse could be felt in both the ulnar and the radial arteries, after fifteen minutes of intermittent positive pressure the fingers lost their white cadaveric appearance and became pink with some cyanosis of the finger tips remaining. Intermittent positive pressure was given continuously for ten days. Throughout this ten day period the patient also received an intravenous heparin drip and analgesics as required. Fifteen days after admission the patient was discharged, he had further physiotherapy and later returned to his former dexterous occupation.

The general trend of treatment seems to consist of blocking the sympathetic ganglion, of instituting heparin therapy and dilating drugs and, where oedema occurs, performing appropriate fasciotomy (Engler et al 1967). As a preventive measure intermittent positive pressure may be instituted early to prevent the onset of oedema and to encourage blood flow in the affected limb.
Results have been uniformly poor in cases of maximally damaged vessels. Arteriotomy is advised if pulsation cannot be felt in the major artery distal to the site of injection.

It is apparent that for therapy to be effective it must be carried out early and to the fullest possible means available.

F. Significance for the dental surgeon.

For the dental surgeon employing intravenous techniques, the following are advised:

(i) The dental surgeon must be able to recognize the symptoms and signs of intra-arterial injection.

(ii) The use of and contra-indications to the use of heparin and an effective vaso-dilating drug should be known (tolazoline - Goodman and Gilman, p.560).

(iii) Oral cortico-steroids may be recommended (prednisone).

(iv) Liaison with an anaesthetist or physician be established so that early referral of the patient for subsequent procedures and close observation be carried out; these include brachial plexus block, arteriotomy, the maintenance of intermittent positive pressure to the limb and, if required, fasciotomy. The limb can be kept raised and warm. Where treatment is unsuccessful, amputation will be required.
Photograph 30.

Lack of arteries in the dorsum of the hand.

(Reproduced from Hollingshead p.541)
Photographs 31, 32.
Superficial and deep arterial patterns at the elbow.

(Reproduced from Hollingshead, p.412 and 370)
CHAPTER 14

THROMBOPHLEBITIS

A. Introduction and causal factors.

This complication may occur from the intravenous injection of drugs. Hutton and Hall (1957), in a study of two hundred cases (where 5 per cent thiopentone sodium was injected intravenously) found one case of thrombosis and three small, painless haematomata. Nordell et al (1972) noticed a high incidence of thrombophlebitis in a coronary care unit where 2 per cent lignocaine was given prophylactically to every second patient. The incidence of thrombophlebitis sixteen to twenty-four hours later was about 50 per cent. They concluded that the lignocaine solution seemed to promote the development of thrombophlebitis in intravenous infusions.

Jamieson et al (1972) reported that thrombophlebitis of the upper limb was an uncommon complication of thiopentone sodium injection. They noted the occurrence of thirty cases of chemical thrombophlebitis during a six month period following an injection of $2\frac{1}{2}$ per cent thiopentone sodium solution. Clinically the onset of pain, redness and slight swelling on the fourth post operative day occurred. On inspection the upper limb showed tender, hard veins beginning at the level of the original injection site and palpable up to the antecubital fossa or higher. In most cases the subcutaneous swelling and redness subsided after a few days but the tenderness and hardness of the veins persisted for weeks or months.

Many patients who developed this complication were alarmed and attended physicians, surgeons, or anaesthetists for relief. They were treated conservatively with compresses and local heat. In those cases
which lasted several months the patients complained of pain not only in the forearm but also in the arm, in the neck and in the shoulder of the same side. There was a tendency to experience coldness and numbness of the hand, especially in cold weather, in the affected limb. In my experience patients who develop complications from sedation procedures, especially local complications of venepuncture, often report to their doctor for treatment. It must be emphasized to patients that they report any of these untoward reactions to the dentist concerned as well so that techniques can be modified and treatment improved to reduce such complications.

Jamieson et al (1972) concluded that their high incidence of thrombosis was due to the particulate solution of thiopentone sodium. 1 g in 50 ml solution contained 6 per cent of the thiopentone sodium in an undissolved state. The explanation for the chemical irritation of the vein was that these solid particles had adhered to and caused damage to the wall of the vein. Failure of the 6 per cent of the thiopentone sodium to dissolve was inexplicable.

Hastbacka et al (1965) commented that intravenous administration of drugs was often followed by thrombophlebitis, especially when combined with infusion therapy. Although in their experience the condition did not lead to pulmonary complications it was often very disturbing for the patient. A review of the literature by these authors indicated that different investigators found the time of onset of the condition varied. Occasionally symptoms did not appear until one or two weeks after the infusion, the average duration of the symptoms was fifty-three days. Hastbacka et al (1965)
listed the following predisposing factors as significant in the development of thrombophlebitis.

(i) Duration of infusion.

Bolton Carter (1951) showed that when duration of infusion was restricted to under eight hours the frequency of thrombophlebitis fell from 52 per cent to 5 per cent. This relationship was later confirmed by others who used infusions lasting over twelve hours and had frequencies as high as 65 per cent (Page et al 1952).

(ii) Site of administration.

Studying the frequency of thrombophlebitis after a single injection of barbiturate, Gjöres (1957) noted a higher incidence of complications when the injection was performed into the veins in the back of the hand (40 per cent) than when given in the cubital fossa (9 per cent). The figures were based on a series of two hundred and fifty-two patients.

(iii) Size of the needle.

Hutton and Hall (1957) assumed that injury to the vein during insertion of the needle was the main cause of thrombophlebitis. Only needles of small gauge were used in their study. Skajaa et al (1961) used three sizes of needles but could not show any difference in this respect.

(iv) Infusion set.

The Report of the Medical Research Council (1957) concluded that using plastic instead of rubber sets achieved a reduction of about 50 per cent in the frequency of thrombophlebitis, but the difference was significant only for infusions lasting over twelve hours.
(v) Method of inserting the needle.

It was suggested by James (1954) that increasing skill with practice of venepuncture reduced the incidence of thrombophlebitis. My experience confirms this point. Other authors denied the significance of whatever the technique used (Jones 1957; Skajaa et al 1961). They showed that the extent of the extravasation around the needle played no role in the incidence of complications.

(vi) Agents infused or injected.

It was suspected that the acidity of the fluid increased the incidence of thrombophlebitis. Bolton et al (1952) however, found no reduction in this complication when the pH of 5 per cent glucose was raised to about pH6 with a phosphate buffer. Skajaa et al (1961) found no difference between the usual infusion fluids and 5 per cent glucose, sodium chloride and blood. However, if nothing was administered through the needle, the incidence of thrombophlebitis was nil if the needle was kept in the vein less than twenty-four hours and 20 per cent for twenty-four to forty-seven hours.

McNair and Dudley (1959) found no local irritation in six patients who had a needle in the vein for seventy-two hours.

Hastbacka et al (1965) summarized findings of a clinical study of infusion thrombophlebitis carried out in one thousand and forty-eight infusions, the veins in the back of the hand were used in all cases. Thrombophlebitis was noted in two hundred and fifty-nine instances (25 per cent). Although the complication was relatively mild in 88 per cent, it was, in most cases, disturbing to the patient. In 32 per cent the symptoms
did not appear until after one week. The average duration of thrombophlebitis was about one month. Complications occurred more often after the injection of the stronger solution; when pethidine was also administered, the incidence increased by one-third.

The duration of the infusion was of paramount importance, the incidence was more than doubled when the duration was extended from two hours up to eight hours.

B. Thrombophlebitis from intravenous diazepam.

References to this complication in the literature are few according to Padfield (1974) in the medical literature but are more frequent in dental literature. Padfield reported his clinical observations of a case of thrombophlebitis in a medical student. After a dose of 30 mg of diazepam thrombophlebitis followed by thrombosis in the cephalic vein from the antecubital fossa to the clavipectoral fascia and probably beyond resulted. He reported to the Committee On The Safety Of Medicines and was surprised to receive limited data of only one report which had been received citing thrombosis after intravenous injection of diazepam.

Since reporting this case Padfield saw another patient with thrombophlebitis associated with diazepam and had heard of two others similarly affected. In the dental literature, thrombosis following intravenous diazepam is more commonly reported but even then not often.

Jenkinson and Tullis (1970) reported the incidence of the complication varying from no cases noted in seventy-eight patients by Moore (1968) to an incidence of 42 per cent presented by Miller (1968) - (number of
Photograph 33.

Extensive thrombophlebitis of the right cephalic vein following an intravenous injection of diazepam in the cubital fossa.

(Photograph of reviewer's patient)
Photograph 34.

Enlargement of the previous photograph.

(Photograph of reviewer's patient)
cases not reported). Jenkinson and Tullis described three cases of venous thrombosis following diazepam injection. A female aged fourteen years received intravenous diazepam in the lateral cubital fossa region. Total dose given was not reported, however, fifteen days later she returned for a further part of her treatment and a thrombus seven inches long was found in the vein previously used for the intravenous diazepam injection. There was no pain and no evidence of inflammation. On a subsequent visit, following treatment in the opposite arm, thrombosis had also occurred but not to the same extent. The two thrombi resolved over a period of six months without additional treatment.

In the second case for a patient aged twenty-six, 17.5mg of diazepam were injected into the lateral aspect of the antecubital fossa. Forty-two days later a painless non-inflamed thrombus four inches long was found in the vein which had been used previously. This complication resolved itself without further treatment or complications. In a third case, a female patient aged twenty-one was given diazepam into a vein in the dorsal aspect of the right hand. 17.5mg was required and five days later a thrombus half an inch in length had developed in the vein injected. The thrombus resolved without complications or treatment.

Diazepam is a colourless, crystalline compound which is insoluble in water. Originally, the intravenous preparation was in solution in glycerol-furol, but recently the solvent was changed and consists mainly of propylene glycol, ethyl alcohol and sodium benzoate in benzoic acid. The original preparation could be diluted to twice its volume in saline or 5 per cent dextrose, but
the present preparation must not be diluted. It was thought that the original solvent may have been the agent which caused the development of venous thrombosis.

Brown and Dundee (1968) found an incidence of 15 per cent of painless, localized thrombosis after giving 35 mg of diazepam and 30 per cent after 50 mg of diazepam, using the original preparation undiluted. Rollason (1968) found no cases of venous thrombosis using the original preparation in diluted form, but he was observing the cases only on the first post operative day. Baker (1969) observed venous thrombosis in 10 per cent of his cases using the newer preparation. The preparation used in three case reports was the newer one in undiluted form as ordered by the manufacturers.

Dundee (1968) found an incidence of six cases of thrombosis out of a series of twenty-one when he injected the diazepam into a vein in the arm to which was applied the sphygmomanometer cuff. It may be that the periodic occlusion of venous return after the injection of diazepam increased the incidence of venous thrombosis but in the cases reported by Dundee blood pressure was not recorded on the same arm used for the injection.

Miller (1968) thought that many cases of venous thrombosis were unnoticed as they were usually painless and patients did not complain. He found an incidence of 42 per cent when he observed his cases six or seven days after the injection. Main (1968) found no cases of venous thrombosis when he used the original preparation, indiluted in a vein in the antecubital fossa and inspected the sites of injection seven days later. None of the thrombi in Miller's three case reports were painful and were found only because of inspection of the area.
There is obviously no clear account of the incidence or aetiology of venous thrombosis following intravenous diazepam. It is interesting that the patient reported by Jenkinson and Tullis developed thrombi on both occasions when she was given diazepam and it may be that some patients' veins are more sensitive to diazepam than others.

One case in my experience involved a twenty-one year old woman who received three separate treatments using intravenous diazepam diluted with 1 ml of atropine (0.6 mg) combined with small doses of methohexitone sodium at later stages. In two administrations spaced five months apart, the patient experienced pain in the left arm following intravenous injection in the antecubital fossa. On both occasions unobstructed aspiration was obtained and thrombosis followed at both sites to lengths of about 5 cm. However, on another appointment the median cephalic vein in the right lateral antecubital fossa region was used. Blood was again aspirated; however, on this occasion the patient felt no pain nor developed thrombosis. I can offer no explanation for this.

Langdon et al (1973) reported on the incidence of thrombophlebitis with diazepam used intravenously in one thousand five hundred cases. Treatment was for gastro-intestinal endoscopy and an incidence of thrombophlebitis of approximately 3.5 per cent resulted. In a few cases the phlebitis was protracted and involved a long segment of the vein. These authors recommended that small veins or veins in the hands be avoided.

If the vein was painful after injection then vigorous flushing of the vein with saline was recommended. The administration of heparin sodium for two to three days
was found effective and this therapy they suggested should be considered in more severe cases. Preliminary results of a randomized prophylactic flush study using saline indicated a decreased severity with flushing. In contrast with the cases reported by Jenkinson and Tullis (1970) those reported by Langdon et al on venous thrombosis following diazepam injection involved pain.

In one case 10 mg of diazepam injected into a large vein in the dorsum of the hand resulted three days later in the patient complaining of a tender cord at the injection site. There was a tender swollen erythematous palpable thrombus four inches long. Local heat and warm soaks were begun. No subsequent extension of the thrombophlebitis was seen but three weeks passed before resolution and painless use of the wrist was achieved. Case two involved another injection of 10 mg of diazepam into a hand vein. Four days later the patient complained of a tender cord in the vein extending from the injection site. Warm soaks and heating pads were advised. When seen one week later a visibly swollen erythematous tender cord extended from the hand into the upper arm. The patient complained of pain in the axilla and on movement of the wrist, elbow or shoulder. Three weeks later segments of thrombus appeared to be liquefying but swelling and erythema persisted. Three years later she still was unable to wear a watch or bracelet because of local tenderness.

Langdon et al (1973) reported on five other patients with obvious clinical signs of thrombophlebitis lasting more than a month, three of whom received injections in the antecubital fossa. All had received conservative local therapy. A further case was reported
of thrombophlebitis that had not resolved after three months, it involved the entire forearm distal to an antecubital injection site in which reactivity of the vein at the time was commented on. In their series of cases venous pain during injection was not uncommon and at times the pain extended all the way up to the shoulder. They found that the speed of the injection and the size of the vein were relevant factors. There was no correlation between the pain at injection and the subsequent appearance of thrombophlebitis. The frequency appeared higher when using small veins and hand veins. Slow injection was a routine, however, with patients tolerant to the drug because of a daily maintenance of diazepam or chlor Diazepoxide, uncommon doses of 40 mg to 60 mg were administered usually with unsatisfactory sedation and phlebitis if a small vein was used. Clinical pulmonary embolism did not occur in any of the cases cited by these authors. Five patients had symptomatic phlebitis lasting more than one month with long segments of vein involved.

After such adverse experience with conservative therapy five other patients with moderate to marked single large vein antecubital phlebitis and two with bilateral phlebitis noted within one to two days of the procedure were admitted to hospital for intravenous heparinization. The response was uniformly dramatic with termination of therapy and complete resolution in thirty-six to seventy-two hours. In the two bilateral cases, heparin was given peripheral to the involved segment in the same vein but the contra-lateral vein resolved first.

In an effort to reduce the incidence of thrombo-phlebitis Langdon et al (1973) carried out a study
involving post-diazepam flushes of heparin sodium, hydrocortisone or saline. This series is being continued. With one saline exception, all of the severe or persistent cases have occurred in patients who have received diazepam without a saline flush.

A complication occurring in approximately 4 percent of recipients sometimes producing annoying protracted residual discomfort is worrisome. These authors recommended that:
(i) small veins be avoided;
(ii) the site of injection be chosen with care or diazepam not be used when phlebitis would be occupationally disabling, such as in the case of typists or surgeons;
(iii) if the vein pain is present after the procedure, the vein be promptly flushed with saline;
(iv) if there are no contra-indications, then other than minor phlebitis should be treated with a two or three day course of heparin therapy;
(v) in patients maintained on anti-anxiety drugs, supplementation with other agents should be considered other than using higher doses, particularly when only small veins are available;
(vi) since there appeared to be a strong tendency for a few individuals to have phlebitis with each administration in these cases diazepam should be avoided.

C. Possible cause of diazepam irritation.

Jusko et al (1973) supported Langdon et al on their view that diazepam precipitation might occur when it is injected too rapidly or when venous blood flow is relatively slow. This would be more likely to occur in situations where a hand vein is used and a wrist strap is applied proximally or distally to the site of puncture
to maintain the patient's arm fixed to an armboard or chair arm. This further restricts venous return and would tend to increase the chance of venous thrombosis, from the hand vein irritation. Jusko et al agreed with Langdon and co-workers' observation that thrombophlebitis occurred less frequently when smaller veins were avoided and when injection of diazepam was followed by vigorous flushing with normal saline.

Jusko et al reinforced the manufacturer's warnings that diazepam should not be fed into a slow intravenous drip infusion. This has been since refuted by Trieger (1976) (personal communication). When used intravenously the solution can be injected slowly, directly into the vein, taking at least one minute for each 5mg injected. The limited aqueous solubility of diazepam necessitates its formation into a solution containing propylene glycol 40 per cent and alcohol 10 per cent buffered with benzoate sodium and benzoic acid 5 per cent and preserved with benzol alcohol 1.5 per cent. Addition of this solution to normal saline results in the formation of a light yellow to white precipitate that can be observed immediately in a diazepam solution. The maximum dilution that produced an observable precipitate after thorough mixing was about fifteen fold, representing a diazepam concentration and a diazepam saline mixture in the range of 0.3 to 0.4mg per ml. The precipitate also formed when the diazepam solution was added to human plasma. In my practice either 10mg per 2ml of diazepam or 20mg per 4ml diazepam is diluted with 1ml atropine sulphate. Thrombophlebitis occurs occasionally. This will be commented on later (Chapter 24).

Siebke et al (1976) studied reactions to
intravenous injections of diazepam. They found that verified or probable thrombophlebitis occurred with increasing frequency following operation, indicating a late onset. One month after discharge 29 per cent of those who had received diazepam in glycoferal-alcohol-benzoic acid complained of tender injection sites, compared with only 10 per cent of the patients who received diazepam in cremophor E L. The difference was significant indicating an influence of the solvent system. Therefore, newer preparations may be found which eliminate venous irritation and subsequent thrombophlebitis.

D. Treatment of thrombophlebitis.

Treatment of thrombophlebitis produced by intravenous diazepam injection consists primarily of rest to the arm combined with hot compresses and/or Hirudoid ointment massaged into the thrombosed vein. The patient may also be warned against the possibility of excessive use of the involved limb with subsequent venous stasis and oedema. In my experience the condition gradually resolves. One patient required antibiotic treatment. A middle-aged woman received diazepam in the dorsal aspect of the hand. She reported that her vein had become very painful to the extent where she had reported to a hospital casualty department. She was given an antibiotic following which the pain from the thrombosed vein subsided. Two months later the patient had a palpable vein of about four inches on the dorsal aspect of the forearm. When a thrombosed vein is painful, red and tender (thrombophlebitis migrans) infection must be suspected and antibiotic therapy given. This situation is rare. Usually the vein is slightly tender and mildly annoying to the patient. Local heat therapy and rest to the arm is
advised. Where an injection of diazepam may be repeated for a long, conservative case in dentistry prevention would seem to be the best course if possible.

A technique is reported by Augspurger (1974) where the end of the butterfly scalp vein set contains a small capillary tubing containing a weak heparin solution. The object is to eliminate clotting of the needle to maintain a clear lumen in the vein. By this technique subsequent injections can be performed through the rubber diaphragm of the catheter plug. A suitably weak solution of heparin can be obtained by diluting 1.5 ml of sodium heparin 1,000 units per ml in a 30 ml bottle of saline solution. The small quantity of heparin will have no significant effect on the coagulation time. If desired, the heparin in the tube can be aspirated before a subsequent administration of drugs. This apparatus eliminates the need for frequent injections of small volumes of drug to maintain needle patency.

This author has no experience of this technique but with the experience of extended appointments involving repeated diazepam injections and the subsequent higher increase in venous thrombosis in these patients, this infusion set up containing the heparin warrants investigation and trial for longer cases. Alternatively, a new vein should be selected for each new administration so as not to excessively irritate a single vein.

Pulmonary embolism is a grave possible result of thrombophlebitis. In its severest form death rapidly occurs. It may be of varying degrees and can be difficult to diagnose. Death is due to inability to oxygenate the blood from an embolus blocking the pulmonary artery.
The most common symptoms and signs of pulmonary embolic disease are relatively non specific and may occur in other cardiopulmonary disorders. Dyspnoea is most common; next are cough and pleural pain. Haemoptysis is encountered in about one third of patients (Merck Manual 12th Ed. p.517). A case of pulmonary embolus possibly from diazepam induced thrombophlebitis has been reported by Hoare (1974). This patient underwent a venoscan to determine which site the embolus originated from. A thrombosis in the cubital fossa from a diazepam injection was the only source discovered.
PART VI

THE EYE.
CHAPTER 15.

INJURIES TO THE EYE DURING INTRAVENOUS DENTAL SEDATION.

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CHAPTER 15.
INJURIES TO THE EYE DURING INTRAVENOUS DENTAL SEDATION.

During intravenous sedation special care must be taken to protect the patients' eyes from injury. This section deals with hazards to the eye. Possible damage may result from physical trauma, excessive drying of the eyes and also from treating a patient with glaucoma.

A. Foreign bodies.

A standard text of intravenous anaesthesia and sedation in dentistry referring to eye complications mentions the importance of protection of the eyes during operative procedures in dentistry under sedation. The use of plastic goggles prevents direct damage to the eyes by dropped instruments or heavier foreign bodies, such as amalgam particles (Drummond-Jackson 1973). A special precaution is the removal of a patients' contact lenses which if rubbed may cause corneal ulceration. Lenses must therefore be removed at the beginning of the appointment (Colvin 1977).

B. Corneal drying effects of atropine sulphate.

Atropine prevents or reduces pharyngeal secretion and eliminates salivary secretion producing a drier operative site. Not only are salivary and pharyngeal secretions reduced but also lacrimal secretion. This action is not mentioned in detail in the standard text (Drummond-Jackson 1973) and the consequences may not be considered by dental surgeons when the complications of using atropine routinely are considered. Sedated patients often keep their eyes open exposing an appreciable part of the cornea to possible dehydration. Keratitis sicca may be induced during extended procedures if the corneal
surface is not artificially lubricated or the eye lids kept closed.

For those patients who may be excessively sensitive to the drying effects of atropine then it should be omitted. These patients would include those suffering from Sjögren's syndrome where an established condition of keratitis sicca would be aggravated by atropine. An alternative to not using atropine and having the problem of a moist operative field is to either tape the eye lids closed, which for an awakening patient can be an alarming experience or to apply an artificial moistening agent, for example, hypomellose, which can be obtained in a 0.5 per cent or a 1 per cent solution. This is a methyl cellulose material (Harrison et al 1966, p.1918).

C. Glaucoma.

Glaucoma is a condition affecting the eye in which intra-ocular pressure increases, producing blindness.

Drummond-Jackson (1974, p.43) suggests that 0.3mg atropine premedication intravenously is unlikely to aggravate an incipient glaucoma in adults. The use of atropine in glaucoma patients is contentious. Open angle and closed angle glaucoma have been described (Kolker and Hetherington 1970, p.206) (photograph p.198-200).

An acute attack of angle closure glaucoma may be precipitated by drugs that dilate the pupil (for example, atropine). The periphery of the iris bulges forward obstructing the trabecular meshwork and thus preventing aqueous humour from reaching the outflow channels. In open angle glaucoma, which may be
Photograph 35

Diagram of normal aqueous outflow in the eye, showing normal aqueous pressure in the anterior chamber.

(Reproduced from Kolker, A.E. and Hetherington, J. 1970 p.4)
Photograph 36

Diagram showing angle closure of the anterior chamber of the eye with restricted aqueous outflow and increased intra-ocular pressure.

(Reproduced from Kolker, A.E. and Hetherington, J. 1970 p.5 and 6.)
Photograph 37

Diagram showing open angle glaucoma due to a defective drainage system from the anterior chamber.

(Reproduced from Kolker, A.E. and Hetherington, J. 1970 p. 5 and 6)
aggravated by anti-cholinergic and corticosteroid drugs, excessive resistance to outflow is caused by changes within the outflow channels themselves mainly within the trabecular meshwork independent of the size of the pupil.

The intra-ocular pressure usually goes higher in angle closure glaucoma than in open angle glaucoma. Angle closure glaucoma tends to develop acutely with pairing of vision, halos and often pain, and is usually bilateral, whereas open angle glaucoma tends to be chronic and commonly occurs without warning symptoms.

Acute angle closure glaucoma is an emergency condition which can cause blindness if not quickly recognized and treated. It nearly always requires intensive medical treatment followed promptly by surgery. Chronic open angle glaucoma usually can be controlled medically for long periods and visual losses occur relatively slowly if control is inadequate. The advisability for the use of intravenous atropine for a patient with controlled glaucoma can be best judged in consultation with the patient's ophthalmologist. As atropine may precipitate an acute attack of glaucoma in an undiagnosed patient the dental surgeon should be able to recognize the signs and symptoms of an acute attack of glaucoma. The patient may then be referred quickly to their ophthalmologist.

Evidence in the literature on the propensity for atropine to precipitate an attack of acute glaucoma is difficult to find. Cases have been reported following operations involving general anaesthesia with atropine as premedication (Hugonnier 1963; Gartner 1958). Gartner and Billet (1958) suggested that acute glaucoma occurred
in the early post operative period after general surgery with sufficient frequency to bring the problem to the attention of ophthalmological surgeons and anaesthetists. They diagnosed four cases out of three thousand four hundred and thirty seven. In none of these four cases did the patient have any awareness of eye trouble before the operation. It is possible that other cases occurred where transient and acute episodes were missed by the surgeon. A similar situation may occur from intravenous sedation where atropine is used in patients who have undiagnosed glaucoma.

The attacks mentioned (Gartner 1958) occurred within forty-eight hours of operation. The patients had red and painful eyes and headaches that caused the surgeon to request eye consultation. All the patients were over the age of fifty years.

Laramande et al (1951) reported five cases in which acute glaucoma followed the parenteral or oral administration of atropine or scopolamine. Three cases were similar to those reported by Gartner and Billet (1958) in that the medication was given before general anaesthesia and was followed by acute glaucoma. The result was attributed to atropine or scopolamine.

Leopold and Comroe (1948) reported a study in which pre-anaesthetic doses of atropine and scopolamine were administered to known glaucoma patients. These cases included a chronic simple glaucoma, a secondary glaucoma but none of the acute narrow angled type. They found dilated pupils in three of eight cases with atropine and seven of eight cases with scopolamine.

Six cases of acute glaucoma were precipitated
by the oral use of belladonna for intestinal disorders (Ullman and Mossman 1950). Schwartz et al (1957) decided that the usual pre-anaesthetic doses of atropine and scopolamine were safe even in glaucoma sufferers. On the reports previously listed their advice is doubtful.

Gartner and Billet (1958) said that general anaesthesia (especially ether) in the early stages caused contraction of the pupils while in the deeper stages mydriasis occurred which would precipitate an acute glaucoma attack. In dental intravenous sedation the only drug likely to produce a mydriasis of the pupils is atropine which can produce angle block reducing outflow of aqueous humour from the anterior chamber. This may result in an increase in intraocular pressure and an attack of acute glaucoma.

Atropine is administered in concentrations of 0.6 mg to 1 mg. The exact concentration of atropine required to initiate an attack of acute glaucoma would vary from patient to patient and cannot be estimated; however, most reports studied do not deal with intravenous atropine but with an oral ingestion or intramuscular injection. A higher concentration could be expected to reach the eye with a greater chance of initiating an acute glaucoma attack, because of intravenous administration. Schwartz et al (1957) and Mehra and Chandra (1965) suggested from their studies that there was no danger in using the belladonna drugs intramuscularly for pre-operative medication. As a preventive measure in case an acute attack occurred these authors suggested that pilocarpine hydrochloride, 1 to 2 per cent or physostigmine salicylate 0.25 to 1 per cent be instilled into the cornea producing miosis to counteract the
potential mydriatic effect of the belladonna drugs and the anaesthetic drugs. Havener (1970) stressed the traditional advice that the treated glaucoma patient may safely receive any anticholinergic systemic drug indicated for the treatment of a general medical disorder. This would suggest that the patient receiving miotic drugs for acute glaucoma may receive atropine intravenously in a usual dose of 0.6 mg to provide a dry field for operative dentistry with intravenous sedation.

Rosen (1962) considered that the dangers from parenteral atropine were minimal and suggested that patients who were anatomically predisposed to angle closure glaucoma may develop an acute attack as a result of the stress surrounding the surgical procedure in general. He concluded that atropine should not be considered an important factor in this regard.

According to Priest (1960) mongols may show sensitivity to atropine especially when it is applied topically to the eyes. Hyoscine is recommended as an alternative. This does not follow from the experience of Holland (1977).

Rosen (1962) compared the amount of systemically administered atropine reaching the eye to the amount available to the eye with the administration of a single drop of 1 per cent atropine solution topically. Extending his calculations for 2 mg of atropine given systemically and evenly distributed in a 70 kg individual only 0.0004 mg reaches the entire eye as compared to 0.6 mg of atropine available when a single drop of a 1 per cent solution is applied.

Rieser (1976) suggested that the fear of producing an attack of angle closure glaucoma could be
dispelled by administering topical pilocarpine solution (2 per cent) to produce miotic pupils pre-atropinization or using morphine as a pre-anaesthetic agent, which also produces a profound miosis. In any patient with known glaucoma (either angle closure or open angle) continuation of glaucoma medication before, during and after operation was advised. In the recovery room, symmetry and shape would confirm the absence of angle closure glaucoma. If the pupils were irregular, asymmetric and mid-dilated an ophthalmologic consultation should be obtained to medically control and eventually surgically correct the attack of angle closure glaucoma.

Regarding Valium the manufacturer (Physicians Desk Reference 1971) states that acute angle glaucoma is a contraindication to the clinical use of diazepam. There is no evidence that benzodiazepines have anti-cholinergic properties of clinical significance (Greenblatt and Shader, 1974). Roberts (1968), Neetens (1975) and Ferreira et al (1969) found no adverse clinical effects of the use of diazepam for glaucoma patients. Other authors, Boergen and Lund (1974) recommended that diazepam should be prescribed to patients suffering from emotional instability to possibly decrease intraocular pressure.

Strathdee (1977) considers diazepam a very safe drug and has not encountered increases in pressure in glaucoma patients on which it has been used. This is supported by the Report of Suspected Adverse Drug Reactions No.4 (1978) p.91-94. In the twelve year period from 1964-1976 no reports of intraocular pressure increases due to diazepam have been received. Diazepam
use appears not to be contraindicated in anxious patients with glaucoma, although caution must be exercised.

Summary.

The implication for the dental surgeon is to recognize the symptoms of glaucoma if encountered in any patient, thereby ensuring rapid follow-up treatment by an ophthalmologist.
PART VII

CARDIAC COMPLICATIONS

PREVENTION AND TREATMENT
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CHAPTER 16

HYPOXIA AND HYPERCAPNIA - CARDIOVASCULAR EFFECTS

Signs of oxygen reduction or carbon dioxide increase in the blood should be recognized by the dental surgeon to prevent cardiac arrest. These signs are reviewed.

Cardiac arrest may be initiated by hypoxia from chronic airway obstruction or hypercapnia from depressant intravenous drugs which reduce tidal volume. In asphyxia, carbon dioxide accumulation and oxygen deprivation combine to produce cardiac arrest.

A. Hypoxic and hypercapnic effects on animals.

The modes of action of the two effects are different as was shown by Clowes et al (1955). These effects were observed in experiments with dogs subjected to varying degrees of hypoxia.

The characteristic response to severe hypoxia initially was an immediate elevation of blood pressure or pulse rate or both. This was followed, as oxygen desaturation of the blood continued, by bradycardia as the hypertension continued. When the blood pressure fell, it did so precipitously, accompanied by a further fall in pulse rate. Cardiac arrest followed within a few minutes. Venous pressure rose only after the final hypertension occurred.

The response to severe hypercapnia was characteristically different from that of severe hypoxia. Respiratory acidosis initially caused a marked but transient hypotension and bradycardia. This was followed by a return of pulse and blood pressure to near control levels, which in turn was succeeded by a gradual decline to cardiac arrest. Marked fluctuations in venous
pressure occurred as a result of intense respiratory efforts before depression developed. The mean venous pressure in their experiments in dogs remained nearly unchanged throughout.

Thrower et al (1961) commented on acid base derangements and myocardial contractility derangement in fifty-six open chest dogs.

A comparison was made of the ventricular contractile force changes accompanying acidosis produced by: (i) reducing total perfusion by means of an extracorporeal oxygenator, and (ii) infusing lactic acid. During acidic states the animals showed a marked decrease in myocardial contractility and arterial blood pressure. This depression occurred despite injection of catecholamines. There was also a decrease in the response to injected levarterenol accompanied by a decrease in pH and carbon dioxide combining power. Death was associated with a near zero carbon dioxide combining power.

Ebert et al (1962) subjected normal dogs to acidotic or alkalotic conditions in the course of a period of profound hypothermia induced during cardiopulmonary by-pass at a high flow rate. Total body oxygen consumption was unchanged by alterations in the blood pH. The function of the heart before and after a period of aortic occlusion was also assessed by left ventricular function curves. Severe depression of ventricular function was noted in the acidotic dogs while definite protection of the heart was afforded by alkalosis.

B. Hypoxic and hypercapnic effects on man.

Clowes et al (1955) also tested induced
hypercapnia in man. The patients were not allowed to collapse into an hypoxic state and respiration was assisted at all times. The period of induced respiratory acidosis ranged from ten to twenty-six minutes. Blood pressure, respiration, electrocardiogram and electroencephalogram readings were taken throughout.

The response of blood pressure and heart rate was quite typical in their series. There was an initial fall followed by a hypertensive state followed in turn by a gradual fall of both pulse and blood pressure.

The mechanism of the circulatory response to hypercapnia differed in several important respects from that due to oxygen lack. Hypoxia was a specific stimulus for the release of adrenalin, which accounted for the initial hypertension and tachycardia. This reaction took place when the arterial oxygen fell below 75 per cent of saturation. Harris (1948) showed that cardiac arrest was related to failure of the heart in severe hypoxia.

Acid base derangements were studied by Thrower et al (1961) in ten patients with terminal shock from various causes. Correction of the metabolic acidosis with an increase in the carbon dioxide combining power could be achieved with an organic buffer and sodium bicarbonate. The vascular response to levarterenol increased in the patients as in the dogs. Results seemed to indicate that death and shock may be due to a decrease in the ability of the blood to carry carbon dioxide, which leads to a build-up of acid cellular products, carbon dioxide narcosis, and death.

With correction of acidosis there is an increased cardiovascular responsiveness to circulating catecholamines.
Brooks and Feldman (1962a) described a clinical syndrome of metabolic acidosis producing delayed recovery in patients after anaesthesia. The patient remained unconscious or very confused at the end of the operation. Peripheral cyanosis was usually present. Respiration was absent or inadequate and was frequently gasping in nature, associated with tracheal or jaw tug. There was dissociation between the thoracic and abdominal respiratory components. These patients appeared to be partially paralysed, but no evidence of neuromuscular block was demonstrable when a motor nerve was stimulated.

The cardiovascular impairment produced a progressive hypotension, usually with a narrow pulse pressure. Cardiac arrhythmias and peripheral cyanosis could occur. The circulatory collapse became irreversible when the pulmonary perfusion was reduced to a critical level and cyanosis became generalized.

Death resulted from circulatory failure despite adequate artificial ventilation and the use of vasopressor drugs.

The clinical picture of an unconscious patient, making inefficient respiratory effort, who was cyanosed and hypotensive resembled that occurring in neostigmine resistant curarization. Biochemical investigation of these patients revealed a gross metabolic acidosis.

Patients displaying this chemical syndrome fell into four main categories, two of which were circulatory arrest, for example, cardiac arrest (metabolic acidosis resulting from total body anoxia); and circulatory insufficiency, for example, low flow pump oxygenators or
post operative haemorrhage (tissue hypoxia causing a metabolic acidosis).

Brooks and Feldman (1962a) treated the condition with a solution containing 2.74 per cent sodium bicarbonate, giving 166 milli-equivalents per 500 ml used. This solution is hypertonic having approximately twice the osmolarity of plasma.

C. Sodium bicarbonate treatment of acidosis.

This section is reviewed further with the section of drug treatment of cardiac arrest (p. 272). The dangers that are present when 2.74 per cent sodium bicarbonate is infused are similar to those with any electrolyte-containing fluid. Care must be exercised to prevent over hydration and gross excess of salt. Most patients presenting for surgery have a moderate degree of dehydration.

It is always preferable to have laboratory facilities available to measure the pH and PCO₂ so that accurate replacement therapy can be given. If this is not available, the following regimen is suggested to treat this potentially lethal condition.

200 ml of 2.74 per cent sodium bicarbonate infused over a period of twenty to twenty-five minutes is quite safe in an average adult patient. This represents about 1 mEq per kg in a 60 kg patient. Because the sodium bicarbonate is initially restricted to the extracellular compartment, high values of plasma bicarbonate are obtained. A further 100 ml of this solution can safely be given over the next one hour without resorting to laboratory control.
Brooks and Feldman (1962a) described a case of cardiac arrest in a patient complaining of severe chest pain in whom sodium bicarbonate produced a marked improvement. The patient collapsed. Cardiac massage was instituted at once, first by external thoracic pressure. Within five minutes the chest was opened, the trachea intubated and internal cardiac massage and artificial ventilation were performed.

The heart was atonic but after a few minutes of massage improved tone and coarse fibrillation appeared with short bursts of ventricular extrasystoles. Effective cardiac massage was carried out for thirty minutes without a spontaneous co-ordinated cardiac contraction. Electrical defibrillation of the heart was repeatedly tried, but without effect, although on occasion short bursts of ineffective nodal rhythm were produced.

At this time the patient was deeply unconscious with dilated pupils (1 ml of 1 in 100,000 adrenalin had been given into the heart). He was making occasional respiratory gasps with pronounced tracheal tug. His extremities were cold and peripheral cyanosis was present.

After fifty minutes of cardiac massage an infusion of 2.7 per cent sodium bicarbonate was run in quickly. After 400 ml had been given the peripheral cyanosis was less marked and the respiratory effort more regular. Electrical defibrillation restored an effective spontaneous cardiac beat. The electrocardiogram showed the rhythm to be a ventricular tachycardia, between 60 to 80 beats per minute, producing systolic blood pressure of 90 mm of mercury. A further 200 ml of sodium bicarbonate was infused slowly during the next thirty minutes. The
patient's condition continued to improve. He became warm and pink and his blood pressure rose to 110/70 mm of mercury. The patient showed signs of returning consciousness, he moved his head from side to side and screwed up his eyes.

This patient developed a profound metabolic acidosis after the cardiac arrest. He presented a clinical picture similar to the cases previously discussed. The inability to defibrillate the heart in the presence of a deficit of bicarbonate ions was also found in another patient and difficulty was also experienced in two dogs. Brooks and Feldman (1962a) commented that metabolic acidosis was associated with cardiovascular, respiratory and central nervous system depression.

D. Causes of carbon dioxide retention.

Carbon dioxide retention can occur in two ways:
(i) from hypoventilation or re-breathing of carbon dioxide (primary carbon dioxide retention); or
(ii) from respiratory depression consequent upon metabolic acidosis (secondary carbon dioxide retention).

The cardiovascular collapse that occurred in metabolic acidosis was reversed by alkaline infusion therapy. Improvement in arrhythmias, increase in cardiac muscle tone and function, and facilitation of defibrillation, have been observed with this treatment. Cyanosis produced by the poor peripheral circulation also appeared to be reversed by sodium bicarbonate in all patients after cardiac arrest.

Brooks and Feldman further commented in The Lancet (1962b) that vasopressors, cerebral stimulants or
digitalis will have little or no effect in the presence of a metabolic acidosis. Calcium gluconate may have a transitory effect on the myocardium which is magnified when the acidosis is corrected with sodium bicarbonate. They reiterated that myocardial contractility was greatly reduced in the presence of a metabolic acidosis.

Ledingham and Norman (1962) concluded from their study that a vital factor in the restoration of efficient myocardial function after circulatory arrest and the prevention of dangerous arrhythmias was the avoidance of hypoxic acidosis. Neither a high PCO₂ nor variation of pH over a wide range, 7.2 to 7.6, seemed responsible for inadequate myocardial function provided there was no accompanying metabolic acidosis.

Del Guercio et al (1963) studied cardiac output and hypoxic acidosis during external cardiac massage in man. In each case 100 per cent oxygen was administered by means of a cuffed endotracheal tube and intermittent insufflation, and yet arterial PO₂ did not rise above 158 mm of mercury (normal 640 mm mercury breathing pure oxygen). Systolic blood pressure measured during external cardiac massage did not reflect the low mean arterial pressures and low cardiac output. Spontaneous heart action could not be restored in two patients but a third patient lived for two hours after resuscitation.

Anderson et al (1963) studied the effects of sodium bicarbonate on myocardial contractile force and cardiac output in nine anaesthetized dogs. They concluded that the increase in cardiac output following intravenous sodium bicarbonate was due to direct myocardial action of sodium bicarbonate plus a fall in systemic vascular
resistance rather than to the slight increase in pressure in the left atrium. Changes in cardiac output and myocardial contractile force appear to follow the changes in arterial blood pH rather than the volume or tonicity of injected fluid. Neither isotonic or hypertonic sodium chloride produced significant changes in cardiac output and myocardial contractile force. Changes in pressure in the left atrium and heart rate following sodium bicarbonate were not statistically significant.

E. Chronic carbon dioxide retention.

Filley (1970) reviewed acid regulation and carbon dioxide retention. Of interest were his comments on the PCO₂ in chronic carbon dioxide retention, which are significant in dental sedation for the patient with chronic pulmonary disease.

Carbon dioxide retention implied changed respiratory control, inadequate peripheral ventilatory response, or both.

(i) Disturbed central respiratory control.

(a) Damage to the central nervous system.

Cerebral vascular damage, especially if the medullary centres are involved, encephalitis and rare cases of idiopathic hypoventilation are the most important examples.

(b) Depression of the central nervous system.

A common cause of transient carbon dioxide retention is the unwise use of sedative drugs. It usually results from failure to recognize carbon dioxide retention in its chronic form. It is just as dangerous to give barbiturates to bronchitics as morphine to asthmatics. Post operative carbon dioxide retention is another obvious example in this category.
(ii) Disturbed peripheral ventilatory response.

Spinal poliomyelitis, infectious polyneuritis and myasthenia gravis are typical examples of failure of the respiratory muscles to respond. Injection of certain antibiotics (kanamycin, polymyxin, neomycin and streptomycin) can all produce neuromuscular blockade and respiratory paralysis. Trauma of many kinds can lead to this form of carbon dioxide retention.

(iii) Disturbed respiratory control response.

The most complex type of carbon dioxide retention occurs in advanced lung disease and especially in patients with chronic airway obstruction. In these cases mechanical pulmonary abnormalities interfere with the response to ventilatory drives and central respiratory controls are secondarily modified. This modification is not simply a poisoning of the respiratory centres or chronic carbon dioxide narcosis, but a readjustment of the body chemistry and the sensitivity to carbon dioxide (and probably hypoxia) so that the work of breathing is minimized. Great obesity (300 lbs or more) is another example of a situation in which the work of breathing is so great that the body chooses to retain carbon dioxide rather than make the effort to maintain arterial PCO₂ at the normal level of 40 mm of mercury.

In chronic carbon dioxide retention the respiratory centres adjust to the high PCO₂ and are relatively insensitive to carbon dioxide increases. The chief dangers in this form of compensation are: that the hypoxemia which must occur to some extent may become the chief respiratory drive; and that iatrogenic depression by sedatives, ordinarily not dangerous, may be fatal to a patient whose unrecognized
compensated carbon dioxide retention is suddenly converted to uncompensated respiratory acidosis with profound acidemia (low pH).

F. Complications of acute carbon dioxide retention.

Patients in acute respiratory acidosis are subject to a large number of complications - cardiovascular, gastrointestinal, renal and cerebral. There are five complications which should be emphasized because they can be the direct result of mismanagement.

(i) Over-sedation. It must be remembered that restlessness and sleeplessness in patients with carbon dioxide retention may be signs of increasing hypoxemia. Sedation without respiratory assistance or adequately controlled oxygen therapy can be fatal.

(ii) Misapplied mechanical ventilatory assistance. In patients who fight the respirator, or in cases when machine pressures, tidal volumes, respiratory rates, or total flows are ill-suited to a patient's needs, acidosis may become worse, not better. The only sure way of knowing that mechanical ventilatory assistance designed to remove carbon dioxide is in fact doing so is to perform frequent measurements of PCO₂ in the blood.

(iii) A third complication, arterial hypocapnia and pH increases in the blood, may result from too rapid a loss of carbon dioxide by mechanical ventilation. Such transient alkalosis may or may not be important depending especially on whether or not the brain undergoes similar sudden fluctuations. Such fluctuations depend on cerebral spinal fluid buffering capacity and cerebral blood flow. Hypoxia reduces cerebral spinal fluid buffering capacity in the brain (Lee et al 1969) and in emphysema apparently
because of changed vasomotor responses to hypoventilation rapid and excessive elimination of carbon dioxide causes convulsions and coma (Rotheran et al 1964).

(iv) Potassium tends to move from tissue cells to plasma in acute respiratory acidosis. Such mobilisation and concurrent use of diuretics and corticosteroids may cause potassium deficiency in respiratory failure. Since chloruresis also tends to occur, a hypochloremic alkalosis may be a complication of respiratory failure and replacement of both potassium and chloride may be necessary.

(v) High concentrations of oxygen may, by removing the hypoxic stimulus in respiratory failure, so depress respiration that carbon dioxide tension may rise rapidly to 150 mm of mercury or higher and the pH may drop precipitously. Such a danger should not lead to the withholding of oxygen since all patients with severe carbon dioxide retention are always quite hypoxemic on air and must receive oxygen. Intermittent use of oxygen is, however, contra-indicated. The solution to the problem lies in: the controlled use of oxygen at low flows; and frequent monitoring of the arterial blood PO2 and PCO2.

In summary, hypercapnia, whether it be of metabolic or respiratory origin, has a depressant effect on the heart. When this effect is realized in the treatment of cardiac arrest the addition of base to the circulation has a beneficial effect on the success rate of recovery from cardiac arrest.
CHAPTER 17

CARDIAC ARRHYTHMIAS

A. General significance.

Cardiac arrhythmias include both the non-dangerous and potentially lethal types. Often seen arrhythmias which are not dangerous are slight tachycardia or slight bradycardia. The dangerous arrhythmias, in particular ventricular tachycardia and ventricular fibrillation can cause death. The possibility is always present of a cardiac arrest or a reduction in blood flow developing due to inadequate cardiac output from an arrhythmia. Their effects and what may potentiate or initiate them, will be discussed with reference to the relevant literature.

Severe arrhythmias may occur in the dental surgery even during routine treatment when local anaesthesia with adrenalin or noradrenalin is used. A death which occurred after intravenous diazepam and pentazocine with lignocaine (vasopressor not stated) in a poor risk patient was reported in the American Society of Oral Surgeons of Southern California Survey (1974). The patient suffered a myocardial infarction.

As an introduction to arrhythmias Wolff (1950) noted the effects of life stress on cardiovascular disorders. There was evidence of two kinds of cardiovascular reactions during stress. (i) A hyperdynamic response, or the reaction of localization for defence; and (ii) a hypodynamic response, by reaction of defeat, quite the opposite to the preparation for fighting. These are the alternative physiological adaptations of the apprehensive dental patient. Stevenson et al (1950) showed electrocardiographic evidence of ventricular
extrasystoles in older persons initiated by discussing significant personal topics. These phenomena were more easily demonstrated in individuals with slightly damaged myocardia. In a series of carefully studied older persons the number of extrasystoles per hundred was found to parallel the intensity of outward manifestations of anxiety.

Wolff (1950) in a group of twenty-five unselected patients with paroxysmal, ventricular and nodal tachycardia and ventricular fibrillation also studied the mode of living and emotional states of his patients. Anxiety states were found to be most significantly related to the occurrence of attacks. These attacks were precipitated during periods of tension associated with anxiety, resentment, conflict and depression. When the immediate emotional response was intense the attack usually occurred at the time of the associated event. When it was less severe the attack occurred sometime later after an intervening period of mounting tension. The patients possessed certain personality traits which rendered them particularly subject to the development of anxiety, resentment and depression in response to only moderately stressful modes of living. Precipitating events such as tripping, postural changes and being suddenly startled were also common and operated especially during stressful life situations and disturbed emotional states.

Wolff (1950) recorded electrocardiograms on a total of thirty-five patients when they were discussing problems of great personal significance which aroused anxiety and resentment. The majority of the patients showed significant changes in heart rate and in the configuration of the electrocardiogram. In eighteen
patients the electrocardiographic changes would have been interpreted as abnormal had they occurred during or after standard exercise tests. These were similar to those previously described by Gold et al (1943) as occurring in certain individuals experiencing severe pain during periods of noxious stimulation.

Prolonged and moderately severe tachycardia (with associated T wave changes) was observed in many patients during periods of tension and anxiety even though they were ostensibly in a basal state. A small group of patients with asthma and without complaints or evidence of cardiovascular disease showed effects in tolerance and changes of heart rate and T waves as great as those observed in patients complaining of palpitations.

As a corollary of this observation, and probably of major significance, are the demonstrations of Schneider (1949) who studied the problem of thrombosis in relation to life stress. Dramatic reductions in clotting time occurred during painful experiences, vigorous effort and periods of alarm or anxiety. The importance of increased clotting potential in persons with narrowed myocardial and cerebral vessels where blood flow was slow, especially in the presence of atheromatous plaques, is self-evident. Also of interest is the comment by Wolff (1950) on the dramatic changes in circulation (decrease) that occur in the skin with stress. (Graham et al 1950).

B. Factors modifying ventricular fibrillation.

Dirken et al (1955) found that injection of acetylcholine was uniformly unsuccessful in terminating ventricular fibrillation in the isolated rabbit heart. Four other methods, (a) arrest of coronary perfusion,
(b) adenosine triphosphate injection, (c) calcium and potassium perfusion and (d) electrical stimulation produced variable results ranging from 28 per cent success with adenosine triphosphate injection to 64 per cent success with the electrical method. Cooling the isolated heart by coronary perfusion and subsequently rewarming it gave consistently good results where other methods failed.

Goodford (1958) also studied ventricular fibrillation in the isolated rabbit heart to determine the effect of factors modifying the metabolism. He found that sodium azite, sodium monoidoacetate and sodium fluoride caused fibrillation, the effect of sodium fluoride being neutralized by magnesium chloride. Fibrillation was also caused by lack of glucose, and could be arrested by adding glucose; the effect of glucose in arresting fibrillation was facilitated by insulin. In other experiments mannose and pyruvate arrested fibrillation due to lack of glucose but lactate could not.

Effect of temperature changes, adrenalin and cyanide were also studied. When all oxygen was removed from the perfusing solution fibrillation was arrested. When adrenalin was perfused through the heart it greatly augmented the rate and force of the beat. This must lead to a greater demand for oxygen which perhaps could not be met by the amount dissolved in the perfusion fluid. As a result there was an oxygen deficiency and a greater tendency to fibrillation. It was possible that the occurrence of ventricular fibrillation in the body as a result of the injection of adrenalin during chloroform anaesthesia had a similar explanation.
It was interesting to note that there were two other circumstances in which fibrillation could not occur in the isolated heart; in the absence of calcium and in the presence of twice the normal concentration of potassium in the perfusion fluid.

Armitage et al (1957) showed that when the ventricles of the isolated heart were fibrillating there was an increased loss of potassium ion as compared with the periods of normal beating preceding. This observation may be related to the fact that fibrillation could be arrested by increasing the potassium concentration in the perfusing fluid.

Goodford's (1958) results indicated that to avoid fibrillation it is necessary to facilitate the active transport of potassium ion into the cell. The high net loss of potassium in fibrillation may be due to insufficient active transport. The defibrillatory effect of an increased concentration of potassium ion may be due to an improved active transport. This conception sheds light on the fibrillatory effect of glucose-free medium which may be due to lack of the substance whose breakdown within the cell normally provides the energy for the active transport of potassium.

Pruitt (1958) drew attention to ventricular arrest and ventricular tachycardia or fibrillation striking those patients whose cardiac mechanism failed without associated post-mortem pathological changes in the heart and its vascular supply. He commented on the predilection of ventricular tachycardia to progress into ventricular fibrillation and death. There were two approaches to the treatment of ventricular standstill
and of ventricular tachycardia or fibrillation, namely the pharmacologic and the mechanical. Pruitt mentioned different forms of treatment of fibrillation but of interest was that an increased awareness of the role of certain cardiac arrhythmias in the development of major and sometimes lethal complications of cardiac disease was an essential prelude to a more determined effort to improve the treatment which may avert these disasters. Ventricular arrest, ventricular tachycardia and ventricular fibrillation are the most sinister among the cardiac arrhythmias and on them attention was centred.

Milton (1959) studied the relation between temperature and changes in ion concentration on ventricular fibrillation induced electrically. At 37 degrees centigrade the isolated rabbit heart perfused with Locke's solution was on the edge of anoxia but at 32 degrees centigrade the oxygen supply was adequate. At the lower temperature the proportion of hearts fibrillating at any given potassium concentration was reduced, so, although the proportion of hearts fibrillating rose as the potassium concentration fell, even when the latter was one quarter of the normal concentration, the proportion was not higher than 67 per cent. The relation of the concentration of calcium ions to the proportion of hearts fibrillating changed from biphasic at 37 degrees centigrade to almost rectilinear at 32 degrees centigrade; the proportion increased as the concentration of calcium ions rose. A reduction in sodium concentration also raised the proportion of hearts fibrillating.
C. Causes of ventricular fibrillation.

In his summary of the causes of fibrillation Burn (1960) found that fibrillation was produced in isolated rabbit atria by rapid stimulation in the presence of acetylcholine and a low concentration of potassium. Ventricular fibrillation was produced by electrical stimulation in the isolated rabbit heart.

Observations were consistent with the view that fibrillation occurred when individual fibres were out of phase. Excitation spread from one fibre which contracted to another which was resting. The excitation was effective only when the refractory period was for one reason or another abnormally short. Then the excitation caused the resting fibre to contract which caused spread of excitation. The essential factor for fibrillation was a shortening of the refractory period (which was usually indicated by a shortening of the action potential).

It was also necessary to throw fibres out of phase. This occurred due to rapid electrical stimulation or to a stream of impulses produced by an ectopic focus established by the use of aconitine. Rapid stimulation possibly acted by depressing the rate of conduction and this depression was not uniform throughout the tissue. A single shock in the vulnerable period may act in the same way. In those cases where rapid stimulation alone produced fibrillation, it may do so by the double effect of shortening the refractory period and of depressing the rate of conduction.

A long refractory period (or the long action potential) of cardiac muscle as compared with that of
skeletal muscle protects the cardiac muscle from fibrillation. Energy is required to maintain its length, for when there is a lack of oxygen or glucose, or in the presence of metabolic inhibitors, the action potential is shortened and fibrillation is facilitated.

Burn and Hukovic (1960), on this theme of the cause of fibrillation, explained that factors which shortened the duration of the action potential, particularly those causing the plateau to disappear, facilitated fibrillation. Those which lengthened the duration of the action potential prevented fibrillation. The reason for the length of the cardiac action potential may therefore be to prevent fibrillation. When the action potential is of normal length the fact that two adjacent fibres are out of phase does not matter; the one which is first to contract is not re-excited by the one which is second to contract, because at that moment the first is inexcitable. If the action potential is short then the first may be already repolarised and may be excited by spread of excitation from the second. Factors which inhibit metabolism shorten the action potential.
CHAPTER 18

SIGNIFICANCE OF ARRHYTHMIAS

Most arrhythmias observed during surgery are not considered clinically significant. (Hughes et al 1966). Nine of their patients had infrequent unifocal ventricular premature contractions. Such an arrhythmia is benign (Buckley and Jackson 1961). Averill (1960) and Hiss et al (1960) found this arrhythmia in 0.65 percent of normal, healthy subjects but observed a threefold increase in persons over forty-five years old.

One instance of sinus arrhythmia was noticed by Hughes et al post-operatively and during operation. Sinus arrhythmia is a normal phenomenon with no clinical significance (Buckley and Jackson 1961, Phibbs 1961). Two patients with normal pre-operative ECGs developed an operative supraventricular pacemaker. This arrhythmia has no clinical significance (Katz 1956).

Six subjects had occasional unifocal supraventricular premature contractions during operation. Two of these had this arrhythmia pre-operatively. Fosmoe (1960) noticed supraventricular premature contractions occurring in 4.9 per 1,000 subjects through all age groups (16 to 55 years). The vast majority of extrasystoles (premature contractions, atrial, nodal, or ventricular in origin) caused no complaints and require no therapy (Scherf 1960). Irving (1961) noticed that a single premature systole did not significantly reduce overall cardiac function.

One patient, a seventy-six year old Caucasian male with a history of systemic heart disease
and congestive heart failure had unifocal supraventricular contractions pre-operatively but during the operative procedure this arrhythmia was followed by atrioventricular nodal escape. This patient was not taking digitalis. Nodal escape (the case where the SA node fails to originate an impulse, and another normally automatic cell in the atria or A-V junctional tissue releases an impulse which is then conducted to the ventricles) was often observed in older age groups in association with sinus bradycardia and may occur because of digitalis intoxication (Bellet 1963) but was usually of no clinical significance (Katz 1956,p.98).

The most important type of arrhythmia developing during an operation was multifocal ventricular premature contractions (VPC). Premature contractions from several areas within the same chamber indicated widespread myocardial irritability and probably denoted advanced myocardial disease. Averill and Lamb (1960) found that of 67,375 asymptomatic subjects only one had definite multifocal VPC. They concluded that multifocal VPC are evidence of heart disease.

Although multifocal ventricular premature contractions were not present in any pre-operative tracing three patients developed this arrhythmia during operation.

Burch and De Pasquale (1964) suggested that the hazards of frequent dental manipulation of short duration should be weighed against the hazards of more prolonged manipulations with fewer visits. They also indicated that under certain circumstances the use of nitroglycerin or pre-operative sedation might increase the tolerance of cardiac patients to oral surgery.
Such decisions are, of course, of extreme importance to the cardiac patient and indicate the necessity for consultation between the oral surgeon and cardiologist. If sedation is beneficial for the cardiac patient, then it is unlikely to be harmful for the normal dental patient who is apprehensive.

Miller et al (1970) carried out a study to delineate the factors leading to cardiovascular complications recorded in the oral surgery outpatient during dental outpatient general anaesthesia. They studied one hundred ASA (American Society of Anesthesiologists) class one patients ranging in age from ten to sixty-nine years. The anaesthetic agents used were methohexitone sodium and halothane, nitrous oxide and oxygen.

The data in this study showed a high incidence of abnormal rhythms, especially those of ventricular origin. This usually high incidence of arrhythmias, especially the chaotic type, has been previously reported and confirms the incidence in this study. (Webb 1954) The presence of halothane played a part in the arrhythmias. Miller et al concluded that the most important preventive factors appeared to be ventilation. During the course of anaesthesia attention to the elimination of carbon dioxide and adequate maintenance of acid base balance was essential to the stability of the rhythm of the heart in the dental outpatient.

Rafel (1972) considered that previous reports of the occurrence of significant electrocardiographic changes were conflicting. Ventricular arrhythmias have developed during induction of anaesthesia with nitrous oxide and halothane (Tolas 1967, Vaník 1968), with cyclopropane (Vaník 1968) with analgesic doses of
nitrous oxide, (Ryder 1970) and with methohexitone sodium-halothane-nitrous oxide combinations (Miller 1970). No arrhythmias were noted with thiopentone sodium (Tolas 1967), methohexitone sodium (Vanik 1968), or lignocaine hydrochloride 2 per cent with 1 in 50,000 epinephrine hydrochloride (Bjorlin and Malmborg 1968; Klein et al 1968) used alone. Cardiac changes were reported with the use of nitrous oxide and thiopentone sodium, nitrous oxide and methoxyflurane (Allen 1970, Allen 1972); atropine with alphaprodine hydrochloride, hydroxyzine hydrochloride, methohexitone sodium and lidocaine (Everett 1970) and with methohexitone sodium, halothane and nitrous oxide (Allen et al 1970). With the use of lignocaine plus diazepam, arrhythmias have been recorded (Driscoll 1972). Arrhythmias have also been reported (Hughes et al 1966, Williams 1963) with local anaesthesia for tooth removal.

In a study (Rafel 1972) a group of 104 patients between the ages of eleven and ninety were selected. Nine of the 104 patients had a history of heart disease. The anaesthetic was administered and the surgery performed with the use of the ECG recording continuously into the post-operative period. The surgery lasted from two to thirty minutes. Five types of anaesthesia were administered. Group A received lignocaine hydrochloride 2 per cent with 1 in 50,000 epinephrine; dosage varied from 2 to 15mls. Group B received prilocaine hydrochloride 4 per cent in doses from 2 to 15mls. Group C received methohexitone sodium 1 per cent intravenously plus nitrous oxide/oxygen. The dose of methohexitone sodium ranged from 2 to 12 mls. Group D received methohexitone sodium 1 per cent plus ligno-
caine. Group E received diazepam 5 mg intravenously plus methohexitone sodium 1 per cent intravenously plus lignocaine. The ECG tracings were studied by a cardiologist and in none of the groups were any arrhythmias seen.

Pre-fatal cardiac arrhythmias were studied by Propper (1975). Whether as a result of the higher incidence of litigation in America or improvements in patient care (and it was hoped that the second reason was the motivating factor) monitoring of the patient's heart rate and rhythm is becoming standard procedure for oral surgeons. Abnormal rhythms could develop suddenly in patients with no history either of a diseased heart or other systemic disease. Recognition of different types of abnormalities of the heart and a knowledge of how to handle them may prevent the occurrence of fatal arrhythmias. Fatal arrhythmias may be prevented by recognition of pre-fatal disturbances when they occur. They may also be avoided by care in minimising any factors which may predispose to arrhythmia.

It is obvious that patients with serious ventricular arrhythmias are not suitable surgical candidates. In patients with diseased hearts, the following four ventricular arrhythmias were considered pre-fatal; ventricular bigeminy or trigeminy, multiple premature ventricular contractions (more than six per minute), R on T phenomena and multifocal premature ventricular contractions.

When an irregular pulse was felt or an irregular heartbeat heard it is impossible clinically to distinguish between atrial or ventricular disturbances. An
electrocardiogram is necessary to confirm the nature of the arrhythmia. Cardiac collapse does not happen precipitately. There were warning signs that may start with pre-fatal arrhythmic beats and lead to a fatal arrhythmia. Propper investigated the use of a pulse monitor on the finger giving a sound to indicate each heartbeat. Irregular heartbeats could be heard with this device; however, patient movement often caused extra sounds that confused the results. Another drawback of the pulse monitor was that when a patient has a severe drop in blood pressure there was not enough pressure to allow the monitor to respond. It would seem, therefore, that when a pulse monitor is needed most a reading would not be given.

Propper considered that while the patient was under anaesthesia it was difficult for an oral surgeon to watch the oscilloscope or ECG paper. An earplug leading to a precordial stethoscope was a convenient way to monitor the oral surgery patient. The earplug can be made from an impression of the surgeon's ear. The connecting tube is led to a two-way valve. Blood pressure can be heard when the air bulb on the blood pressure apparatus is squeezed; heart and breath sounds will be heard when it is released. The stethoscope lets the surgeon hear abnormalities of the heart rate and rhythm; strength of heart sounds, rales, rhonchi, obstruction of the lower airways; and a regurgitation of gastric contents and still concentrate on the surgery.

Ventricular bigeminy or trigeminy.

Coupling of a premature ventricular beat with a normal beat is called ventricular bigeminy. When
three beats are joined it is called trigeminy. These premature ventricular beats can lead to other ventricular dysrhythmic problems. If a bigeminal rhythm is heard in an anaesthetised patient, surgery should be stopped and a diagnosis established. If the coupled beats do not disappear and the patient's condition continues to deteriorate, appropriate therapy includes the administration of 1mg per kg of lignocaine intravenously without epinephrine.

Multiple premature ventricular contractions (PVCs).

Multiple PVCs may lead to ventricular tachycardia, an arrhythmia that can be fatal. More than six PVCs per minute is a matter of concern. Ventricular tachycardia consists of repeated multiple premature ventricular contractions. It has both a benign and malignant form. It is a dangerous arrhythmia in that it is not always associated with a severely damaged myocardium, but the condition is frequently followed by ventricular fibrillation which is usually fatal. Cardiovascular collapse can occur in the malignant form of ventricular tachycardia with a pulse rate as low as 100. Diagnosis on the ECG may be difficult. Atrial and nodal tachycardia with ventricular separation may simulate this arrhythmia. If a ventricular tachycardia is of the malignant kind immediate action must be taken. There will be a sudden loss of pressure followed by shock. Restoration of blood pressure with vasopressors and fluid then countershock to the precordium at 400 W seconds may be suitable treatment for this problem.

R on T phenomenon.

The R on T phenomenon relates to ventricular contraction when the heart is repolarizing and is in its
most vulnerable period. This sequence of events, a cardiac contraction in the vulnerable period, can initiate ventricular fibrillation.

Multifocal premature ventricular contractions (PVCs).

Multifocal PVCs come from different areas of the ventricles. They can be from two areas of the ventricles called bi-directional. The QRS complexes are of different shapes when they arise from different areas of the ventricles. The bizarre patterns of ventricular fibrillation seem to arise from the patterns of multifocal PVCs. Propper (1975) quotes Corday and Irving (1961) that immediately prior to the onset of ventricular fibrillation the electrocardiogram may reveal many premature ventricular systoles, usually of multifocal origin, which have the appearance of bizarre ventricular complexes.

Propper (1975) suggested that pre-operative assessment of cardiac arrhythmias should not be taken lightly. Surgery on patients with complete AV heart block or first or second degree heart blocks should be avoided unless it is absolutely necessary. Bradycardias are arrhythmias that denote beating of the heart of less than 60 per minute. In talking about arrhythmias in anaesthesia Corday and Irving say that sinus bradycardia is the most common warning sign of cardiac arrest.

Recognition of arrhythmia also helps to detect acute myocardial infarctions. Besides the arrhythmias that will be heard, elevation of the S-T segment may be noted on an ECG. 100 per cent oxygen delivered under positive pressure is a starting point for treatment of arrhythmias when the patient is under general anaesthesia. This may be followed by measures to correct
hypotension. Vasopressors and fluids are given to restore blood pressure. Lignocaine, 1mg per kg, may be given intravenously in a bolus dose and repeated if necessary every three to four minutes to treat ventricular arrhythmias. Use of this drug is contraindicated in atrioventricular block and sinus bradycardia. Countershock may be tried as a further measure.

In discussion, Propper (1975) says that arrhythmias can cause haemodynamic disturbances. If the ventricular rate is normal the arrhythmia is seldom accompanied by haemodynamic disturbances; but if it is rapid, disturbances of varying degrees will usually occur. If the heart is not pumping effectively, or too fast (more than 180 beats per minute) for ventricular filling, there is a drop in cardiac output and a rise in peripheral resistance that prevents blood from reaching vital organs. Corday and Irving (1961) used an electromagnetic flowmeter technique to measure blood to the vital organs of dogs during arrhythmias. Their measurements of cerebral circulation showed a decrease of 40 to 75 per cent with ventricular tachycardia. Frequent premature systoles lower the coronary circulation as much as 25 per cent.

The outlook is grave when pre-fatal arrhythmias occur in a patient with a diseased heart, especially if there is coronary artery disease. Therapy is not necessarily required when these same arrhythmias occur in a patient without heart disease. The question the oral surgeon and cardiologist must answer is 'what is the significance of ventricular arrhythmias when the patient's condition is further compromised by anaesthesia and surgery?'
In conclusion, Propper says that pre-fatal arrhythmias can develop in apparently normal patients who are having oral surgery. The oral surgeon should be able to recognize these abnormalities and know how to deal with them.

Termination of ventricular fibrillation in man by externally applied electric countershock.

Zoll (1956) reported on the successful termination of ventricular fibrillation in four patients by countershock applied externally across the closed chest and demonstrated that external countershock was an immediately effective, safe and clinically feasible procedure. The efficacy of this technique in defibrillating the ventricles was clearly established by the repeated observations (eleven times in these four patients) of the immediate termination of ventricular fibrillation after countershock. On one occasion, ventricular tachycardia also ceased after external countershock, suggesting that this procedure may prove valuable clinically in stopping other arrhythmias as well as ventricular fibrillation. These authors were able to stop atrial fibrillation, atrioventricular nodal tachycardia and ventricular tachycardia in the laboratory with this technique.

The amounts of externally applied current necessary to stop ventricular fibrillation in these patients ranged from 240 to 720 volts. As with external resuscitation from ventricular standstill with the cardiac pacemaker, successful defibrillation depends on immediate recognition of the emergency and prompt application of the external defibrillator. Although external countershock can be applied easily and quickly,
delays in its application constitute the major limitation of successful resuscitation.

Defibrillation may be followed by ventricular standstill or recurrent fibrillation, especially when associated with anoxia from prolonged circulatory arrest. It may then be necessary to apply an external cardiac pacemaker or to use the defibrillator repeatedly and to employ other resuscitative measures such as vasopressors and artificial respiration with oxygen. Immediate recourse to electrical stimulation is dependent on the heart being adequately oxygenated. If there is doubt then external cardiac massage and assisted ventilation must be applied first. Continuous cardiac monitoring in the operating room would enhance the likelihood of successful external resuscitation by providing immediate recognition of the onset of the arrest (Zoll 1956).
CHAPTER 19
ARRHYTHMIAS DURING DENTAL TREATMENT

Sudden death during dental procedures may occur from disturbances in cardiac rhythm. Arrhythmias may occur under local and general anaesthesia.

Williams et al (1963) studied the electrocardiographic changes during oral surgical procedures with local anaesthesia. Anaesthesia in all cases consisted of a mandibular block or a local tissue infiltration with 1 to 2 ml of 2 per cent lignocaine (lignocaine with 1 in 100,000 adrenalin)

Of the 63 patients studied, 26.2 per cent developed cardiac arrhythmias coincident with the anaesthetic injection or the operative procedure. Clinical cardiovascular collapse occurred in one patient; this was associated with an arrhythmia.

Premature ventricular contractions occurred most frequently and accounted for 50 per cent of the arrhythmias noted. One patient who demonstrated atrial fibrillation and an occasional premature contraction in the control record developed two ectopic ventricular foci, and paired premature ventricular contractions. In another patient, sinoatrial slowing was marked and associated with nodal escape beats. This particular arrhythmia was associated with clinical shock. Transient atrioventricular dissociation with interference occurred in one patient who demonstrated premature atrial contractions in the control record.

Only two of the sixteen who developed a significant disorder of the heart beat were found to
have clinically demonstrable heart disease. One patient had chronic cor pulmonale, the other patient had a clinical diagnosis of arteriosclerotic heart disease.

Age was not a critical factor. 37.5 per cent of the patients were above the age of 60 years and 62.5 per cent were less than 60 years old. Significantly, three of the 63 patients admitted to prior syncopal episodes in the dental chair and none of these three developed an arrhythmia.

The group premedicated with atropine was too small for meaningful analysis. However, three of the premedicated patients developed operative arrhythmias.

Williams et al concluded that the mechanisms responsible for the production of the various arrhythmias observed were not clear. Simple clinical observations, however, indicated that involuntary breath holding and performance of the Valsalva manoeuvre were frequent during the operative procedure in almost all the patients.

The development of cardiac arrhythmias during dental extraction was exceedingly common. It was not the purpose of their report to imply that all shock-like states occurring during dental anaesthesia or dental surgery were of cardiac origin. However, the relative frequency of cardiac arrhythmias suggested that disorders of the heartbeat on occasion may be the forerunners of more serious alterations in cardiac functions which resulted in shock.

Kaufman, in a letter to the editor of The Lancet (1965) described the occurrence of arrhythmias in patients undergoing general anaesthesia consisting of
thiopentone, suxamethonium and nitrous oxide/oxygen and halothane for dental extractions. Little change during intubation in the electrocardiogram (ECG) was noted but when the tooth was removed ventricular tachycardia, ventricular extra-systoles, coupled beats and even multifocal ventricular extra systoles occurred. This response to the stimulus of dental extractions was so predictable that it was possible to tell when the extraction was being performed by looking at the ECG monitor.

The arrhythmias often ceased when the stimulus was removed but in some instances they disappeared only when anaesthesia was discontinued and oxygen administered.

Kaufman (1965) commented that the cause of these ventricular arrhythmias may be related to increased PCO₂, or the release of catecholamines by the stimulus of dental extraction during light anaesthesia with the halogenated anaesthetic. Patients with cardiovascular disease may be more sensitive to pressor amines and halothane but arrhythmias have also occurred in some apparently normal patients undergoing dental extractions. (Williams et al 1963).

Recently lignocaine without adrenaline infiltrated around the teeth which were to be extracted during general anaesthesia prevented arrhythmias during extractions in the upper jaw but not in the lower jaw, a region where local analgesia by infiltration was not entirely satisfactory.

ECG changes in patients undergoing dental extractions under local analgesia in the dental surgery
were seen. Tachycardia and ventricular extra-systoles were observed, even in normal subjects when the needle pierced mucosa before the injection of any local analgesic solution. If analgesia was wearing off more rapidly than was expected because of the use of solutions without adrenalin, the stimulus of extraction produced sinus tachycardia of up to 150 per minute, a heart rate likely to be detrimental to the patient with a fixed cardiac output. Kaufman suggested that these arrhythmias might explain the sudden death of patients that occasionally occurred during dental extractions.

The case for avoiding local analgesic solutions containing adrenalin may have been overstated for the amount injected may well be insignificant compared with the amount secreted by the patient, particularly if analgesia is inadequate. The danger of accidental intravenous injection could be alleviated by the use of dental syringes which allowed aspiration before injection.

Johnstone, in a letter to the Editor, Lancet (1966) quoted Harvey and Levine (1952), that the mere sight of a medical instrument may precipitate ventricular tachycardia in a susceptible patient.

The alleviation of pre-operative anxiety combined with the gentle induction of an adequate depth of anaesthesia will minimize the reflex and combined effects of propranolol and atropine will insulate the heart from all the autonomic influences likely to be provoked by fear, anaesthesia and surgery. It is not yet clear whether the complete protection provided by these drugs is really necessary before the induction of anaesthesia in all patients. The routine use of a digital pulse monitor will give early warnings of the need for specific
therapy.

Hughes et al (1966) studied cardiac arrhythmias during oral surgery with local anaesthesia in seventy-seven oral surgical procedures on sixty-five patients. A two per cent solution of lignocaine with 1 in 100,000 epinephrine was used for local anaesthesia. Older patients with cardiovascular disease had a greater incidence of pre-operative and operative arrhythmia than those of the same age with clinically normal cardiovascular systems. The incidence of arrhythmias increased with the duration of the procedure. No consistent relationship between quantity of anaesthetic and arrhythmia was noted. The arrhythmias which occurred during operation were unifocal ventricular premature contractions (four patients), one patient with a wandering pacemaker and one patient with an occasional supraventricular premature beat. One of the four patients with ventricular premature contractions and the patient with the wandering pacemaker had second procedures without development of arrhythmia.

These authors found the development of operative arrhythmia greater in patients with cardiovascular disease. Though their sample in age range was small the older patients seemed to be more susceptible to arrhythmia before and during surgery. The incidence of arrhythmia increased with the duration of the procedure. No consistent relationship between the quantity of anaesthesia and arrhythmia was noted. The maximum quantity of anaesthetic (2 per cent lignocaine solution with 1 in 100,000 adrenalin) used was 8.8 mls (176 mg of lignocaine, 0.099 mg of adrenalin). This was well
within the maximum limits of 500 mg of lignocaine as discussed by Adriani (1959) and of 0.2 mg of adrenalin as recommended by the New York Heart Association (1955).
CHAPTER 20

TREATMENT OF CARDIAC ARREST

Prevention of cardiac arrest is a primary consideration in dental practice. Should cardiac arrest occur, knowledge of the development of the technique of treatment, and of the effectiveness of the technique and the ability to improve the patient's chances of recovery are of enormous importance to the dental surgeon and to the patient.

The technique of closed chest cardiac massage with assisted ventilation has changed little from that suggested by Kouwenhoven et al (1960). The method is recommended by the American Heart Association (1973). However, some controversy followed the introduction of this technique with reference to its effectiveness up to 1966.

A. Open chest cardiac massage.

Before 1960 the technique for the treatment of cardiac arrest during surgery was as described by Clemetson (1959) in his report of open chest cardiac massage carried out outside the hospital for a woman during childbirth when she experienced cardiac arrest in a nursing home. Clemetson commented that open cardiac massage was feasible even when patients are not in an operating theatre and that there should be no hesitation in opening the chest when the heartbeat has ceased. Successful open chest cardiac massage outside the operating theatre was reported by Snyder (1960) and the technique described by Kay (1961) (p.204-205). However, evolution of other techniques has provided the dental profession and others with procedures which may be carried out more readily in the dental surgery.
B. Precordial thump

Successful treatment of cardiac arrest by a chest blow was reported by Brandenburg (1959). Stephenson and co-workers (1953) have shown that the primary cause of low recovery rate in cardiac arrest was delay in instituting treatment. This delay stemmed from mental confusion in the operating room, plus the lack of simple instruments at hand on the wards. There was an obvious place for the chest blow in the treatment of cardiac arrest victims while assistants gathered equipment. Brandenburg agreed with Hosler (1958) that one should not repeatedly strike the chest. If there was not an immediate response a new approach should be taken. In Brandenburg's report the physician was on hand at the time of the arrest and the patient was given three heavy blows on the chest which produced a cardiac rhythm. It was thought that in this case the heart was initially in asystole.

Scherf and Bornemann (1960) demonstrated the effectiveness of mechanical stimulation of the heart in the management of cardiac resuscitation by thumping the precordium.

They found that blows to the chest wall over the heart not only prolonged life but also repeatedly awakened automatism in the ventricular muscle of patients succumbing to cardiac disease. All their patients had some degree of coronary
artery disease; five had acute myocardial infarctions; two had complicating pericardial involvement, tamponade and pericardial adhesions, respectively; two died from extra cardiac causes, one with pulmonary embolus and the other with respiratory decompensation. In these cases as deterioration of the heart muscle progressed, periods of cardiac or only ventricular standstill became more frequent. During standstill the response to mechanical stimulation varied with the degree of deterioration within the cardiac muscle. At first a single ectopic beat appeared with each blow. With progressive hypoxia, a chain of ectopic beats would appear with the ventricular complexes becoming wider and developing into ventricular flutter or fibrillation. Subsequently, the response was less and less. Complexes of low voltage, with evidence of injury currents, appeared terminally as coupled or single beats. Chains of ectopic beats were more prolonged in two patients without cardiac disease. In two others, ventricular fibrillation followed thumping and in the former, coordinated action from a blow during fibrillation could be established. This could not be duplicated.

An objection to this method of resuscitation which these authors saw was that, as in two of their cases, a single blow or its resulting tachycardia may lead to ventricular fibrillation. Any impulse reaching the heart during the vulnerable phase may have this effect. In their opinion, the implications of standstill are of such gravity that the risk of fibrillation must be taken. As a calculated risk, the method, if employed early,
afforded a better chance of avoiding this complication. The earlier the blows were applied and the better the condition of the myocardium the more normal should be the response; that is to say, the more likely a single blow would be to elicit a single ectopic beat. It is this response that is obtained when the exposed heart is stimulated mechanically or a blow is directed over the precordium of a normal subject.

Scherf and Bornemann recommended this technique as a routine measure to re-establish automaticity or to maintain cardiac activity while mouth-to-mouth resuscitation was employed and electrical stimulation or the use of certain pressor amines was prepared. Blows to the precordium should be tried even if ventricular fibrillation is suspected.

This method succeeded in preserving life by evoking ectopic beats which may reawaken cardiac automatism. In the normal heart mechanical stimulation elicited a single response. In the altered, damaged or hypoxic myocardium a blow may produce a multiple response manifested by tachycardia or even fibrillation.

C. External cardiac massage

Closed chest cardiac massage was developed by Kouwenhoven et al. (1960) from their observations that countershock must be sent through the chest promptly to be effective in arresting ventricular fibrillation or else cardiac anoxia would develop to such a degree that the heart no longer resumed forcible contraction without assistance. They found that external defibrillation was not likely to be followed by the return of spontaneous heart action unless the countershock was applied within three minutes or less of the
onset of ventricular fibrillation.

Their study was undertaken to determine a means of extending this time limitation without opening the chest. A method was thought of that would provide adequate circulation to maintain the tone of the heart and the nourishment of the central nervous system. This method was to be at once readily applicable, safe to use and requiring a minimum of equipment.

The technique of rhythmic compression of the heart against the vertebral column was developed to provide a blood pressure sufficient to cause circulation and maintain vitality of the brain and heart until such time as defibrillating machines and drugs could be brought to the patient. The technique was coupled with mouth-to-mouth or mouth-to-nose artificial respiration to ventilate the lungs. The use of this technique on twenty patients gave a survival rate of 70 per cent. They concluded that anyone anywhere could initiate cardiac resuscitative procedures. All that was needed were two hands. External cardiac compression has been studied extensively and is now a basic technique for resuscitation in drowning accidents, electrocutions and in any situation where personnel trained in the technique are available.

D. External cardiac compression and ventilation.

Kouwenhoven and colleagues (1960) noted that when the operator was working alone there was some tidal volume produced during cardiac massage. Safar and colleagues (1961) confirmed the circulatory efficiency of closed chest cardiac massage. However, they found that it could not be relied upon for
pulmonary ventilation. Sternal pressure failed to reoxygenate five or six hypoxic curarised subjects. Therefore, rhythmic sternal pressure must be accompanied by intermittent positive pressure ventilation. Coordinated ventilation and compression were desirable.

Rhythm, which was unimportant during artificial respiration alone, proved important during closed chest cardiac massage as it prevented confusion as to when the massaging operator should pause. The necessary timing of the lung inflations was impossible with the use of pressure cycled automatic resuscitators. Intermittent inflation of the lungs should be performed by a method which permits inflation rates, inflation pressures, flow rates and volumes to be changed at will. This was provided by the use of exhaled air, resuscitation and hand operated equipment such as a bellows or bags (Safar et al 1961).

E. Complications of external cardiac massage.

Baringer et al (1961) with experience in ill patients with the use of external cardiac compression found that it was generally successful in maintaining an effective circulation, thus allowing time for additional equipment and personnel to be mobilized. They suggested it may be even more effective than internal cardiac massage. And finally, the simplicity of the procedure permitted its use under conditions in which thoracotomy and internal massage would not be feasible.

Their study of post-mortem examinations on forty-six of their patients disclosed a significant
number of complications of external cardiac massage. Rib fractures were common and occurred in fifteen of the patients, involving two to eight ribs. It is probable that this could be minimized if care was taken to exert pressure only over the sternum and to use no more pressure than was necessary to maintain an effective pulse. Incidence of rib fracture decreased with increase in experience of the personnel using the technique. Four patients were found to have haemothorax and haemopericardium was noted in two patients but was not associated with rib fractures. Morgan (1961) reported a case of laceration of the liver from closed chest cardiac massage.

F. Effectiveness of the technique.

Since the introduction of the technique, studies have been done to evaluate its efficiency and effectiveness and to outline any possible dangers or complications associated with rhythmic compression of the sternum. Kouwenhoven and colleagues were able to produce a systolic pressure of 100mm of mercury with a mean of 50mm of mercury in the femoral artery in dogs with ventricular fibrillation. After half an hour, during which closed chest cardiac massage was continued without interruption, normal sinus rhythm returned immediately in response to a shock from an external defibrillator. They also reported the successful resuscitation of twenty patients by the same technique of closed chest cardiac massage; fourteen patients were alive and showed no signs of damage to the central nervous system. Three of the twenty patients were in ventricular fibrillation and were successfully defibrillated by an external defibrillator. The duration of cardiac massage varied from one to sixty-five minutes.
Weale et al (1962) doubted the efficacy of external cardiac massage compared to internal cardiac massage. They investigated the state of the atrioventricular fibrillation. Weale objected to the fact that previous authors (Kouwenhoven et al 1960 and Nixon 1961) had submitted signs of pupillary size and survival rate as successful signs for tissue perfusion. Also submitted as adequate signs of perfusion was palpation of the carotid and radial pulses. As electrocardiographic monitoring or indirect or direct inspection of the heart was not possible, information was often lacking as to whether the condition treated was ventricular fibrillation or asystole. The distinction must not be overlooked since it seemed that cardiac compression of either type was more successful in asystole.

Weale also argued that the presence of a palpable and recordable pulse in the carotid or radial artery was poor evidence for the adequacy of tissue perfusion. The presence of a pulse only confirmed fluid continuity with its site of origin. It did not indicate flow, for an artery pulsates even at its site of ligation.

An analysis of arterial pressure tracings nevertheless gave useful comparative information. The most important factor was the mean arterial pressure. If this was raised and the mean venous pressure was not, then improved oxygen perfusion occurred. The systolic upthrust, so marked in external compression, was too transient as important testimony for flow. Allowing for the different anatomical configurations of the main arterial and venous trees, the peaks were of roughly equal amplitude. This suggested that during ventricular fibrillation the arterial and venous trees formed a
liquid continuum and that competence of the atrioventricular valves, at any rate the tricuspid, was abolished. The high venous pressure pulses illustrate the fallacy of regarding a pressure pulse as good evidence of forward flow.

Weale commented that restoration of life may depend on small margins. If internal cardiac compression gave a measurable advantage over external, making it the method of choice when trained personnel were available, it was still an imperfect substitute for spontaneous cardiac contraction. That external massage may bridge a gap before medical assistance is obtained is incontestible. But its ease of performance, coupled perhaps with a subconscious surgical reluctance and ethical considerations, must not be allowed to obscure a possible success rate of almost 50 per cent (Briggs et al 1956) obtainable with internal cardiac compression.

Arterial and venous pressure tracings recorded in nineteen dogs in which ventricular fibrillation had been induced showed that: (i) in ventricular fibrillation the venous pressure was considerably raised; (ii) both internal and external compression give rise to pressure pulses in the venous tree, probably the result of atrioventricular valve incompetence; and (iii) internal cardiac compression produces a higher mean arterial and a lower mean venous pressure than external cardiac compression (Weale 1962).

Wetherill and Nixon (1962) reported a case of spontaneous cessation of ventricular fibrillation
during external cardiac massage. Primary or secondary ventricular fibrillation which was resistant to treatment while the heart muscle was anoxic, ceased during external cardiac massage. This was very good evidence that the massage provided an adequate coronary circulation. The absence of brain damage provided evidence of adequate cerebral blood flow during the forty minutes of massage. At the time of the cardiac arrest the patient was being monitored by the ECG.

Del Guercio and colleagues (1963) studied arterial blood flow in three patients who did not survive cardiac arrest. Only one of the flows determined could be considered compatible with life when considered as cardiac index. This flow was calculated to be 1.74 litres per minute. Even this flow represented half the normal resting cardiac index for this patient. All other flows in the study represented even smaller fractions of the resting cardiac index. Scrutiny of the indicator dilution curves themselves suggested inefficient stroke output and valvular incompetence during external cardiac massage.

Many cases of so-called cardiac arrest are similar to a case of theirs in which extremely poor total perfusion had existed long before the heart finally stopped altogether. Even the low flow during closed chest cardiac massage was greater than the flows measured before cardiac arrest in this patient. The marked metabolic acidosis in all three cases reflected prolonged low perfusion and tissue hypoxia. This could be corrected to some extent with addition of base, as in their third case, but higher cardiac outputs would have been needed for ultimate resuscitation.
Arterial pressures determined by direct canulation or sphygmomanometry correlated poorly with flows produced by the resuscitative efforts. Critical analysis of the pulse wave contours and the planometric calculation of mean blood pressures indicated, as pointed out by Weiser et al (1962) and their group that the brief systolic ejection spike, no matter how high, produced very little elevation in mean blood pressure above the irreducible minimum or residual diastolic pressure (this residual diastolic pressure during the rest phase being 39 mm of mercury in the second case).

External cardiac massage produced a very low rate of blood flow in their three patients. That these flows were insufficient to sustain life or achieve resuscitation was supported by the increase in hypoxic acidosis. Cardiac output during open chest cardiac massage in man should also be measured since higher flows may not be possible by the open chest technique. When one is dealing with true cardiac arrest in a salvageable patient, palpation of a pulse wave alone is not a good sign of adequate perfusion during external compression.

Del Guercio and colleagues (1963) followed up this study with a comparison of blood flow during external and internal cardiac massage in man (1965). In this investigation cardiac output and other cardiorespiratory variables were measured in man during attempts at both external and internal cardiac resuscitation. In three patients it was possible to measure total blood flow during the use of each of the methods.
From their experience, direct massage of the heart through thoracotomy incision produced significantly more physiological blood flow than compression of the heart through the intact chest. Metabolic acidosis from anaerobic glycolysis following cardiac arrest was shown by Ledingham and Norman (1962) to be proportional to the period of circulatory arrest and severe depression of myocardial contractible force following anoxic cardiac arrest as demonstrated in dogs by Miller and his group (1964). The method of choice following cardiac arrest is that method which can be shown to produce the highest total blood flow, since severe acidosis occurs rapidly. Sodium bicarbonate and amine buffers were used in their patients in attempts to correct acidosis, but were of little value in the absence of adequate circulation. A high cardiac output is necessary to compensate for the effects of hypoxia and acidosis, and beyond a certain point the effects of oxygen deficit are irreversible even without cardiac arrest.

Severe degrees of venoarterial admixture across the pulmonary circulation made adequate oxygenation of what little blood was flowing difficult in these patients. The cause of this is unknown, since adequate ventilation through an endotracheal tube with frequent aspiration was always practised. The resulting arterial hypoxaemia even during the administration of high concentrations of oxygen, complicated the treatment of cardiac arrest.

These authors concluded that when the clinical tragedy of cardiac arrest strikes, restoration of cardio-respiratory function to levels as near normal as possible
as quickly as possible must be accomplished. The convenience or ease with which a method of resuscitation can be performed is not so important as delivering adequate quantities of oxygenated blood to the tissues. In their experience, they had delayed using external cardiac massage too long. External cardiac massage appeared to be half as effective as internal cardiac massage (Del Guercio et al 1965).

MacKenzie et al (1964) studied the haemodynamic effects of external cardiac compression. Their report described three cases in which systemic arterial pressure, central venous pressure and cardiac output were measured during spontaneous heart action, during external cardiac compression, then in the immediately following period of spontaneous heart activity. They also observed that during cardiac massage not only was there a very considerable reduction in coronary filling time and coronary filling pressure, but that the pressure gradient across the coronary vascular bed was much reduced. The transmission of venous pressure pulses to the periphery may also lead to a reversal of the normal arteriovenous pressure gradient at capillary level. This unusual and highly artificial circulatory state may well disturb metabolic function in such sensitive areas as the brain. These authors have no doubt of the value of external cardiac compression as a frequently lifesaving measure. They strongly suggest however, that the place of internal cardiac massage in resuscitation should be considered. If for any reason cardiac massage has to be continued for more than a brief period, and if circumstances and personnel permit, internal massage would seem to be by far the most efficient method of producing a forward flow of blood and may well be less damaging to an already
ailing myocardium.

Harley (1966) reflected on cardiopulmonary resuscitation. Ventilation perfusion relationships are severely disturbed during cardiopulmonary resuscitation. This results in a large intrapulmonary venous arterial shunt and a pronounced increase in the physiological dead space. The shunt produces a large alveoloarterial oxygen tension difference unrelieved by oxygen tension and was usually less than 100 mm of mercury even during adequate ventilation with pure oxygen when it should have been over 650 mm of mercury. Harley commented on Del Guercio et al (1965), where they found the venous admixture during closed and open chest cardiopulmonary resuscitation to be 38.3 per cent and 46.7 per cent respectively whereas the normal figure was only 3 per cent. Thus ideally, in order to maintain satisfactory tensions of oxygen and carbon dioxide in the arterial blood, the patient should be ventilated with large tidal and minute volumes of pure oxygen.

The important physiological disturbances preceding the accompanying cardiopulmonary resuscitation were summarized as follows (Harley 1966):
(i) Before cardiopulmonary resuscitation was started the arrested ischaemic heart is distended by rapidly rising venous pressure.
(ii) During cardiopulmonary resuscitation a severe derangement of ventilation perfusion relationships in the lungs created a large intrapulmonary venoarterial shunt and physiological dead space. The former establishes a big alveoloarterial oxygen tension difference, with resultant severe arterial hypoxaemia, unless the patient was ventilated with pure oxygen. The large physiological dead space created a ventilatory problem.
(iii) A disappointingly low cardiac output was provided by cardiopulmonary resuscitation, especially by the closed chest technique. This results in stagnant anoxia and progressive metabolic acidosis. The wide arteriovenous oxygen difference of stagnant anoxia enhanced the arterial hypoxaemia caused by the large intrapulmonary veno-arterial shunt. There was evidence to suggest that metabolic acidosis lowered the threshold for ventricular fibrillation (Gerst et al 1963), induced or sustained cardiac asystole and lowered myocardial contractility, thereby reducing cardiac output if the heart was restarted. These effects progressively reduced the chances of resuscitating the heart.  
(iv) A low mean arterial pressure was associated with high, easily palpable systolic pressure peaks. These did not indicate adequate forward flow.  
(v) A high mean venous pressure was accompanied by very high systolic pressure peaks which may damage the pulmonary and systemic capillaries.

Harley suggested that permanent recovery was unlikely to follow closed chest cardiopulmonary resuscitation applied for fifteen or more minutes, and the open technique maintained a much better cardiac output. It was, therefore, open to doubt whether we are justified in persisting with the closed method for long periods if good facilities for opening the chest and pericardium are at hand. If a satisfactory heartbeat has not been obtained after ten minutes of closed chest cardiopulmonary resuscitation and the function of the brain is satisfactory, the decision to open the chest should be made, and this decision should certainly not be delayed for more than fifteen minutes. The longer the opening of
the chest is deferred the less likely it is to succeed, thereby bringing this procedure into disrepute.

The best guides to adequate cerebral circulation are small reactive pupils, a positive blink reflex, lightening of the level of unconsciousness, struggling, and spontaneous respirations. Deep unconsciousness, absence of spontaneous respiration, and fixed dilatation of the pupils for fifteen minutes denote that the brain is dead and that further efforts at resuscitation should be abandoned. Peripheral cyanosis will usually have developed, and serum acid base studies, if made, will have demonstrated progressive metabolic acidosis.

Harley (1966) in summary stated that progressive deterioration of the patient during cardiopulmonary resuscitation was associated with a diminishing chance of success. The sense of urgency must therefore not be abandoned with the onset of cardiopulmonary resuscitation.

Open chest cardiopulmonary resuscitation is about twice as effective as a closed chest technique; and in the event of failure of the latter the chest should be opened after ten to fifteen minutes, provided that suitable facilities are available and cerebral function is satisfactory (non dilated pupils).

Brown and Scott (1970) reviewed open chest cardiopulmonary resuscitation with reference to 184 cases with some suggestions to future improvements. These authors had a success rate of 37.3 per cent of cardiac arrest patients who survived initially and 10.3 per cent were ultimately discharged well. They suggested that key factors in successful resuscitation appeared to be:
(i) awareness and ability of various hospital personnel to recognise an arrest and to quickly initiate resuscitation procedures;
(ii) immediate availability of resuscitation equipment for definitive treatment in cardiorespiratory arrest. To these ends training of hospital personnel and judicious placement of resuscitation equipment appear to be of paramount importance.

Wildsmith and colleagues (1972) found that an initial electrocardiogram recording taken during resuscitation in 95 per cent of cases showed that the highest success rate was obtained in patients with ventricular fibrillation, the lowest in those with asystole, who not only had a lower initial resuscitation rate but only 1 per cent with asystole were classed as survivors. Other arrhythmias (mainly bradycardia but including ventricular tachycardia and multiple extrasystoles) were associated with intermediate success rates. Their results were from intensive care units. In their initial treatment of patients, external cardiac massage was used; however, supportive drugs, ECG monitoring, defibrillation and anaesthetists were quickly on hand.

In general it can be seen that the longer the patient undergoes external cardiac massage the lower his chances of surviving. However, in the absence of hospital facilities at short notice external cardiac massage does have a place ideally suited to the dental surgery. Efficient training of the staff in this procedure is mandatory.
CHAPTER 21

DRUGS IN THE TREATMENT OF CARDIAC ARREST

Drug treatment of cardiac arrest involves the use of co-ordinated electrocardiogram (ECG) monitoring and drug administration. I believe that there is a limited place for drug use in the dental surgery, and a brief background of the use of drugs used in the treatment of cardiac arrest will help to reinforce the principles involved in maintaining a weakened heart or in preventing cardiac arrest.

Pruitt (1958) proposed this dilemma in the treatment of potentially lethal cardiac arrhythmias by pharmacologic means. The heart in ventricular standstill may be roused by drugs which improve atrioventricular conduction, but these same drugs may increase the irritability of a myocardium already predisposed to ventricular fibrillation by the ischaemic effects of ventricular arrest. The heart in ventricular tachycardia may be quieted by drugs which reduce its irritability, but these same drugs, unless they promote a reversion to a physiologically more effective rhythm, may depress further the failing myocardial function.

Flagg (1959) gave a brief resume of the drugs used in cardiac resuscitation at that time. These were: adrenalin; procaine; procaine amide and oxygen.

A. Adrenalin.

The American Dental Association (1972) recommended the use of 1 ml adrenalin 1:1,000 into any suitable vein or into the base of the tongue. If the dental surgeon was familiar with the use of cardiotonic and vasoconstrictor drugs then mephentermine 45 mg, ephedrine
25 - 50 mg, metaraminol 10 mg, levarterenol 0.5 mg or phenylephrine 2 mg are suggested for use. However, drug therapy should not seriously interrupt the procedures for cardiac compression and pulmonary support.

The effects of adrenalin are directly opposite to those of acetylcholine:
(i) the heart rate is accelerated;
(ii) cardiac output is enhanced;
(iii) the tone of the heart and force of contraction are increased;
(iv) cardiac systole is shortened;
(v) the work of the heart is increased; and
(vi) oxygen consumption is increased.

Adrenalin acts directly on the myocardium and, in addition to tachycardia, adrenalin may cause increased myocardial irritability.

Premature ventricular systoles may occur and may be the precursors of more serious ventricular arrhythmias or fibrillation.

Adrenalin is suggested in asystole where the heart is not in ventricular fibrillation. The dose of 0.2 ml to 0.3 ml of a 1 in 1,000 solution (diluted ten-fold) may be injected, preferably into the right atrium or right jugular vein. If the heart is in ventricular fibrillation electrical defibrillation must be attempted, but if cardiac arrest occurs without ventricular fibrillation an electrical countershock is contra-indicated. Ideal use of all cardiac drugs requires concurrent use of an electrocardiogram (Flagg 1959).

For fibrillation, procaine amide may be given intracardially; massage should be continued and 100 per
cent oxygen administered (Flagg 1959). Adrenalin under these conditions has a place in rendering a flabby ventricle more firm and improving the arterial pressure evoked by cardiac compression. But adrenalin itself does not defibrillate the dog's heart, even with massage, and time should not be wasted trying to stop fibrillating human hearts with adrenalin. Adrenalin is now not recommended for injection intravenously or into the heart (Holland 1977).

B. Procaine.

Procaine elevates the threshold of ventricular muscle to electrical stimulation. The short duration of action resulting from its rapid enzymatic hydrolysis and its prominent central nervous system effects limit the therapeutic value of procaine as an anti-fibrillatory and anti-arrhythmic agent.

C. Procaine amide.

Pronestyl is a more effective agent to prevent or control tachycardia. Procaine amide hydrochloride (U.S.P.) is supplied in 10 ml vials containing 100 mg per ml for intramuscular and intravenous injection. Its duration of action is more satisfactory and the relationships between cardiac and central nervous system effects are more favourable than procaine.

Procaine amide depresses the excitability of both atrium and ventricle to electrical stimulation and allows conduction in the atria, the bundle of His and ventricles. Ventricular extrasystoles caused by blockage of the coronary arteries are suppressed.

The prophylactic and therapeutic value of procaine amide for reducing the incidence and severity of arrhythmias encountered during cardiac surgery is
well established. The intravenous dose of procaine amide is 200 to 500 mg at a rate not exceeding 25 to 50 mg per minute. Severe hypotension is a drawback and should be watched for carefully. Procaine and procaine amide are now only of historical interest as lignocaine followed by beta blockers are now preferred to control tachycardia (Holland 1977).

The only really effective way to defibrillate the heart is by electrical counter shock. The importance of creating a uniform state of depolarization in all muscle fibres by this procedure is emphasized (Flagg 1959).

D. Lignocaine.

Lignocaine has replaced procaine amide. It is preferred for the treatment of ventricular arrhythmia. Its anti-arrhythmic action develops very rapidly on intravenous injection and declines quickly when infusion is discontinued. When used in the treatment of ventricular extrasystoles or ventricular tachycardia the effect of a single intravenous dose of 100 mg disappears within ten to twenty minutes (Harrison et al 1963).

When used in the treatment of ectopic ventricular rhythms, lignocaine is administered only intravenously. A primary dose of 25 to 50 mg may be followed by continuous infusion of 1 to 2 mg per minute with constant ECG monitoring (Lown et al 1967).

E. Oxygen.

Effective cardiac massage as judged by maintaining the mean arterial pressure must be supported by 100 per cent oxygen to ensure a supply of oxygenated blood to the myocardium. Electrical stimulation is
useless unless it is done before the heart is cyanotic. Adrenalin and Pronestyl are much more likely to be effective if oxygen is distributed equally throughout the heart muscle. Areas of anoxia in the myocardium apparently set up electrical potentials which continue to discharge as stimuli from ectopic foci.

In summary, Flagg (1959) says that the success or failure of resuscitation of the heart depends on oxygen. Attempts to defibrillate the heart, by external means, after a period of sixty seconds will be unsuccessful because of the accumulated hypoxia unless oxygen is used also.

F. Practical considerations.

Rowe (1959) in outlining treatment of cardiac arrest with drug therapy detailed numerous situations and their drug management. His comments are perhaps too wide reaching for the dental surgery situation. They are mentioned to point out the wider ramifications of the post emergency management of the cardiac arrested patient. Drugs injected into peripheral vessels during cardiac arrest prior to the onset of cardiac massage would not be carried through the circulation rapidly enough to be effective, and it is doubtful if drugs administered into the cardiac chambers diffuse sufficiently in the absence of cardiac action to reach the site where they are active. When adequate ventilation of the lungs is established and effective cardiac massage is being performed, the emergency of cardiac arrest is over and one may pause figuratively to chart the course of future action. (Rowe 1959).

If, after a short period of massage, the heart beats well, maintaining a good blood pressure and output,
the dramatic phase of therapy is over and one would do well to consider the cause of the episode. Any alterable cause of hypoxia must be dealt with effectively. If arrest occurred from a sudden decrease in the high blood concentration of carbon dioxide, more careful and regular ventilation must be taken to avoid such sudden changes. If the cause appeared to have been an overdose of medication or anaesthetic, appropriate counteracting medications may be given. Particularly if the episodes of so-called vasovagal origin occurred during stimulation of the pharynx, larynx, trachea, bronchi, lung, vagus nerve or bile ducts and the operation which precipitated arrest was not completed, arrest may recur. It may be wise before repeating any manipulation of the structures to administer 0.5 to 1mg of atropine in an attempt to prevent recurrence (Rowe 1959).

If the force of cardiac action is insufficient, the heart flabby and failing to beat satisfactorily, administration of calcium salts may be very effective. These may be administered either as the gluconate or chloride (1 to 2g intravenously; 4 to 8ml of a 10 per cent solution) and the dose can be adjusted by the response of the myocardium, remembering that the total dose of calcium gluconate must be higher to be equally effective as the chloride. If administration of calcium is ineffective one may consider the administration of molar sodium lactate (40 to 160ml intravenously) not only for its effects on the expected systemic and cardiac metabolic acidosis but also apparently for the nutrient effect of the lactate ion on the myocardium. One must beware of multiple ventricular premature
contractions during the administration of molar sodium lactate, and attempt to adjust the dose so as to obtain increased force of contraction and increased irritability without producing too much irritability of administering so much sodium that retention of fluid becomes a significant problem post operatively. When decreased cardiac irritability is a problem, one may consider the administration of adrenalin (0.2 to 0.5ml of 1 in 1,000 solution) and on occasion this may be very effective. Such an effect is very transient, however, and repeated doses, or administration of adrenalin in oil (0.5 to 1ml of 1 in 500) may be required. (Rowe 1959).

If ventricular fibrillation is present, the heart should be massaged vigorously for several minutes to restore systemic and cardiac oxygenation in the hope that ventricular fibrillation will revert spontaneously to a sinus rhythm. If this does not occur, and particularly if the fibrillation is coarse, with very poor myocardial tone and considerable cardiac dilatation, it may be unwise to administer calcium chloride or adrenalin to improve the tone of the myocardium before defibrillation is attempted. The preferred method of defibrillation is administration of sufficient electrical current through the myocardium to depolarize all the fibres simultaneously in the hope that when contraction begins again it will begin in an organized fashion with restoration of the normal beat. This current may be administered most safely and efficiently by the various commercial cardiac defibrillators, but any adequate current source, including the standard 110-120 volt 60 cycle alternating current which is domestically available (U.S.A.), can be successful.
With makeshift apparatus using the standard household current the surgeon must exercise sufficient caution to avoid self-electrocution. If electrical defibrillation is not practicable, defibrillation may be accomplished by administering 10 per cent potassium chloride solution intravenously. (Rowe 1959).

It is unusual with adequate oxygenation, massage and drug therapy to fail to establish organized cardiac action. However, it is difficult to maintain sufficient cardiac output and systemic arterial pressure after an organized beat has been restored, and consequently at the present time only approximately one third of patients with cardiac arrest survive the episode. In the therapy of such cardiogenic shock after resuscitation one may administer levarterenol intravenously (1-norepinephrine) in a sufficient concentration (4 to 16 mg per litre, or more is required) to obtain the desired effect. Levarterenol (Levophed) under these circumstances appears to be nearly an ideal drug since it increases the venous tone, the force of myocardial contraction, the coronary blood flow and the systemic arterial blood pressure. Since restriction of fluid becomes important in therapy at this point it is wise to increase the concentration of levarterenol as required, rather than to increase the rate of administration of the fluid in which the Levophed is contained. When multiple premature ventricular contractions or other arrhythmias are a problem after resuscitation, one may consider administration of various myocardial depressants such as quinidine (up to 650 mg intravenously slowly), procaine amide (up to 1 g total not exceeding a rate of 100 mg per minute), lidocaine (0.5 mg to
lmg per kg intravenously), or procaine. One must remem-
ber, however, that the myocardium is also damaged by the
episode of arrest, and massage with depression by these
drugs may be dangerous; therefore, the blood pressure
and electrocardiogram must be watched carefully during
their administration (Rowe 1959).

Once adequate cardiac action is restored and
peripheral blood pressure maintained, anticipated diffi-
culties with the brain, the lungs, and the kidneys may
occur. If there has been significant hypoxia of the
central nervous system, oedema of the brain will almost
surely occur. In its therapy many advise the use of
prolonged hypothermia and there is general agreement
that hyperpyrexia must be avoided. Intravenous adminis-
tration of hypertonic solutions of glucose (50ml of 50
per cent solution) and/or urea (1g per kg as 30 per cent
solution) produced temporary cerebral dehydration which
may tide the patient over the most difficult phase, and
the administration of anti-convulsants may be required.
The total volume of fluid administered must be kept at a
minimum until adequate renal function is assured to avoid
both cerebral and pulmonary oedema. The latter may re-
quire major therapeutic efforts since both cardiac and
renal insufficiency are common in the recovery phase.
Should the period of renal hypoxia have been sufficient
to produce tubular necrosis one must anticipate effective
therapy of oliguria or anuria. Each of these, cerebral
damage, pulmonary oedema and renal tubular necrosis, con-
stitutes its own major medical problem too extensive to
consider further here. Rowe (1959) and Phillips (1964)
give a more detailed account of procedures to be used.
These are too extensive to be considered for use in the
dental surgery.
Cardiac arrest once constituted an acute emergency generally requiring thoracotomy and cardiac massage. Drug therapy is a secondary but very important consideration once the acute emergency is resolved, with its aims the restoration and maintenance of effective cardiac action and prevention of recurrence of arrest. Survival of many subjects will depend on the post operative care of central nervous system damage from hypoxia, pulmonary congestion and oedema, and renal insufficiency secondary to tubular necrosis (Rowe 1959).

Medical treatment of cardiac arrest has not varied greatly from that detailed by Phillips (1964). In the dental surgery the use of drugs is not stressed. Bell (1975) and Drummond-Jackson (1973) emphasize the use of external cardiac massage and ventilation initially.

Drummond-Jackson (1973) suggested a list of drugs which may be used subsequently with external cardiac massage and ventilation. These are: isoprenaline; adrenalin; metaraminol; calcium chloride; sodium bicarbonate; and lignocaine.

G. Acidosis.

Stewart (1964) studied the management of cardiac arrest with special reference to metabolic acidosis. The occurrence of acidosis after cardiac arrest had not received much attention, although the aetiological importance of hypercapnia had been recognized for some time. The acidosis which follows cardiac arrest may be of metabolic or respiratory type. Jude et al (1961) commented that metabolic acidosis, if present, should be corrected, and Martin (1961) stated
that sodium bicarbonate solution in a dose of 44.5 mEq per litre should be given intravenously in an adult if cardiac collapse persists beyond five minutes. It may be repeated every ten minutes for six doses. Sodium bicarbonate reverses metabolic acidosis readily detected by proper laboratory procedures. Brooks and Feldman (1962a) noted metabolic acidosis in two cases of cardiac arrest and suggested that sodium bicarbonate should be given in every case of cardiac arrest. Stewart et al (1962) suggested that the correction of acidosis was an important factor in resuscitation. Bicarbonate therapy is more likely to be required as the time from onset of cardiac arrest increases. Stewart et al (1962) recommended that sodium bicarbonate solution (8.4 per cent or 1 mEq per ml) be made available for the treatment of cases of cardiac arrest. This is now currently accepted. Holland (1977) also recommended using a solution which contains 100 mEq in 100 ml.

If the period of circulatory arrest was thought to have been very short (less than thirty seconds) bicarbonate therapy was unlikely to be necessary but if there was any doubt 50 mEq may be given to an adult. In an adult subject with normal acid base equilibrium this dose will cause only slight alkalosis. If the period of circulatory arrest is thought to have been long - two to three minutes or more - or if external cardiac massage has been carried out for twenty minutes or more, an initial adult dose of 150 to 200 mEq was recommended. The need for further therapy was indicated by acid base measurements (Stewart et al 1962).
H. Summary and conclusion.

The importance of being prepared for the eventuality of cardiac arrest as a factor in improving the chances of a successful outcome cannot be over emphasized. Staff training in basic life support procedures is a necessity in dental practice. These techniques are relatively simple to do. Drug treatment on the other hand can be very complex to balance appropriately and an electrocardiogram is required. Reversal of acidosis increases the success rate of external cardiac massage and sodium bicarbonate should therefore be on hand.

For management of the cardiorespiratory collapsed sedated patient I advise that the procedures as outlined by the National Health and Medical Research Council for basic external cardiopulmonary resuscitation be followed. This article suggests (p.25) that tongue obstruction can be relieved by protruding the mandible. In my experience this is not always so. A Guedel's airway must also be at hand to bypass effective anatomical obstruction. If the sedative drug can be reversed this should also be done to help reduce respiratory and cardiovascular depression (ref. p.317).

The level of expertise in resuscitation will depend on the training of the dental surgeon and his staff. A basic minimum of expertise expected must be a thorough understanding of basic cardiopulmonary resuscitation by all general dental surgeons and their surgery staff.
PART VIII

PREVENTION OF CEREBRAL COMPLICATIONS
CHAPTER 22

HYPOXIA AND CEREBRAL DAMAGE

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CHAPTER 22

HYPOXIA AND CEREBRAL DAMAGE

Cerebral damage due to hypoxia is a potential major complication from the use of intravenous sedation. Familiarization with causes of cerebral damage enables a more wary approach to be made to the treatment of patients with sedation techniques by the dental surgeon.

A. Resilience of brain to nutrient lack in animals.

Gerard (1938) commented that the bloodstream supplied individual tissue cells with food and oxygen and removed wastes so supplying the needed energy for maintenance and function. Grant et al (1939) studied anoxemia of the central nervous system produced by temporary complete arrest of the circulation in cats. Animals subjected to the longest periods of circulatory arrest compatible with chronic survival showed complete disintegration and necrosis of the entire cortex. The basal ganglia, thalami, hypothalamic and geniculate nuclei showed diffuse and patchy loss of cells and varying degrees of degeneration of the remaining cells. The subcortex was spongy, diffusely or focally demyelinated, and showed marked glial proliferation. Except for some scattered cells, the ganglion cells were normal in the pons, medulla and the spinal chord (basic function maintenance nuclei). The pyramidal tracts showed secondary degeneration throughout the length of the neuraxis.

Consequently in evaluating possible central nervous system damage from hypoxia, the first signs to look for would be changes in personality, reflex control and intelligence, aspects of behaviour mediated by cortical
function. Thalamic effects would be demonstrated by changes in temperature regulation whereas there would be no effects upon respiratory and cardiac reflexes as the pons, medulla and spinal chord are the most resistant regions.

Grant et al (1939) commented that if there was an oxygen lack for about three minutes cortical effects would result; if oxygen lack continued for five and a half minutes thalamic effects would appear; and, after about seven minutes absolute necrosis takes place. Weinberger et al (1940a) studied temporary arrest of the circulation of the central nervous system in the cat. After seven and a half minutes of complete circulatory arrest complete destruction and liquefaction necrosis of the cerebral cortex occurred. The motor and visual cortex sustained the earliest and most profound damage. The olfactory, orbital and temporal regions of the cortex were the least susceptible. Lamina I, and to a lesser extent Lamina II, were the least vulnerable of the cortical layers, while Laminae III and IV were the most vulnerable. The Purkinje cells rank next to the nerve cells of the cerebral cortex in susceptibility. The lateral geniculate nucleus was the most vulnerable of the basal nuclei in the cat, followed, in the order of susceptibility, by the hypothalamic nuclei, the thalamic nuclei, the globus pallidus and the caudate nucleus.

Kabat et al (1941) studied recovery of function following arrest of the brain circulation in dogs. They divided the course of recovery into six stages.

(i) Period of early return of function.
(ii) Period of hyperactive coma.
(iii) Period of quiescent coma.
(iv) Period of apathy and severe ataxia.
(v) Period of residual ataxia.
(vi) Recovery.

Complete arrest of the brain circulation resulted in disappearance of the corneal reflex in ten seconds and of respiratory function in twenty to thirty seconds.

Arrest of the cephalic circulation caused spinal shock, which passed off gradually after blood flow was restored. Arrest of the brain circulation for six minutes or less resulted in apparently complete recovery of function, while brain stasis for eight minutes or longer resulted in permanent severe damage to the brain.

Relatively soon after restoration of function of the vital centres a period of hyperactivity and reflex hyperirritability ensued which persisted for several hours. This period was characterized by the vigorous, rapid, co-ordinated running movements of all four limbs carried out with the animal lying on its side in a coma. No epileptiform convulsions were observed following complete arrest of cephalic blood flow.

Coma persisted for as long as twenty-four hours after only four minutes of arrest of the brain circulation. The coma was characterized by loss of auditory reflexes, vestibular and other righting reflexes in addition to loss of function of the cerebral cortex. Early in coma a moderate spasticity was evident, while later a flexor rigidity suggestive of involvement of the basal ganglia became apparent.

Following coma, a transition period lasting several days characterized by gradually improving function
of the cerebral cortex and of the righting mechanisms, as well as by severe ataxia of cerebella type was observed.

In dogs that recovered consciousness, the most persistent neurological dysfunction was ataxia. This gradually disappeared, leaving an animal which could not be distinguished by their (Kabat et al) methods of examination from the normal.

The permanently defective brain function produced by eight minutes of arrest of brain blood flow consisted of loss of function of the cerebral cortex, loss of auditory reflexes, of the ability to stand and walk, of emotional reactions and vocalization, as well as dysfunction suggestive of striatal involvement.

Grenell (1946) studied the effects of temporary arrest of cerebral circulation for periods of two to ten minutes in the dog. This was designed to elucidate precisely how long not only the brain as a whole, but especially localized areas of the brain, could withstand complete absence of blood borne nutrients before irrecoverable structural abnormalities resulted with their neurological sequela. Grenell noted that susceptibility differences were marked in different areas of the brain and a certain degree of local selectivity or specificity of lesions was evident as was found previously (Weinberger et al 1940a; Kabat et al 1941).

He also found a grading of resistance which, from lowest to highest degree of resistance was as follows: Cerebral cortex (isocortex), cerebella cortex (Purkinje's cells), sensory and integrative centres of brain stem, pons and medulla oblongata, cerebral cortex (allocortex) and
finally, large motor cells of brain stem, pons, medulla oblongata, and spinal chord. He noted that lesions observed clinically in patients were often similar to those that he reported in experimental animals.

B. Resilience of the brain to nutrient lack in man.

Mandel and Berry (1959) correlated human brain changes in cardiac arrest with the duration of cardiac standstill and the survival period. They concluded that the cortex of the brain and the cerebellum in the cases studied appeared to be most sensitive to oxygen deficiency as was found in previous animal experiments (Weinberger et al 1940a; Kabat et al 1941; Grenell 1946). As the period of anoxia increased, changes were more diffuse in the brain with less selectivity.

Adams et al (1966) studied the effects of systemic hypotension upon the human brain in eleven patients. Reduced cerebral blood flow associated with systemic hypotension of varying speed of onset, intensity and duration produced a spectrum of changes ranging from lesions confined to the arterial boundary zones of the cerebrum and cerebellum to a purely diffuse destruction of neurons throughout each location. There were also intermediate stages in which both types of changes in varying proportions were seen. They suggested that the combination of diffuse neuronal loss in the cortex of the cerebrum and cerebellum and the virtual normality of the Ammons horns in some cases constituted a neuropathological entity characteristic of sustained moderate hypotension.

C. Maximum cardiac arrest time and irreversible damage in man.

A leading article from The British Medical
Journal (1960) referring to cardiac arrest and the central nervous system made the point that the limit of three minutes after which neural damage occurred due to lack of blood to the brain varied depending on the pre-existing cerebral hypoxia. For this reason no fixed time limit should be given suggesting that there is a three minute margin of safety in all situations of cerebral hypoxia.

Cases are reported of circulatory arrest of two minutes producing a state of tetraplegia and coma followed by death two and a half months later (Biemond 1958). In another case the period of arrest was only one minute but the result was that the patient remained in a decorticate state for six and a half months (Meyer 1956). In both instances there was evidence of cardiorespiratory distress before the onset of cardiac arrest. On the other hand, the opposite, but extremely rare situation is represented by a report of complete recovery after six minutes of true circulatory arrest (Wolff 1950). Obviously, resuscitative measures must always be maintained in the hope of a favourable outcome whatever the duration of the circulatory arrest.

The neurological sequelae range from slight impairment of the intellect, memory, or vision, to epilepsy, dementia, decerebrate rigidity, and death. Clinically the minor abnormalities may be the more important after apparent recovery in that they are most easily overlooked. A slight impairment of intellect or memory or a minor personality change may be first noted by the patient's relatives or employer rather than by his physician. This would be the situation should this complication result from sedation procedures as patients may be assumed to be under the extended effects of a tranquilliser (if they
exhibit memory loss, ataxia and general cloudiness of intellect). The query could be raised - have they experienced some degree of loss of cortical function?

An important effect from temporary arrest of blood flow to the brain is vasodilatation and engorgement of the vascular bed. The delayed cerebral oedema which this causes - developing in the course of days rather than hours - may lead to further damage to nervous tissue. Therefore, the intravenous administration of hypertonic fluids forms an important part of the management of cases of cardiac arrest. Another delayed complication is hyperthermia, which may also require treatment.

D. Cyanosis.

The first obvious sign of hypoxia which may be noticed during sedation or general anaesthesia where non-continuous monitoring methods are used is cyanosis of the tissues. Lundsgaard and Van Slyke (1923) defined cyanosis as the blueness of the skin, mucous membranes or organs caused by changes in capillary blood (usually due to the presence of unusual amounts of reduced haemoglobin). Cyanosis is a very late sign which may not always be noticed in its early stages. Comroe and Botelho (1947) commented on the unreliability of cyanosis in the recognition of arterial anoxemia. They noted that for some years excellent diagnosticians differed widely in their ability to recognize visually the presence of arterial anoxemia. These observations became evident early in their studies:

(i) that the detection of cyanosis depended not only upon variables in the patient but also upon variables in observers, and

(ii) that cyanosis was a poor guide for the detection of arterial anoxemia of slight to moderate degree.
Comroe and Botelho felt from their studies that in the majority of cases arterial anoxemia was probably unrecognized until the saturation of haemoglobin with oxygen had fallen below 85 per cent; in some it was unrecognized even at the 70 per cent to 75 per cent level. They tested both a student group and a physician group (which included physicians, anaesthetists and cardiologists who had wide experience in the detection of cyanosis). They found little difference between the groups in the ability to recognize various levels of hypoxemia by observations of the patient's degree of blueness.

They concluded that,
(a) concerning the ability of the observers to detect cyanosis the majority of one hundred and twenty-seven of these observers were unable to detect the presence of definite cyanosis until the arterial oxygen saturation fell to approximately 80 per cent; 25 per cent of observers did not note definite cyanosis even at arterial saturation levels of 71 per cent to 75 per cent;
(b) there were marked variations in the ability of an observer to note cyanosis in different subjects or even in the same subject at different times. There were wide variations in colour estimations when five to ten observers watched cyanosis develop in the same subject at the same time.

The detection of cyanosis was dependent on not only variable factors in the patient but also upon the individual observer's ability to note colour changes.

Dripps and Comroe (1946) suggested that slight anoxemia produced effects upon circulation and respiration which could escape even careful clinical observations. In some individuals the respiratory and circulatory responses
were absent or poor, even with moderate degrees of anoxemia. A possible means of overcoming these difficulties may be afforded by the physiological monitoring system introduced by Stephens (1970) which purports to detect early compensatory changes in the small vessels when anoxic or hypercapnic stresses are placed on the cardiovascular system.

Although other signs (mental confusion, delirium) have been suggested as indications for oxygen therapy, they do not represent early changes. The extent of an arterial anoxemia could be determined accurately in patients only by direct analyses of arterial blood (Comroe and Botelho 1947).

Conclusion.

In the heavily sedated patient showing no obvious signs of cyanosis a degree of arterial hypoxaemia may be present. If this is sustained over a long period of time some degree of cerebral damage may occur. Minimal amounts of drug must be used and verbal contact with the patient maintained as a valuable monitor as frequently as possible.

E. Hypotension and cerebral anoxia.

During intravenous sedation procedures in dental practice the most likely cause of cerebral hypoxia is transient hypotension. Bourne (1957) studied this aspect with reference to fainting during induction of anaesthesia in the upright patient. He held it to be the cause for collapse in many healthy young patients being anaesthetized for dental work in the seated upright position. In dental surgeries where sedation is practised the supine position is used predominantly for sedation thereby decreasing the chances of cerebral damage from hypotension. Weiss and
Wilkins (1937) pointed out that the heart as well as the brain was endangered by the ischaemia of fainting which may, in subjects kept upright, cause instantaneous death from asystole or ventricular fibrillation.

F. Hypoxia induced cerebral damage - prognosis.

Bellville and Howland (1957) commented on the prognosis after severe hypoxia in man. Four patients suffered severe hypoxia during general anaesthesia. The use of the electroencephalogram in prognosis in these cases was discussed. At that time there were no standards for evaluating prognosis after hypoxia. They suggested that the following parameters must be considered in prognosis. These were:

(i) did the electroencephalogram become flat;
(ii) how long did this lack of activity persist; and
(iii) what was the time interval between the correction of hypoxia and a reappearance of fast activity?

In general, prognosis was favourable if the electroencephalogram did not become flat after hypoxia, or, if it became flat, prognosis may be good if the fast activity was restored within one hour. The appearance of a file pattern carried a grave prognosis.

G. Supine versus seated position: syncope.

Coplans (1962) carried out a broad evaluation for and against the safety of the sitting posture and hypoxia in dental anaesthesia. Commenting on patients of all age groups he suggested that the aged and infirm and cardiac patient may best be treated in the sitting position whereas Bourne's (1957) study referred only to unaccountable collapse in healthy, young dental patients. Coplans noted
that it was not difficult to understand how some anaesthetists utilise limited hypoxia without even seeing one of the anoxic disasters of all grades of severity that are so frequently reported by their colleagues. It was, he says, after all, a question of degree: not only degree of hypoxia but degree of understanding possessed by the anaesthetist, degree of fitness of the patient, and degree of accuracy possessed by the anaesthetic apparatus at all pressures over the vital range of 5 per cent to 10 per cent oxygen. This matter of degree must also apply to techniques of intravenous sedation, patient selection and evaluation and knowledge of those employing these techniques.

Fainting and collapse in dental practice was reviewed by Hannington-Kiff in 1969, and by Bourne (1966). Fainting was supposedly rare in patients in the supine position, however, it was believed to be more likely to happen with women in late pregnancy. Kerr and colleagues (1964) studied the inferior vena cava in late pregnancy. Normally, in late pregnancy, the inferior vena cava was usually completely occluded and venous return ensured by alternative collateral channels. Through radiological studies it was shown that venous return occurred via the azygous vertebral veins. In the lateral position this obstruction was at least partially relieved. Consequently as there is some impediment to inferior vena caval blood flow it would suggest that fainting and cerebral hypotension would be more likely to occur in the female patient in late pregnancy.

A rare cause of hypotension in the supine position involves the loss of normal circulatory reflexes. Circulatory reflexes may be absent in neuritis due to alcoholism, porphyria (contraindication to use of
barbiturates - methohexitone sodium (Dean 1970)) and infective polyneuritis. Acute loss of circulatory reflexes may be found in alcoholic intoxication and in poisoning due to barbiturates. (Barraclough and Sharpey-Schafer 1963).

Cerebrovascular accidents also cause interruption of the reflex pathways. Severe hypotension in the supine posture was precipitated in chronic neuritis by minor decreases in blood volume, artificial respiration, and therapeutic doses of hypnotics or drugs used for psychotherapy (Barraclough and Sharpey-Schafer 1963).

H. Summary.

Obvious causes of cerebral hypoxia due to respiratory obstruction are not reviewed. These include: anatomical obstruction (tongue, lymphoid tissue); foreign body obstruction (packs, fluid, dental material); and vomitus.

More insidious causes of hypoxia, for example, fainting and hypotension (drug induced), are unlikely to occur in the dental situation with the patient in the supine position and drug doses minimised as much as possible. Huddy (1966) even suggested that the supine posture decreased the possibility of foreign material entering the lungs.

Hypotension, whether of insidious or acute onset, may be difficult to detect visually. The severe consequences of cerebral damage resulting from hypotension make this a major complication of which the dental surgeon must be aware and for which he must be constantly on the alert. Pre-sedation blood pressure should be taken as a baseline recording.
PART IX

ANAESTHETIC DEATHS
CHAPTER 23

REDUCTION OF COMPLICATIONS BY

ANALYSIS OF DEATHS

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CHAPTER 23

REDUCTION OF COMPLICATIONS BY ANALYSIS OF DEATHS

A. Inadequate reporting and assessment of circumstances leading to death from anaesthesia.

The development of thorough post-mortem studies will elucidate the mechanisms of death associated with anaesthesia. These must include quantitation and distribution of anaesthetic agents, serologic examination, and biochemical determinations with the complete autopsy and correlation with thorough and accurate clinical data by an interested and physiologically orientated committee. As more basic data are accumulated, the unexplained death should become a rarity. The information so gained will protect the anaesthetist, promote medical progress, and serve the public interests by reducing mortality.

Lawrie (1962) commented on the reporting of deaths associated with anaesthesia in Scotland and suggested that the whole situation seemed to be quite unrealistic. The definition of death under an anaesthetic, where the patient died while anaesthetized was easy to show, however, patients dying twelve to twenty-four hours later or even four months later, from whatever cause following anaesthesia were a lot more difficult to classify. This difficulty in defining anaesthetic deaths led in 1961 to the following formulation of categories of death due to an anaesthetic.

(i) Deaths which occurred during the actual administration of a general or a local anaesthetic or during an operation performed under a general or local anaesthetic.

(ii) Deaths which were considered to be clinically due to the anaesthetic.

(iii) Deaths which occurred in the immediate post operative
period, ordinarily not exceeding twelve hours following a general anaesthetic, from which consciousness was not regained.

B. Hypoxia

Bourne (1961) suggested that the main problems encountered in dental anaesthesia related to hypoxia. This may be induced by an anaesthetic containing less than 20 per cent oxygen in inspired gases, or by an unrecognized faint occurring on induction or during an anaesthesia leading to transient total cerebral hypoxia due to reduced cerebral blood flow.

C. Improved patient selection

Goldman (1964) estimated that approximately two million anaesthetics were administered for a National Health Schedule of dental cases per year in the years 1952 to 1960. He analysed the causes of deaths under general anaesthesia in dental cases from 1952 to 1961, dividing them into the types of agents used. The total number in that period of ten years was one hundred and thirty-four deaths. He commented that there had been a considerable reduction in the total number of deaths in that period, compared to the previous decade, and that no risk to life should be allowed to arise during a dental procedure.

Goldman suggested quite definitely that of the ten deaths that occurred in 1958 at least three could have been avoided if a more careful patient selection had been made.

D. Increase in death with intravenous administration

Goldman found a higher incidence of problems in patients receiving intravenous anaesthesia. This agreed with figures published by Seldin (1958) in America quoting
deaths under general anaesthesia from 1950 to 1956 in which thiopentone sodium was responsible for the highest number of deaths for any one agent. Goldman suggested that a reduction in the number of deaths was more likely to be achieved by the elimination of difficulties and the prevention of crises than by any improvement in the methods of dealing with emergencies. In the majority of administrations, emergencies should not arise.

E. Operator anaesthetist

Constable (1964) commented on causes of death in the dental chair. He remarked on the operator-anaesthetist concept where it was suggested (The Lancet, 3rd February, 1962) that the Ministry of National Health should give a more positive lead to discourage this practice by not paying for an anaesthetic administered by the surgeon instead of condoning "an undesirable state of affairs" by offering a reduced fee. This statement was answered by an editorial in the British Dental Journal of 20th February, 1962 on dental anaesthesia which put an entirely different point of view. The editorial concluded: "There is a good case for discouraging the operator-anaesthetist where multiple extractions are to be done. To deter him still further than at present from providing his skill in emergencies or from brief operations is not justified by current experience or by history, nor could it be said to be in the interest of patients until such time as there is a complete specialist anaesthetist service readily available throughout the country for dental operations, the dental operator-anaesthetist remains an essential part of the health service."

F. Other causes - cardiac and respiratory

In 1964 the position, so far as the Medical
Protection Society was concerned, was of general disapproval of the dual role, while appreciating that there were circumstances when the dental surgeon was left with very little choice. Until 1964 there had not been substantial numbers of cases to which the Society could ascribe the death of the patient solely to this practice.

The cases with which they had been concerned in recent years arose mainly from the following three causes:
(i) Cardiac failure in persons subsequently found to have some cardiovascular disorder.
(ii) Overdosage. A case noted by Bourne (1966) illustrates this possibility. A healthy girl, aged seven, anaesthetized lying down by the dentist who was to perform the dentistry. She was given intravenously first phenobarbitone 100 mg then pethidine 12.5 mg with hyoscine 9.2 mg then methohexitone 40 mg followed by injections in the mouth of 6.6 ml of a solution containing 2 per cent lignocaine with 1 in 80,000 adrenalin. Ten minutes later a further injection of methohexitone 40 mg was given intravenously. Respiration ceased and the dentist was inadequately equipped to deal with this emergency. The child died next day in hospital.
(iii) Obstructed airway; almost invariably caused by an inhaled throat pack.

The most common cause of death reported by Constable was due to obstructed airway and two of the cases he quoted were due to swabs or pieces of swabs being drawn into the patient's airway causing pharyngeal obstruction.

Alexander et al (1965) compared factors in tonsillectomy mortality with those in dental procedures. A study of a pediatric age group by the Baltimore
Anaesthesia Study Committee revealed that tonsillectomy produced the highest number of anaesthetic deaths among children.

G. Hypotension.

Bourne (1966) analysed the deaths of thirty-seven dental patients anaesthetized in the upright position, whose first sign of trouble was when they collapsed. These patients were young and healthy, all were anaesthetized in the upright position and in all but one, there was a sudden unaccountable collapse.

These two factors, the upright position and collapse (or hypotension) were constant. All others were variable. It made no difference what anaesthetics were used or who gave them. The trouble happened when the anaesthetic was given by a specialist anaesthetist, a general medical practitioner, or a second dentist.

Bourne estimated that collapse associated with the administration of a general anaesthetic to dental patients was common. He suggested that well over half the dentists in the country had seen the condition.

Sudden unaccountable collapse in healthy, young patients was totally alien to his experience of such patients anaesthetized in the horizontal position in operating theatres, where this has never occurred. Such collapse could be due only to the upright position, traditional in dentistry. Unfortunately, the onset of collapse during dental anaesthesia is almost impossible to detect by ordinary means until the patient is in extremis, as Bourne concluded from a personal case he observed. The presence of a second practitioner would not prevent these disasters. The only remedy was to abandon the upright position.
Bourne commented on deaths with dental anaesthetics again in 1970. Sixteen subsequent deaths were analysed; all but one of them occurred in dentists' surgeries. Case sixteen received local analgesia.

In all cases the patient was seated upright, was in most cases treated by a consultant anaesthetist and at autopsy no cause for death could be found. Damage done by anoxia was detectable in the brain only in a survival period of at least twenty-four hours.

Bourne considered the upright position of the patient to be the main cause of death, not the anaesthetic. Fainting can occur lying down but in this position it is rare and probably never results in either coma or death. Young, healthy patients anaesthetized lying down for whatever purpose, including dental extraction, did not suddenly collapse and die unaccountably.

Fainting is common with local analgesia. Of three thousand consecutive dental outpatients treated sitting up under local analgesia at the University of Bristol's Dental Teaching Hospital nearly all of them for extractions, no fewer than fifty-nine (2 per cent) had fainting reactions, nearly a third of them to the extent of losing consciousness. Most fainted during injection of the anaesthetic or extraction of the teeth, but occasionally an attack would occur before treatment was started or after it was finished. With general anaesthesia, fainting is probably less common, but, as with local anaesthesia, it may occur at any stage of treatment (Hannington-Kiff 969).

In a fainting attack the level to which the blood pressure falls is variable and may fluctuate. If a patient
is kept upright or semi-upright, in a severe attack (which is liable to occur with great suddenness in young patients) the blood supply to the brain is lost and there will also be a reduction in the blood supply to the heart. Death may be immediate, from asystole or ventricular fibrillation, or in varying degrees delayed, from brain damage. In a less severe faint, the brain will be only partially starved of blood, breathing may continue and the brain suffers damage, lethal or sub-lethal, with the passage of time. Rarely, the subject may recover quickly from the faint while still upright and suffer no serious sequel. An attack occurring in a subject lightly unconscious under an anaesthetic is difficult to detect by ordinary means until the patient is in extremis. This may be an indication for routine use of a sensitive monitor of tissue perfusion (Stephens 1970) for detecting early cardiovascular changes to stress.

Bourne makes the interesting comment that there is a need for further studies of the circulation in man under dental anaesthetics given with the subjects sitting up. They might follow the lines of those in recumbent subjects made recently by Robinson et al (1969) but should include means of detecting changes in muscle blood flow as, for instance, by forearm plethysmography.

H. Arrhythmia.

Bourne considered also reflex cardiac arrhythmias. Kaufman (1965) observed cardiac arrhythmias during extractions under halothane and had suggested that premedication with a beta blocking agent may guard against possible cardiac arrest from this cause. It is doubtful, however, whether these arrhythmias are of clinical significance. They are common accompaniments of other simple procedures
occurring in 17 per cent of patients undergoing sigmoidoscopy and in 10 per cent of healthy medical students while swallowing a nasogastric tube. Their occurrence was noted in response to the stimulus of intubating the trachea; but few, if any, anaesthetists today would regard this as a hazard, let alone one requiring premedication with a beta blocker. Moreover, as noted above, collapse in the dental chair was not uncommon before the introduction of halothane, where nitrous oxide was the anaesthetic almost universally used. The possibility of collapse from arrhythmia cannot, in the present state of knowledge, be entirely excluded although it does seem unlikely.

Coplands and Curson (1973) also commented on deaths associated with general dental anaesthesia. While valuable information about the relative safety of different treatment methods could sometimes be obtained from mortality statistics, they drew attention to several pitfalls in the evaluation of the Registrar-General's figures relating to dental anaesthesia. Failure to appreciate these pitfalls may have led to widely divergent conclusions being drawn from the same data.

I. Identity of administrator.

Drummond-Jackson (1960) claimed that the figures for 1957 and 1958 of deaths associated with general dental anaesthesia showed that the death rate where medical anaesthetists were involved was ten times higher than that where dentally qualified anaesthetists were involved. Schofield (1966) stated that it had been shown by careful analysis of coroners' inquests over the preceding eight years that dental surgeons were twelve times as safe as medically qualified administrators of dental anaesthetics and that the so-called operator-anaesthetist was even safer.
Bourne, on the other hand, claimed that neither the training of the administrator nor the presence of a second practitioner affected the mortality rate, but that the upright posture was the only constant feature associated with collapse. Coplans and Curson (1973) suggested that none of these conclusions bore close analysis. Drummond-Jackson (1960) and Schofield (1966) compared dissimilar groups of patients with incomplete figures for the total number of anaesthetics administered by each category of administrator. Bourne's conclusions were based on an analysis of thirty-seven deaths, and in thirteen of them it had not been possible to establish the identity of the administrator. In a more recent case the anaesthetist was described as a consultant, which initially was assumed to mean consultant in anaesthetics. Examination of the inquest records disclosed that the administrator was in fact a consultant in infectious diseases.

J. Place of death.

The Joint Subcommittee of the Ministry of Health (1967) in its report (p.24) found that of the twenty-five deaths reported during the period 1962 to 1967, seventeen had taken place in hospital. This observation was widely interpreted as implying that two-thirds of the fatal accidents occurred in hospital, this assumption forming the background to part of the debate in the conference on General Anaesthesia in Dentistry. The Registrar-General's statistics on which the Ministry of Health's report based its observations did not at that time attempt to differentiate between place of death and place of collapse. In 1968 however, this differentiation was made, and while all eleven anaesthetic deaths in that year took place in
hospital seven of the accidents which led to death occurred in dental surgeries. Clearly, as resuscitation techniques improve so will the proportion of hospital deaths increase, irrespective of the place of initial collapse. Conclusions which ignore this point are valueless.

Coplans and Curson decided in October 1969 to do their own study because the reports of the various studies were confusing. They found that even copies of the inquest documents did not necessarily provide what they considered to be the most significant clinical information. Indeed, the posture of the patient at the time of the accident was very rarely stated, and many other important details were either missing or referred to in an ambiguous manner. It became apparent that a complete and valid analysis could only be achieved following personal communication with all the medical and dental personnel in each case. While preparing for this task the following two cases came to their notice from newspaper reports and persuaded them that further studies based on the available information were at present of limited value. The two cases involved a five year old girl who died after a tooth extracted under local anaesthesia was inhaled and a woman who received intravenous injections of pethidine, hyoscine and methohexitone and a local anaesthetic injection of lignocaine from a dentist prior to the performance of conservative dentistry. The patient convulsed and collapsed and was found, on inquest, to have a ruptured congenital cerebral aneurysm.

In spite of their relevance to dental mortality statistics neither of these cases appeared among the deaths listed by the Registrar-General as being associated with any form of anaesthesia or, indeed, any aspect of dentistry.
With the assistance of the Registrar-General's office Coplans and Curson were able to trace both cases. The first death had been classified as being due to inhalation and ingestion of an object, other than food, causing obstruction or suffocation. The second had been classified as due to subarachnoid haemorrhage. The reason that neither of these deaths were included in the Registrar-General's Dental List was, apparently, because this list included only those deaths where a dental manoeuvre was classified as the underlying cause from a sequence reported on the death certificate.

There were many other categories into which deaths, highly relevant to these studies, could leak and the material hitherto analysed may well be incomplete. The data may, perhaps, be taken to indicate trends but unfortunately they may indicate trends in classification rather than trends in clinical outcome.

Coplans and Curson recommended that conclusions based on the analysis of statistics for deaths associated with dental treatment be viewed with the greatest possible caution.

Laskin (1974) in an editorial comment reviewed the safety of ambulatory general anaesthesia given in dental offices by anaesthetically trained oral surgeons. He noted the safety of general anaesthesia as administered by the oral surgeon documented in the American Society of Oral Surgeons and the Southern California Society of Oral Surgeons surveys published in 1974. While each was done independently they both arrived at the same conclusion, complications resulting from general anaesthesia in the office were uncommon. Moreover, when they did occur, the
oral surgeon had both the knowledge and experience to deal with them in an efficient and effective manner. General anaesthetic complications, referred to in these reports, were the predominant group reported.

The American Society of Oral Surgeons survey noted that a third of their members did not return the questionnaire regarding mortality and morbidity from general anaesthesia in the dental office. It was unlikely, on the basis of the great publicity given to mortality cases in dentistry in general and oral surgery in particular, that very many cases went completely unreported in the various communications media. The current data should at least be a very close approximation to the Society's actual experience in 1972, the date of the previous survey. In the survey the questionnaires asked whether sedation with local anaesthesia was used. Three hundred and four oral surgeons said that they used this routinely, one hundred and fifty-two said that they used it occasionally and forty-six said that they never used this procedure. Of those who used sedation with local anaesthesia, five hundred and forty-one used it intravenously, one hundred and sixty orally, sixty-two intramuscularly and sixty-two used inhalation sedation. The most commonly used drug was diazepam (nine hundred and forty) with methohexitone (four hundred and sixty), pethidine (three hundred and sixty-six) and pentobarbitone (one hundred and eighteen) in descending order of popularity. The serious complications are tabulated on page 304.

The purpose of the study was to determine as accurately as possible the mortality experience of the members of the American Society of Oral Surgeons in relation to the number of general anaesthetics given in a single year, 1972.
Eleven deaths were reported - seven in which the primary technique was general anaesthesia and four in which local anaesthesia was used. In three of four local anaesthetic complications there was supplementation with intravenous agents. This mortality figure is probably accurate for the reasons previously cited, however the possibility of additional mortalities occurring in the offices of the unreporting third of the society members is recognized. Only one case of death involving the use of diazepam and lignocaine was reported; the patient was of poor physical status, cause of death was myocardial infarction and the agents used were lignocaine, pentazocine and intravenous diazepam. Of note however, is that at least a third of the fatalities were normal, healthy individuals. These patients received methohexitome and nitrous oxide/oxygen and it was not stated whether the patients were sitting up or lying down. One patient died from cardopulmonary collapse, one patient from aspiration of vomitus and the third patient, who received halothane, had an arrhythmia and a cardiac arrest. The remarks on this third case were that the patient was extremely apprehensive and in future pre-operative sedation would be advised. In comparing the mortality rate with another branch of surgery (tonsillectomy) it was found that according to an oral communication in September 1973 with Mauer (Mortality Statistics Branch, Division of Vital Statistics, The National Centre for Health Statistics in Washington) a relatively minor surgical procedure, tonsillectomy and adenoidecotomy - also usually elective and in many other ways similar to routine oral surgical procedures - was associated with a mortality of about fifty cases per million operations performed annually. By comparison
<table>
<thead>
<tr>
<th>CEREBRAL</th>
<th>CARDIAC</th>
<th>RESPIRATORY</th>
<th>ANAPHYLACTIC</th>
<th>OTHER</th>
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<tr>
<td>Epileptic (17)</td>
<td>Arrhythmia (13)</td>
<td>Asthmatic (18)</td>
<td>Methohexitone (9)</td>
<td>Thrombophlebitis (2)</td>
</tr>
<tr>
<td>CVA (3)</td>
<td>Arrest (8)</td>
<td>Acute problems (13)</td>
<td>Penicillin (6)</td>
<td>Lung aspiration (2)</td>
</tr>
<tr>
<td>Ischaemia (3)</td>
<td>Infarct (6)</td>
<td>Pneumonia (itis) (8)</td>
<td>Lignocaine &amp; methohexitone (2)</td>
<td>Arterial injection (8)</td>
</tr>
<tr>
<td>Hypoxia (2)</td>
<td>Congestive failure (2)</td>
<td>Pulmonary edema (2)</td>
<td>Carbocaine (2)</td>
<td>Tissue damage (6)</td>
</tr>
<tr>
<td>Other (8)</td>
<td>Other (9)</td>
<td>Other (11)</td>
<td>Other (4)</td>
<td>Psychotic reaction (2)</td>
</tr>
</tbody>
</table>

more than five and a quarter million anaesthetics by oral surgeons on a generally older and less healthy patient population resulted in only eleven mortalities in an office rather than in a hospital environment. Although it is understood that all deaths from tonsillectomy and adenoidectomy are not related to anaesthesia, it is probable that general anaesthesia is the most common complicating procedure resulting in fatality. These data emphasise the excellent record achieved by the oral surgeon in the management of anaesthesia for the ambulatory patient (American Society of Oral Surgeons and Southern California Society of Oral Surgeons survey 1974, Lytle 1974).

K. Summary

It is difficult to assess actual causes of death under the present medical reporting and coroner's inquest situations as many relevant details are omitted from these reports. In many of the situations the surgeon involved may leave out details of the case. International variations of anaesthetic practice, for example, the supine position for anaesthesia which is routinely adopted in Sydney private practice but is not routinely adopted in the United Kingdom government clinics, occur. For example, I have seen (1976) at a prominent dental teaching establishment the seated position used for induction and at a government children's dental clinic nearby, children subjected to upright anoxic nitrous oxide anaesthesia for short procedures. Is this unsafe practice or has it been found by experience to be both safe and convenient? There is a lack of agreement in regard to the importance of factors such as vomiting and aspiration in the supine position which influences the retention of the use of the upright
position. Where reflexes are not seriously obtunded (in sedation procedures) but where the drugs can have hypotensive effects, patients are routinely treated in the supine position. Therefore, sudden hypotension should not be a problem provided the patient is not obstructed, adequate respiration is maintained and sedative drugs are not used to excess.

The background of the administrator of the anaesthetic does not seem to be significant. Whether it be the dental practitioner, consultant anaesthetist or medical practitioner in the English situation did not seem to have marked effect on the incidence of problems. The operator-anaesthetist practice has come under attack recently and is being steadily abandoned through being indefensible legally for longer conservative cases. However, short emergency extractions are still a problem since, at present, availability of anaesthetists for this aspect of practice is impractical.

In contrast, general anaesthesia and sedation as practised by specialist oral surgeons in America, where the background to anaesthesia has had a very strong bias towards dentistry, may be practised by the operator only, by the operator plus an anaesthetist, by the operator plus a dental nurse anaesthetist, by the dentist and a medical practitioner or by the oral surgeon and an anaesthetist. In all these possibilities and in the specialist's hands there seems to be no marked increase in mortality for any one group of applications. In terms of dental sedation with local anaesthesia there are one to two rare reports mentioned. The patients died from defects in the anatomy of their vascular systems leading to aneurysms, stroke, collapse or infarction. Indications are that where a surgeon has had extensive training at post graduate level in general anaesthesia the mortality
rate is very low and the very absence of reports in the literature of problems with local anaesthesia and sedation with methohexitone sodium and diazepam in a healthy group suggests that the mortality rate with this procedure also is very low.
PART X

POST SEDATION COMPLICATIONS
CHAPTER 24

POST SEDATION COMPLICATIONS

A CLINICAL SURVEY

A. Introduction

A disadvantage of the intravenous use of diazepam is the duration of its action, which may outlast the dental appointment. This effect has been mentioned by Baird and Hailey (1972, 1973) and supported by Korttila and Linnoila (1975) but has been refuted by Ghoneim et al (1975). Their subjects showed no evidence of re-tranquilization after recovery. These three studies attempted to relate plasma diazepam levels with patients' subjective feelings of tranquilization.

B. Aim of the investigation

A questionnaire was arranged to determine if patients experienced prolonged effects from a sedation appointment on the following day. The drugs employed were diazepam, atropine sulphate (4ml diazepam diluted with 1ml atropine sulphate), methohexitone sodium, and local anaesthesia (lignocaine).

C. Method

The questionnaire was designed to test the incidence of post sedation complications (ref. p. 310). Two hundred and sixty-one patients were asked to tick the appropriate box opposite any complication they noticed during the week following their appointment. The questionnaire was returned one week later.

The patients' ages ranged from twenty years to sixty years. The sedation technique used in all cases was intravenous diazepam, atropine sulphate, methohexi- tone sodium and local anaesthesia. Loss of patient
PATIENT QUESTIONNAIRE SHEET OF POST SEDATION COMPLICATIONS

1. Did you experience any of the following conditions on the day after the sedation was given?

   PLEASE TICK ANSWER
   (a) drowsiness ........................................... □ □
   (b) dizziness ................................................ □ □
   (c) loss of memory ......................................... □ □
   (d) excitability ........................................... □ □
   (e) depression ........................................... □ □
   (f) poor vision ........................................... □ □
   (g) insomnia ................................................ □ □
   (h) hallucinations ....................................... □ □
   (i) nausea .................................................. □ □
   (j) any other condition? ............................... □ □
   (Please indicate over page).

2. Did any of these symptoms extend beyond the day after? .................................................. □ □
   If so, for how many days? ............................... days.

3. Do you feel that any of the above symptoms affected your ability to carry on your normal daily activities? ................................................................. □ □

4. Did you experience — (1) any pain in the arm (localised) .................................................. □ □
   — (2) any pain extending up the vein at any time after the intravenous sedation □ □

5. Did you read the post-operative instructions for patients who have had sedation? ........................ □ □

6. Would you undergo intravenous sedation again? ....................................................................... □ □

7. Would you recommend intravenous sedation to your friends? .................................................. □ □

8. Can the person who cared for you following this sedation appointment verify the above answers?  □ □

   It would be appreciated if you would kindly give any further details bearing on the above questions which may be helpful, on the other side of this page.
consciousness was kept to a minimum. Consciousness was judged by the ability of the patient to respond to vocal commands.

The patients in the younger age group (less than 20 years) tended to require deeper sedation with more frequent periods of unconsciousness - this group was excluded for this reason.

Males and females were grouped together because of the overall small sample size.

No controls could be used as these patients would not accept dentistry initially without sedation. Doses were adjusted according to the patients' needs as judged by their responses during treatment (i.e. lower dose as age increased, as older patients were more affected by the sedative drugs). Results were analysed statistically for any significant associations between drug dosage, age and reported complications.

D. Results

The incidence of complications are set out in Table 3 (p.321). Graphs and Tables for Dizziness and Drowsiness for each age group sedated are shown in the appendix (p.318). Because of the small sample sizes in the older age groups higher drug dose ranges and ages were grouped as in Tables 9 and 18 (p.327, 334). The observed differences in the percentage of patients reporting drowsiness in both age groups were subjected to Students "t" test at the 0.05 level of chance.

In relating the 20-29 years age group to the 30 plus age group a significant difference became apparent; the younger group was more drowsy. Within the 20-29 years (less than 30 years) group those who had higher doses of
sedative were significantly more drowsy.

The mean doses of each sedative drug were calculated for each age group (under 30 years, over 30 years), for the whole group and for those patients who reported drowsiness and dizziness (ref. Tables P.328,335). Differences in the mean doses were compared statistically for each age group and to the whole groups and considered statistically significant at the 0.05 level of chance.

Patients in the under 30 years age group received a significantly higher dose of diazepam than the over 30 years group. For those patients reporting dizziness the under 30 years age group received a significantly higher dose of diazepam than the over 30 years group.

In the average methohexitone sodium dose group (Table p. 335) the younger patients received a significantly higher dose. The younger group who reported dizziness received a higher dose of methohexitone sodium than the older group (Table p. 335).

The under 30 year olds reporting complications (Table p. 328) received more than the mean dose of diazepam for their age group (18.8mg and 20.6mg compared with 18mg for all under 30 year olds) whereas the over 30 years with complications received less than the mean for their group (15.8mg and 15.7mg compared with 17mg). This may have been due to a general tendency of the older group not to mention complications which they did not consider troublesome.
E. Discussion of results

(i) Drowsiness

This was the most frequent complication reported (39%), evident on the first post operative day. One patient reported drowsiness for 5 days after her appointment following extensive oral surgery. She received 20mg of diazepam and 150mg of methohexitone sodium and was conscious throughout the procedure.

As far as possible the drug doses were adjusted for age according to the patients' apparent needs. The older the patient the lower the doses of sedative drugs required. An increase in the number of complications with an increase in age was therefore not expected. However, there was a statistically higher incidence of drowsiness and dizziness in the younger age group. This was the reverse of what may be expected as older patients would be more sensitive to drug effects; however the younger group clinically appeared to have more trouble coping with stress than the older age groups. A higher drug dose was often required, with a higher incidence of complications (ref. Graphs A and B, p.336,337).

(ii) Dizziness

Fifteen per cent of patients reported dizziness on the day following sedation. One female patient (23 years) received 15mg of diazepam and 250mg of methohexitone sodium over 2½ hours and reported drowsiness and dizziness for 4-5 days post sedation.

(iii) Memory loss

Following sedation 23 patients (9%) reported memory loss. One 22 year old patient experienced memory
loss for 3 days after sedation. He received 30mg of diazepam and 400mg of methohexitone sodium over a period of 3½ hours.

Another patient, male (20 years) forgot half a day, 2½ days after sedation. He received 20mg of diazepam and 300mg of methohexitone sodium over a period of 2 hours. The patient made deliveries to a number of stores and when he returned to work at lunch time could not remember where he had been all that morning.

(iv) Excitability

One per cent of patients reported excitability – this was an uncommon complication.

(v) Depression

Nineteen patients reported depression with or without crying spells one day after sedation. In the majority of reports this was unusual behaviour for that particular patient.

(vi) Visual Disturbance

Six patients (2%) reported blurred vision on the day after sedation which improved as the day proceeded. No cause can be presented for this, other than a prolonged sensitivity to atropine sulphate.

(vii) Insomnia

Four patients (2%) reported inability to sleep on the night following sedation (after 24 hours). These patients had received drug doses in higher ranges.

(viii) Hallucinations

No patients reported hallucinations.
(ix) Nausea

Eleven patients (4%) reported nausea following sedation. Most of these patients received higher doses. One patient vomited 20 minutes after the start of the appointment. She arrived with a migraine type headache, had a history of migraine and the headache subsided after the attack of vomiting.

(x) Thrombosis

Six patients complained of a tender hard cord which developed in the injected vein during the week after their appointment. There was no apparent relationship to dose or duration. Two patients received only minimal amounts of sedation (10mg diazepam and 10mg methohexitone sodium) for procedures lasting only 10 minutes.

My clinical impression was that the true incidence of thrombosis is much higher as many patients had thrombosed veins which they were not aware of and had not complained of. One patient had an infected thrombosis which required antibiotic therapy.

(xi) Local pain at injection site

Patients complained of pain at the time of puncture of the needle (14%). This may have been due to skin puncture or inadvertant puncture of a sensory nerve track (ref. p. 149), or penetration of the vein wall. This complication is difficult to reduce.

(xii) Rash

Two types of rash were noted by patients:

(a) Nervous rash confined to the anterior aspect of the neck (the so-called blush area). This was very
commonly noted at the time of the appointment by the dental surgeon (ref. Photo p.97).

(b) An allergic rash due to one or more of the drugs used (ref. Photo p.68). This is a very rare event in the literature. Three patients were aware of the neck rash and one patient showed an allergic type rash without past history of taking any of the drugs used for sedation. This rash is seen to involve the neck, chest and abdomen and showed the urticaria characteristic of allergic reactions. The blush reaction type rash is confined to the neck and upper chest region.

(xiii) Generalised pain at injection site

Twenty-five patients (10%) reported pain at the injection site as the diazepam was being injected. This was increased in small veins or with too rapid an injection rate.

(xiv) Haematoma

This complication was noted by eight patients (3%) and was not troublesome (ref. Photo p.135).

(xv) Others

Patients were asked to note any other complications. One patient had paraesthesia of the right thumb for four weeks after the appointment. One patient, twenty-four hours after sedation, wanted to get out of bed but could not. This effect lasted for two to three minutes and may have been due to inadvertant post hypnotic suggestion.

A female (27 years) reported uncontrollable shaking of her whole body but particularly her mouth, of one day duration. This may have been an extra pyramidal reaction.
E. Conclusion

Prolonged effects from intravenous diazepam and methohexitone have been shown to occur. They increase with an increase in dose - this is in agreement with Baird and Hailey (1972). Full recovery from the effects of intravenous diazepam does not occur for many hours and therefore suitable care and supervision of the patient are required after the initial apparent recovery. If it is thought that a patient's responsibility is suspect (Ogg 1972) intravenous sedative medication must not be given.

Larson et al (1977) reported four cases which demonstrated the prompt and effective reversal of diazepam induced delirium and coma by the administration of physostigmine. If this proves to outlast the extended effects of the diazepam then physostigmine reversal of diazepam may become a welcome routine procedure in dental diazepam sedation, thereby minimising any extended effects of the drug. Patients may then be more effectively protected against harming themselves and others post-operatively from sedative effects.

"There is always a group of patients who require some form of sedation for dental procedures and to our patients we must always strive to be kind." (Markley 1976) To this I would add, "and at all times to be careful".
APPENDIX
**LIST OF TABLES**

<table>
<thead>
<tr>
<th>Table No.</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:</td>
<td>Anaesthetic and sedation complications.</td>
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<tr>
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<td><strong>CLINICAL SURVEY</strong></td>
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<tr>
<td>2:</td>
<td>Age distribution of patients in the clinical survey.</td>
<td>321</td>
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<td>3:</td>
<td>Incidence of post sedation complications.</td>
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<td><strong>DIAZEPAM</strong></td>
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<tr>
<td>4:</td>
<td>Distribution of patients per age group per diazepam dose (mg).</td>
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<td>5-7:</td>
<td>Distribution of Patients reporting a complication per diazepam dose (mg).</td>
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<td>8:</td>
<td>Comparison of complications within age groups for diazepam (10-20mg and 25-40mg).</td>
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<tr>
<td>9:</td>
<td>Distribution of complications according to 20-29 yrs and over 30 yrs for diazepam (10-20mg and 25+ mg).</td>
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<td>10-12:</td>
<td>Comparison of average diazepam dose for patients under 30 yrs and over 30 yrs reporting a complication.</td>
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<td><strong>METHOHEXITONE SODIUM</strong></td>
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<td>13:</td>
<td>Distribution of patients per age group per methohexitone dose (mg).</td>
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<td>14-16:</td>
<td>Distribution of patients reporting a complication per methohexitone dose (mg).</td>
<td>330-332</td>
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Table No:                          Page

17:  Comparison of complications within age
     groups for methohexitone (under 100mg
     and over 100mg).                   333

18:  Distribution of complications according
     to 20-29 yrs and 30+ yrs for
     methohexitone.                     334

19-21: Comparison of average methohexitone
       dose for patients under 30 yrs and
       over 30 yrs reporting a complication. 335
### TABLE 2
AGE DISTRIBUTION OF PATIENTS

<table>
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<td>139</td>
<td>(53)</td>
</tr>
<tr>
<td>30-39</td>
<td>71</td>
<td>(27)</td>
</tr>
<tr>
<td>40-49</td>
<td>22</td>
<td>(8)</td>
</tr>
<tr>
<td>50-59</td>
<td>21</td>
<td>(8)</td>
</tr>
<tr>
<td>60-69</td>
<td>8</td>
<td>(3)</td>
</tr>
<tr>
<td><strong>TOTAL A</strong></td>
<td><strong>261</strong></td>
<td></td>
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### TABLE 3
SURVEY OF SEDATION COMPLICATIONS

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<th>COMPLICATIONS</th>
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<td>Drowsiness</td>
<td>101</td>
<td>(39)</td>
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<tr>
<td>Dizziness</td>
<td>39</td>
<td>(15)</td>
</tr>
<tr>
<td>Memory Loss</td>
<td>23</td>
<td>(9)</td>
</tr>
<tr>
<td>Excitability</td>
<td>3</td>
<td>(1)</td>
</tr>
<tr>
<td>Depression</td>
<td>19</td>
<td>(7)</td>
</tr>
<tr>
<td>Visual Disturbance</td>
<td>6</td>
<td>(2)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4</td>
<td>(2)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>(4)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>6</td>
<td>(2)</td>
</tr>
<tr>
<td>Local Pain at injection site</td>
<td>37</td>
<td>(14)</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>(1)</td>
</tr>
<tr>
<td>Generalised pain at injection site</td>
<td>25</td>
<td>(10)</td>
</tr>
<tr>
<td>Haematoma</td>
<td>8</td>
<td>(3)</td>
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TABLE 4

TOTAL NUMBERS AGE GROUP DIAZEPAM DOSAGE (mg)

<table>
<thead>
<tr>
<th>DOSE (mg)</th>
<th>20-29 yrs</th>
<th>30-39 yrs</th>
<th>40-49 yrs</th>
<th>50-59 yrs</th>
<th>60-69 yrs</th>
<th>TOT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% 139</td>
<td>% 71</td>
<td>% 22</td>
<td>% 21</td>
<td>% 8</td>
<td>B</td>
</tr>
<tr>
<td>Sub.</td>
<td>grp.</td>
<td>grp.</td>
<td>grp.</td>
<td>grp.</td>
<td>grp.</td>
<td>A%</td>
</tr>
<tr>
<td>10</td>
<td>34 (24)</td>
<td>13 (18)</td>
<td>8 (36)</td>
<td>8 (38)</td>
<td>6 (75)</td>
<td>69:26</td>
</tr>
<tr>
<td>15</td>
<td>22 (16)</td>
<td>13 (18)</td>
<td>3 (14)</td>
<td>4 (19)</td>
<td>1 (13)</td>
<td>43:16</td>
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<tr>
<td>20</td>
<td>65 (47)</td>
<td>42 (59)</td>
<td>10 (45)</td>
<td>8 (38)</td>
<td>1 (12)</td>
<td>126:48</td>
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<tr>
<td>25+</td>
<td>18 (13)</td>
<td>3 (4)</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>23:9</td>
</tr>
</tbody>
</table>

TOTAL L   139  71  22  21  8  261 (100)

\[
\frac{L_{261}}{A_{53}} (261) 53 \quad (27) \quad (8) \quad (8) \quad (3)
\]

* See next page
TABLE 5

DROWSINESS-DIAZEPAM

<table>
<thead>
<tr>
<th>DOSE (mg)</th>
<th>20-29 yrs</th>
<th>x% 64% Sub. grp.</th>
<th>30-39 yrs</th>
<th>x% 29% Sub. grp.</th>
<th>40-49 yrs</th>
<th>x% 7% Sub. grp.</th>
<th>50-59 yrs</th>
<th>x% 4% Sub. grp.</th>
<th>60-69 yrs</th>
<th>x% 1% Sub. grp.</th>
<th>TOT C%</th>
<th>A% B%</th>
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<tr>
<td>10</td>
<td>16 (25x47)</td>
<td>8 (32) (62)</td>
<td>2 (29) (25)</td>
<td>2 (50) (25)</td>
<td>1 (100) (17)</td>
<td>29 (11x42)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>15</td>
<td>6 (9)(27)</td>
<td>4 (16) (31)</td>
<td>0 (0) (0)</td>
<td>2 (50) (50)</td>
<td>0 (0) (0)</td>
<td>12 (5x28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>20</td>
<td>30 (47)(46)</td>
<td>13 (52) (31)</td>
<td>4 (57) (40)</td>
<td>0 (0) (0)</td>
<td>0 (0) (0)</td>
<td>47 (18x37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25+</td>
<td>12 (19)(67)</td>
<td>0 (0) (0)</td>
<td>1 (14) (100)</td>
<td>0 (0) (0)</td>
<td>0 (0) (0)</td>
<td>13 (5x57)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL M</td>
<td>64 (46)</td>
<td>25 (35)</td>
<td>7 (32)</td>
<td>4 (19)</td>
<td>1 (13) 101 (39x39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ M_0^{\%} \]
\[ \bar{A}^{(261)} (25) \]
\[ M_0^{\%} \]
\[ \bar{L}^{(46)} (35) \]

* The subgroup \( x\% \) expresses the number of patients in each dose level who report a specific complication to the total number of patients in that dose level from Table 4.
**TABLE 6**

**DIZZINESS-DIAZEPAM**

<table>
<thead>
<tr>
<th>DOSE (mg)</th>
<th>20-29 yrs</th>
<th>30-39 yrs</th>
<th>40-49 yrs</th>
<th>50-59 yrs</th>
<th>60-69 yrs</th>
<th>TOT</th>
<th>D %</th>
<th>A %</th>
<th>B %</th>
</tr>
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<tr>
<td></td>
<td>x %</td>
<td>x %</td>
<td>x %</td>
<td>x %</td>
<td>x %</td>
<td>x %</td>
<td>x %</td>
<td>x %</td>
<td>x %</td>
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<tr>
<td>sub. grp.</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>(12) (9)</td>
<td>3</td>
<td>(33) (23)</td>
<td>1</td>
<td>(50) (13)</td>
<td>1</td>
<td>(33) (13)</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>2</td>
<td>(8) (9)</td>
<td>1</td>
<td>(11) (8)</td>
<td>0</td>
<td>(0) (0)</td>
<td>1</td>
<td>(33) (25)</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>14</td>
<td>(56) (22)</td>
<td>5</td>
<td>(56) (12)</td>
<td>1</td>
<td>(50) (10)</td>
<td>1</td>
<td>(33) (13)</td>
<td>0</td>
</tr>
<tr>
<td>25+</td>
<td>6</td>
<td>(24) (63)</td>
<td>0</td>
<td>(0) (0)</td>
<td>0</td>
<td>(0) (0)</td>
<td>0</td>
<td>(0) (0)</td>
<td>0</td>
</tr>
</tbody>
</table>

| TOTAL N   | 25   | (18) | 9    | (13) | 2    | (9) | 3    | (14) | 0   | 39  | (15) | (15) |

<table>
<thead>
<tr>
<th>N %</th>
<th>A % (261) (10)</th>
<th>(3)</th>
<th>(1)</th>
<th>(1)</th>
<th>(0)</th>
<th>(15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L %</td>
<td>(18) (13) (9)</td>
<td>(14)</td>
<td>(0)</td>
<td></td>
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<td></td>
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## Table 7

**Anterograde Memory Loss - Diazepam**

<table>
<thead>
<tr>
<th>DOSE (mg)</th>
<th>20-29 yrs</th>
<th>30-39 yrs</th>
<th>40-49 yrs</th>
<th>50-59 yrs</th>
<th>60-69 yrs</th>
<th>TOT yrs</th>
<th>B%</th>
<th>A%</th>
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<tr>
<td></td>
<td>sub.</td>
<td>grp.</td>
<td>sub.</td>
<td>grp.</td>
<td>sub.</td>
<td>grp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>5 (31) (15)</td>
<td>0 (0) (0)</td>
<td>2 (100) (25)</td>
<td>1 (100) (13)</td>
<td>1 (100) (17)</td>
<td>9 (3) (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>2 (13) (9)</td>
<td>0 (0) (0)</td>
<td>0 (0) (0)</td>
<td>0 (0) (0)</td>
<td>0 (0) (0)</td>
<td>2 (1) (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>5 (31) (8)</td>
<td>3 (100) (7)</td>
<td>0 (0) (0)</td>
<td>0 (0) (0)</td>
<td>0 (0) (0)</td>
<td>8 (3) (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25+</td>
<td>4 (25) (22)</td>
<td>0 (0) (0)</td>
<td>0 (0) (0)</td>
<td>0 (0) (0)</td>
<td>0 (0) (0)</td>
<td>4 (2) (17)</td>
<td></td>
<td></td>
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**TOTAL** | 0 16 (12) 3 (4) 2 (9) 1 (5) 1 (13) 23 (9) (9) |

\[
\frac{O}{A} (261) \hspace{1cm} (6) \hspace{1cm} (1) \hspace{1cm} (1) \hspace{1cm} (0) \hspace{1cm} (0) \hspace{1cm} (9) \\
\frac{O}{L} \hspace{1cm} (12) \hspace{1cm} (4) \hspace{1cm} (9) \hspace{1cm} (5) \hspace{1cm} (13) \hspace{1cm} 325
### TABLE 8

**COMPARISON OF COMPLICATIONS WITHIN AGE GROUPS**

**DIAZEPAM**

<table>
<thead>
<tr>
<th>DOSE (mg)</th>
<th>20-29 yrs</th>
<th>30-39 yrs</th>
<th>40-49 yrs</th>
<th>50-59 yrs</th>
<th>60-69 yrs</th>
<th>TOT yrs</th>
<th>Sub grp %</th>
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<td>10-20</td>
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<td>68</td>
<td>21</td>
<td>20</td>
<td>8</td>
<td>238</td>
<td></td>
</tr>
<tr>
<td>25-40</td>
<td>18</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>139</strong></td>
<td><strong>71</strong></td>
<td><strong>22</strong></td>
<td><strong>21</strong></td>
<td><strong>8</strong></td>
<td><strong>261</strong></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>DROWSINESS</th>
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<td>10-20</td>
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<tr>
<td>25-40</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
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<tr>
<th>DIZZINESS</th>
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<tbody>
<tr>
<td>10-20</td>
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<tr>
<td>25-40</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
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<table>
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<th>MEMORY LOSS</th>
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<tr>
<td>25-40</td>
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<tr>
<td><strong>TOTAL</strong></td>
</tr>
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</table>
### TABLE 9
**DIAZEPAM - COMPLICATIONS.**

<table>
<thead>
<tr>
<th>DOSE (mg)</th>
<th>20-29 yrs Sub.</th>
<th>30+ yrs Sub.</th>
<th>TOT</th>
<th>Sub.</th>
</tr>
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<td></td>
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<td>grp.</td>
<td>yrs %</td>
<td>grp.</td>
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<tr>
<td>10 - 20</td>
<td>121 (85)</td>
<td>117 (80)</td>
<td>238 (92)</td>
<td></td>
</tr>
<tr>
<td>25+</td>
<td>18 (89)</td>
<td>5 (21)</td>
<td>23 (100)</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>139 (85)</td>
<td>122 (78)</td>
<td>261 (100)</td>
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</tbody>
</table>

**DROWSINESS**

<table>
<thead>
<tr>
<th>DOSE (mg)</th>
<th>20-29 yrs Sub.</th>
<th>30+ yrs Sub.</th>
<th>TOT</th>
<th>Sub.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yrs %</td>
<td>grp.</td>
<td>yrs %</td>
<td>grp.</td>
</tr>
<tr>
<td>10 - 20</td>
<td>52 (85)</td>
<td>36 (75)</td>
<td>88 (100)</td>
<td>37 (75)</td>
</tr>
<tr>
<td>25+</td>
<td>12 (88)</td>
<td>1 (22)</td>
<td>13 (100)</td>
<td>1 (22)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>64 (85)</td>
<td>37 (75)</td>
<td>101 (100)</td>
<td>44 (47)</td>
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</table>

**DIZZINESS**

<table>
<thead>
<tr>
<th>DOSE (mg)</th>
<th>20-29 yrs Sub.</th>
<th>30+ yrs Sub.</th>
<th>TOT</th>
<th>Sub.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yrs %</td>
<td>grp.</td>
<td>yrs %</td>
<td>grp.</td>
</tr>
<tr>
<td>10 - 20</td>
<td>19 (78)</td>
<td>14 (60)</td>
<td>33 (100)</td>
<td>20 (60)</td>
</tr>
<tr>
<td>25+</td>
<td>6 (50)</td>
<td>0 (0)</td>
<td>6 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>25 (83)</td>
<td>14 (47)</td>
<td>39 (100)</td>
<td>14 (47)</td>
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</table>

**MEMORY LOSS**

<table>
<thead>
<tr>
<th>DOSE (mg)</th>
<th>20-29 yrs Sub.</th>
<th>30+ yrs Sub.</th>
<th>TOT</th>
<th>Sub.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>yrs %</td>
<td>grp.</td>
<td>yrs %</td>
<td>grp.</td>
</tr>
<tr>
<td>10 - 20</td>
<td>12 (78)</td>
<td>7 (47)</td>
<td>19 (100)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>25+</td>
<td>4 (22)</td>
<td>0 (0)</td>
<td>4 (100)</td>
<td>2 (11)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>16 (83)</td>
<td>7 (37)</td>
<td>23 (100)</td>
<td>13 (56)</td>
</tr>
</tbody>
</table>
TABLE 10
COMPARISON OF
AVERAGE DIAZEPAM DOSAGE PER
AGE GROUP

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>N</th>
<th>AVERAGE DOSE (mg)</th>
<th>S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 yrs</td>
<td>139</td>
<td>18</td>
<td>0.5</td>
</tr>
<tr>
<td>&gt;30 yrs</td>
<td>122</td>
<td>17</td>
<td>0.5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>261</td>
<td>17.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

No significant difference (P<0.05)

TABLE 11
DROWSINESS - DIAZEPAM

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>N</th>
<th>AVERAGE DOSE (mg)</th>
<th>S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 yrs</td>
<td>64</td>
<td>18.8</td>
<td>0.8</td>
</tr>
<tr>
<td>&gt;30 yrs</td>
<td>37</td>
<td>15.8</td>
<td>0.8</td>
</tr>
<tr>
<td>TOTAL</td>
<td>101</td>
<td>17.7</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Difference <30 to >30 years significant (P<0.05) (t=2.6)

TABLE 12
DIZZINESS - DIAZEPAM

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>N</th>
<th>AVERAGE DOSE (mg)</th>
<th>S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 yrs</td>
<td>25</td>
<td>20.6</td>
<td>1.3</td>
</tr>
<tr>
<td>&gt;30 yrs</td>
<td>14</td>
<td>15.7</td>
<td>1.3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>39</td>
<td>18.8</td>
<td>1.01</td>
</tr>
</tbody>
</table>

Difference <30 to >30 years significant (P<0.05) (t= 2.7)
### TABLE 13

**TOTAL NUMBERS PER AGE GROUP PER METHOHEXITONE DOSAGE**

(A=261)

| DOSE (mg) | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | TOT. | F% | A% | %
|-----------|-------|-------|-------|-------|-------|------|----|---|---
| yrs | 13% | 71% | 22% | 21% | 8% | grp. | % | F | %
| sub.% yrs | | | | | | grp. | | |

| 0 - 100 | 56 (40) | 32 (45) | 12 (55) | 17 (81) | 6 (75) | 123 (47) |
| 101-200 | 53 (38) | 27 (38) | 7 (32) | 3 (14) | 2 (25) | 92 (35) |
| 201-300+ | 30 (22) | 12 (17) | 3 (14) | 1 (5) | 0 (0) | 46 (18) |

| TOTAL L | 139 (100) | 71 (100) | 22(100) | 21 (100) | 8 (100) | 261(100) |
|
| $\frac{L}{A}$ | $\frac{(261)}{53}$ | (27) | (8) | (8) | (3) |
### TABLE 14

**DROWSINESS-METHOHEXITONE SODIUM**

<table>
<thead>
<tr>
<th>DOSE (mg)</th>
<th>20-29</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>TOT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x% yrs</td>
<td>x% yrs</td>
<td>x% yrs</td>
<td>x% yrs</td>
<td>x% yrs</td>
<td>x% TOT</td>
</tr>
<tr>
<td></td>
<td>% sub. yrs</td>
<td>% sub. yrs</td>
<td>% sub. yrs</td>
<td>% sub. yrs</td>
<td>% sub. yrs</td>
<td>%</td>
</tr>
<tr>
<td>grp.</td>
<td>grp.</td>
<td>grp.</td>
<td>grp.</td>
<td>grp.</td>
<td>grp.</td>
<td>grp.</td>
</tr>
<tr>
<td>0 - 100</td>
<td>26(42)(46)</td>
<td>12(48)(38)</td>
<td>2(29)(17)</td>
<td>3(75)(18)</td>
<td>1(100)(17)</td>
<td>44(17)(36)</td>
</tr>
<tr>
<td>101-200</td>
<td>23(36)(43)</td>
<td>8(32)(30)</td>
<td>3(43)(43)</td>
<td>1(25)(33)</td>
<td>0(0)(0)</td>
<td>35(13)(38)</td>
</tr>
<tr>
<td>201-300+</td>
<td>15(23)(50)</td>
<td>5(20)(42)</td>
<td>2(29)(57)</td>
<td>0(0)(0)</td>
<td>0(0)(0)</td>
<td>22(8)(47)</td>
</tr>
<tr>
<td>TOTAL Q</td>
<td>64(100)(46)</td>
<td>25(100)(35)</td>
<td>7(100)(32)</td>
<td>4(100)(19)</td>
<td>1(100)(13)</td>
<td>101(39)</td>
</tr>
<tr>
<td>x% A%</td>
<td>(261)</td>
<td>(25)</td>
<td>(10)</td>
<td>(3)</td>
<td>(2)</td>
<td>(0.5)</td>
</tr>
<tr>
<td>Q% x%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOSE (mg)</td>
<td>20-29 yrs</td>
<td>30-39 yrs</td>
<td>40-49 yrs</td>
<td>50-59 yrs</td>
<td>60-69 yrs</td>
<td>TOT H</td>
</tr>
<tr>
<td>----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-------</td>
</tr>
<tr>
<td>sub.</td>
<td>25% x%</td>
<td>9% x%</td>
<td>2% x%</td>
<td>3% x%</td>
<td>0% x%</td>
<td></td>
</tr>
<tr>
<td>grp.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 100</td>
<td>9 (36)(16)</td>
<td>4 (44)(13)</td>
<td>1 (50)(8)</td>
<td>3 (100)(18)</td>
<td>0 (0)(0)</td>
<td>17 (7)(14)</td>
</tr>
<tr>
<td>101-200</td>
<td>6 (24)(11)</td>
<td>4 (44)(15)</td>
<td>1 (50)(14)</td>
<td>0 (0)(0)</td>
<td>0 (0)(0)</td>
<td>11 (4)(12)</td>
</tr>
<tr>
<td>201-300+</td>
<td>10 (40)(33)</td>
<td>1 (12)(8)</td>
<td>0 (0)(0)</td>
<td>0 (0)(0)</td>
<td>0 (0)(0)</td>
<td>11 (4)(24)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TOTAL R</th>
<th>25 (100)(18)</th>
<th>9 (100)(13)</th>
<th>2 (100)(9)</th>
<th>3 (100)(14)</th>
<th>0 (0)(0)</th>
<th>39 (15)(15)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$\frac{R_{x}}{A_{x}}$ (261) (10)</td>
<td>(3)</td>
<td>(1)</td>
<td>(1)</td>
<td>(0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\frac{R_{x}}{L_{x}}$ (18)</td>
<td>(13)</td>
<td>(9)</td>
<td>(14)</td>
<td>(0)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**TABLE 16**

**ANTEROGRADE MEMORY LOSS—METHOHEXITONE SODIUM**

<table>
<thead>
<tr>
<th>DOSE (mg)</th>
<th>20-29 yrs x%</th>
<th>30-39 yrs x%</th>
<th>40-49 yrs x%</th>
<th>50-59 yrs x%</th>
<th>60-69 yrs x%</th>
<th>TOT %</th>
<th>I %</th>
<th>F %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sub. grp.</td>
<td>sub. grp.</td>
<td>sub. grp.</td>
<td>sub. grp.</td>
<td>sub. grp.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 100</td>
<td>5 (30)(9)</td>
<td>2 (66)(6)</td>
<td>1 (50)(8)</td>
<td>1 (100)(6)</td>
<td>0 (0)(0)</td>
<td>9</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>101-200</td>
<td>4 (24)(8)</td>
<td>1 (34)(4)</td>
<td>1 (50)(14)</td>
<td>0 (0)(0)</td>
<td>1 (100)(50)</td>
<td>7</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>201-300+</td>
<td>7 (46)(23)</td>
<td>0 (0)(0)</td>
<td>0 (0)(0)</td>
<td>0 (0)(0)</td>
<td>0 (0)(0)</td>
<td>7</td>
<td>3</td>
<td>15</td>
</tr>
</tbody>
</table>

TOTAL S  

<p>| | | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>S%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(261) (6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1)</td>
<td>(1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

332
### TABLE 17

#### COMPARISON OF COMPLICATIONS WITHIN AGE GROUPS

**METHOHEXITONE SODIUM**

<table>
<thead>
<tr>
<th>DOSE (mg)</th>
<th>20-29 yrs grp %</th>
<th>30-39 yrs grp %</th>
<th>40-49 yrs grp %</th>
<th>50-59 yrs grp %</th>
<th>60-69 yrs grp %</th>
<th>TOT yrs grp %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 100</td>
<td>56</td>
<td>32</td>
<td>12</td>
<td>17</td>
<td>6</td>
<td>123</td>
</tr>
<tr>
<td>100-300</td>
<td>83</td>
<td>39</td>
<td>10</td>
<td>4</td>
<td>2</td>
<td>138</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>139</strong></td>
<td><strong>71</strong></td>
<td><strong>22</strong></td>
<td><strong>21</strong></td>
<td><strong>8</strong></td>
<td><strong>261</strong></td>
</tr>
</tbody>
</table>

**DROWSY**

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>26 (46)</td>
<td>12 (38)</td>
<td>2 (17)</td>
<td>3 (18)</td>
<td>1 (17)</td>
<td>44 (36)</td>
<td></td>
</tr>
<tr>
<td>38 (46)</td>
<td>13 (33)</td>
<td>5 (50)</td>
<td>1 (25)</td>
<td>0 (0)</td>
<td>57 (41)</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>64 (46)</strong></td>
<td><strong>25 (18)</strong></td>
<td><strong>7 (32)</strong></td>
<td><strong>4 (19)</strong></td>
<td><strong>1 (13) 101 (39)</strong></td>
<td></td>
</tr>
</tbody>
</table>

**DIZZY**

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>9 (16)</td>
<td>4 (13)</td>
<td>1 (8)</td>
<td>3 (18)</td>
<td>0 (0)</td>
<td>17 (14)</td>
</tr>
<tr>
<td>16 (19)</td>
<td>5 (13)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>22 (16)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>25 (18)</strong></td>
<td><strong>9. (13)</strong></td>
<td><strong>2 (9)</strong></td>
<td><strong>3 (14)</strong></td>
<td><strong>0 (0) 29 (15)</strong></td>
</tr>
</tbody>
</table>

**MEMORY**

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (9)</td>
<td>2 (6)</td>
<td>1 (8)</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>11 (13)</td>
<td>1 (3)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>14 (10)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>16 (12)</strong></td>
<td><strong>3. (4)</strong></td>
<td><strong>2 (9)</strong></td>
<td><strong>1 (5)</strong></td>
<td><strong>1 (13) 23 (9)</strong></td>
</tr>
<tr>
<td>DOSE (mg)</td>
<td>20-29 yrs</td>
<td>Sub. grp. %</td>
<td>30 + yrs</td>
<td>Sub. grp. %</td>
<td>TOT</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
<td>-------------</td>
<td>----------</td>
<td>-------------</td>
<td>-----</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>56</td>
<td></td>
<td>67</td>
<td></td>
<td>123</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>83</td>
<td></td>
<td>55</td>
<td></td>
<td>138</td>
</tr>
<tr>
<td>TOTAL</td>
<td>139</td>
<td></td>
<td>122</td>
<td></td>
<td>261</td>
</tr>
</tbody>
</table>

| DROWSY    |           |             |          |             |     |             |
| < 100     | 26        | (46)        | 18       | (27)        | 44  | (36)        |
| > 100     | 38        | (46)        | 19       | (35)        | 57  | (41)        |
| TOTAL     | 64        | (46)        | 37       | (30)        | 101 | (39)        |

| DIZZY     |           |             |          |             |     |             |
| < 100     | 9         | (16)        | 8        | (12)        | 17  | (14)        |
| > 100     | 16        | (19)        | 6        | (11)        | 22  | (16)        |
| TOTAL     | 25        | (18)        | 14       | (11)        | 39  | (15)        |

| MEMORY    |           |             |          |             |     |             |
| < 100     | 5         | (10)        | 4        | (6)         | 9   | (7)         |
| > 100     | 11        | (13)        | 3        | (5)         | 14  | (10)        |
| TOTAL     | 16        | (12)        | 7        | (6)         | 23  | (9)         |
### TABLE 19
COMPARISON OF
AVERAGE METHOHEXITONE DOSAGE PER
AGE GROUP

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>N</th>
<th>AVERAGE DOSE (mg)</th>
<th>S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 yrs</td>
<td>139</td>
<td>156</td>
<td>6.5</td>
</tr>
<tr>
<td>&gt;30 yrs</td>
<td>122</td>
<td>127</td>
<td>7</td>
</tr>
<tr>
<td>TOTAL</td>
<td>261</td>
<td>143</td>
<td>5</td>
</tr>
</tbody>
</table>

Difference < 30 to > 30 years significant (P<0.05) (t=3.0)

### TABLE 20
DROWSINESS - METHOHEXITONE

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>N</th>
<th>AVERAGE DOSE (mg)</th>
<th>S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 yrs</td>
<td>64</td>
<td>165</td>
<td>10</td>
</tr>
<tr>
<td>&gt;30 yrs</td>
<td>37</td>
<td>141</td>
<td>14</td>
</tr>
<tr>
<td>TOTAL</td>
<td>101</td>
<td>156</td>
<td>8</td>
</tr>
</tbody>
</table>

Significant difference (P<0.05) — None.

### TABLE 21
DIZZINESS - METHOHEXITONE

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>N</th>
<th>AVERAGE DOSE (mg)</th>
<th>S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 yrs</td>
<td>25</td>
<td>188</td>
<td>17</td>
</tr>
<tr>
<td>&gt;30 yrs</td>
<td>14</td>
<td>116</td>
<td>16</td>
</tr>
<tr>
<td>TOTAL</td>
<td>39</td>
<td>162</td>
<td>14</td>
</tr>
</tbody>
</table>

Difference < 30 to > 30 years significant (P<0.05) (t=3.1)
GRAPH A

Percentage of patients reporting drowsiness per total number in each drug dose group for diazepam and methohexitone sodium per age group.
Graph B

and methohexital sodium per age
each drive dose group for diazepam

dizziness per total number in

Percentage of patients reporting
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BIBLIOGRAPHY


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